IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GILEAD SCIENCES, INC., GILEAD PHARMASSET LLC, and GILEAD SCIENCES LIMITED,

Plaintiffs,

v.

ABBOTT LABORATORIES, INC., and ABBVIE, INC.,

Defendants.

C.A. No. 13-2034

JURY TRIAL DEMANDED

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COMPLAINT

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Gilead Sciences Limited

INTRODUCTION

1. This case involves a scheme by two large pharmaceutical companies, Defendants Abbott Laboratories, Inc. ("Abbott") and AbbVie, Inc. ("AbbVie"), to attempt to eliminate competition and dominate the market of drugs to treat the hepatitis C virus, known as "HCV." To execute their scheme, the defendants falsely and knowingly represented to the United States Patent and Trademark Office ("PTO") that they invented highly valuable methods of treating HCV that were, in fact, invented by plaintiffs Gilead Sciences, Inc. Gilead Pharmasset LLC, Gilead Sciences Limited, and their predecessor Pharmasset, Inc. (collectively "Gilead") and others. Defendants made these representations despite the knowledge that the inventions for which they claimed ownership had, in fact, been developed by their competitors

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2. In the past few years, many leading pharmaceutical companies, including Gilead and Defendants, have sought to develop new methods of treating chronic HCV, a debilitating virus that attacks the liver and can cause death. Until recently, the standard of care treatment for HCV included the administration of an injectable medication called pegylated interferon for up to 12 months. Treatments employing interferon have a variable cure rate, and the drug can cause serious and sometimes permanent side effects, including severe flu-like symptoms, hemolytic anemia, worsening of cardiac disease, weight loss, skin rashes, hair loss, muscle or bone pain, diarrhea, and vomiting.

3. Based on recent scientific advancements, it is now believed that millions of HCV sufferers worldwide can be cured by the use of a combination of drugs called Direct Acting

Antivirals ("DAAs"), administered in pill form without interferon. These therapies promise high cure rates—90% and higher—much shorter treatment durations—as little as 8 weeks—and dramatically reduced side effects.

4. Given these benefits, there has been intense competition in the pharmaceutical industry to bring the first such innovative combination therapy to market, including between Gilead and Defendants. As of the date of this complaint, Gilead and Defendant AbbVie are widely recognized as being the two companies most likely to first bring an all-oral, interferon free combination therapy to market.

5. Gilead's combination therapy is the two drugs, Sofosbuvir, also known as PSI-7977 or GS-7977, and Ledipasvir, also known as GS-5885 (together, "the Gilead Combination"). Sofosbuvir is what is known as a NS5B inhibitor, while Ledipasvir is what is known as an NS5A inhibitor. Gilead acquired Sofosbuvir in 2011 when it acquired Pharmasset. Gilead developed Ledipasvir independently.

6. The Gilead Combination promises to revolutionize the treatment of HCV, offering the ability to cure HCV within as short as 8 weeks with all-oral interferon-free therapy. No longer will patients be required to endure nearly a year of therapy with inferior drugs like interferon that may not work at all. Notably, the promise of Sofosbuvir has already been partially realized. On December 6, 2013, just 8 months after Gilead filed a new drug application for Sofosbuvir, the FDA approved Sofosbuvir as a treatment for HCV in combination with certain other drugs for durations as short as 12 weeks. This approval was hailed throughout the scientific and popular press, including in the *New York Times* and the *Wall Street Journal*. Gilead is marketing Sofosbuvir as SOVALDI^{TM}, in 400 mg tablets.

7. The opportunity to combine Sofosbuvir with Ledipasvir or other Gilead NS5A or third-party compounds deemed appropriate for patients was the primary reason Gilead acquired Pharmasset, for which it paid $11 billion.

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Gilead ultimately announced its acquisition of Pharmasset on November 21, 2011, and completed the transaction on January 17, 2012.

10. While discussions in support of the Gilead-Pharmasset acquisition were ongoing, on September 16, 2011, Gilead filed a provisional patent application covering the Gilead Combination that disclosed that it could be used for as little as 12 weeks. In late 2011 and early 2012, after the transaction with Pharmasset had closed, Gilead publicly disclosed its intention to

conduct clinical studies of the Gilead Combination, including studies of the combination for a12-week treatment duration.

11. During this same time frame, Abbott (now AbbVie) published results from clinical trials of its proposed combination, which is far less patient-friendly than Gilead's. AbbVie's proposed combination therapy is a combination of four drugs. In addition to the potential patient inconvenience of possibly taking more pills, more drugs mean more potential drug-drug interactions and side effects for patients.

12. On information and belief, REDACTED

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13. On information and belief, Abbott executives and "inventors" conspired and carried out the initial steps of the company's scheme by filing serial fraudulent patent applications asserting that Abbott had invented methods of treating HCV using PSI-7977 as well as the Gilead Combination (as well as thousands of combinations of Abbott's other competitors' HCV compounds). The first of these applications is dated October 21, 2011.

14. Gilead first learned of the defendants' fraud in the days after Abbott's patent applications first published on April 25, 2013. At that time, Gilead learned not only of the applications' existence for the first time but also the speed with which AbbVie (Abbott's successor-in-interest) had sought to receive patents based on those applications. At the time Gilead learned of the applications, the applications were already in condition for allowance.

15. On May 1, 2013, the same date that the PTO issued notices of allowances for the first two of AbbVie's patents, Gilead notified AbbVie of its legal obligation to inform the PTO of Gilead's prior pending patent application covering the Gilead Combination. AbbVie failed to do so. The PTO then issued Patent Nos. 8,466,159 (the '159 patent) [attached hereto as Exhibit A] and 8,492,386 (the '386 patent) [attached hereto as Exhibit B] to AbbVie on June 18 and July 23, 2013, respectively, to the following AbbVie "inventors":

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16. These two patents purport to claim, as AbbVie's invention, methods of treating HCV genotype 1 that comprise administering PSI-7977 and GS-5885 to HCV patients for 12 weeks, with and without ribavirin. But AbbVie invented no such thing. That combination therapy is the invention of Gilead and Pharmasset, not AbbVie.

17. Indeed, AbbVie cannot make, use or sell the Gilead Combination without violating the United States patent laws. Both PSI-7977 and GS-5885 are protected by United States Patents Nos.7,964,580, 8,334,270, and 8,580,765 (PSI-7977) and 8,088,368, 8,273,341, and 8,575,118 (GS-5885), respectively, owned by Gilead Pharmasset LLC. Any attempt by AbbVie to make, use or sell the Gilead Combination in the United States would infringe those patents, willfully so.

18. Despite this, and despite its knowledge of Gilead's prior application for the Gilead Combination, AbbVie continues to this day to assert that it invented the Gilead Combination, both in the United States and abroad. For example, since securing the fraudulent allowance of the '159 and '386 patents, AbbVie has pursued additional claims regarding other potential combination therapies that employ Sofosbuvir. On December 16, 2013, the PTO

allowed Application Number 13/656,012, which claims, as AbbVie's invention, 12-week methods of treatment for HCV using PSI-7977 and any NS5A inhibitor; AbbVie paid the issue fee the very next day. Again, AbbVie invented no such thing.

19. Similarly in Europe, AbbVie has pursued a patent application covering the use of Sofosbuvir and GS-5885 for 12-week treatment of HCV genotype 1. In so doing, it presented Gilead's clinical trial data on the Gilead Combination to the European Patent Office and asserted that Gilead "adopted" AbbVie's "invention." There is no truth to such claims.

20. Because AbbVie cannot lawfully manufacture the Sofosbuvir-containing therapies claimed in the '159 and '386 patents and the allowed '012 application, its patenting activity for those therapies has only one potential purpose—to enforce them against the Gilead Combination or future Gilead combinations, either to attempt to block them from the market or to extract royalties from Gilead.

21. As detailed further herein, AbbVie's conduct in pursuing this conspiracy is fraudulent, intentional and in willful violation of the Patent Laws of the United States, the Delaware Deceptive Trade Practices Act and common law of Slander of Title and Tortious Interference with Prospective Business Relations, REDACTED

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. As detailed herein, Gilead seeks restitution and damages for this unlawful conduct forthwith, as well as the invalidation of the currently issued AbbVie patents that claim therapies using Sofosbuvir and an injunction against any further attempts by AbbVie to claim methods of treating HCV using Sofosbuvir, or combinations of Sofosbuvir and Ledipasvir, as AbbVie "inventions."

THE PARTIES

22. Gilead is a company organized under the laws of the State of Delaware with its principal place of business at 333 Lakeside Drive, Foster City, California. Its mission is to advance the care of patients suffering from life-threatening diseases worldwide, including human immunodeficiency virus (HIV), HCV, liver diseases, serious cardiovascular and respiratory conditions, cancer, and inflammation.

23. Gilead Pharmasset LLC is a limited liability corporation organized under the laws of the State of Delaware with its principal place of business at 333 Lakeside Drive, Foster City, California, and is the owner of the patents related to Sofosbuvir and Ledipasvir, including but not limited to the following issued U.S. Patents: 7,964,580, 8,334,270, and 8,580,765 (PSI/GS-7977 - Sofosbuvir) and 8,088,368, 8,273,341, and 8,575,118 (GS-5885-Ledipasvir).

24. Gilead Sciences Limited is a private limited liability company incorporated under the laws of Ireland with its registered offices at IDA Business & Technology Park, Carringtonhill, Co. Cork, Ireland.

25. On information and belief, Abbott is a company organized under the laws of the State of Illinois with its principal place of business at 100 Abbott Park Road, Abbott Park, Illinois. Abbott is involved in the discovery, development, manufacture, and sale of health care products. On January 1, 2013, Abbott separated into two companies: Abbott and AbbVie.

26. On information and belief, AbbVie is organized under the laws of the State of Delaware with its principal place of business at 1 North Waukegan Road, North Chicago, Illinois. AbbVie is a global, research-based biopharmaceutical company.

JURISDICTION AND VENUE

27. This action arises under the Patent Laws of the United States of America, 35 U.S.C. § 1 *et seq.* and with respect to the state law claims, under the laws of the State of Delaware

28. This Court has subject matter jurisdiction over this action under 28 U.S.C. §§ 1331, 1338 and 35 U.S.C. § 1, *et seq.*, based on an actual controversy between Gilead, on the one hand, and Defendants, on the other hand, for declaratory judgment of patent non-infringement, invalidity and unenforceability under 28 U.S.C. §§ 2201 and 2202.

29. This Court has exclusive jurisdiction over those of Gilead's state law claims that for their determination depend on one or more substantial issues of federal patent law over which this Court has exclusive jurisdiction under 28 U.S.C. § 1338.

30. This Court has supplemental jurisdiction under 28 U.S.C. 1367(a) over those of Gilead's state law claims that form part of the same case or controversy under Article III of the United States Constitution.

31. This Court has personal jurisdiction over Abbott because Abbott is registered with the Delaware Department of State to transact business in Delaware and, on information and belief, regularly transacts business in Delaware.

32. This Court has personal jurisdiction over AbbVie because AbbVie is organized under the laws of Delaware and, on information and belief, regularly transacts business in Delaware.

33. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(b) and (c).

34. On information and belief, Abbott and AbbVie are each subject to personal jurisdiction in this judicial district, and thus reside in this judicial district under 28 U.S.C. § 1391(b)(1) and (c)(2).

35. In short, three of the five parties to this lawsuit are entities created under Delaware law and a fourth, Abbott Laboratories, Inc., an Illinois corporation, is subject to personal jurisdiction in Delaware and thus, under 28 U.S.C. § 1391 (c)(2), is deemed to reside there, creating proper venue under 28 U.S.C. § 1391(b)(1) since all defendants reside in the District of Delaware.

FACTUAL ALLEGATIONS COMMON TO ALL COUNTS AND TO THE EXISTENCE OF A CASE OR CONTROVERSY

A. Hepatitis C

36. Hepatitis C virus ("HCV") is a group of related viruses classified into at least six distinct HCV genotypes (GT 1-6). The most prevalent type of HCV in the United States is GT 1. HCV is highly contagious and is spread by contact with HCV-infected blood. It can cause serious liver damage, including cirrhosis, liver cancer, and liver failure requiring liver transplant surgery.

37. The prevalence of HCV infection in the U.S. has been estimated between 3.2 and 5.2 million people. Since 2007, more people have died from HCV than from HIV in the U.S. HCV infection is the cause of half of all liver cancer deaths in the U.S. and the most common indication for liver transplants.

38. Most HCV-infected individuals carry the virus for life and thereby remain contagious and able to transmit the virus to others. This is true irrespective of whether an individual's HCV infection progresses to chronic form.

39. Traditionally, chronic HCV infection has been treated with a combination of antiviral medicines—ribavirin, interferon, and, more recently, protease inhibitors. This course of therapy may involve several pills taken throughout the day as well as interferon injections. These medicines have relatively limited efficacy and must be taken for prolonged periods—24 to 48 weeks—thereby exacerbating the physical and emotional toll on the infected individuals and their families, which can cause patients to discontinue treatment.

40. These treatments also can have serious side effects with those associated with interferon being most prevalent. Side effects associated with interferon are frequent and can be permanent, and may include flu-like symptoms, serious hemolytic anemia, worsening of cardiac disease, weight loss, skin rashes, hair loss, muscle or bone pain, diarrhea, and vomiting.

41. Recently, scientists have discovered drugs that can directly attack the virus, without the need for interferon. These drugs are known as direct acting anti-viral agents, or "DAAs." Treatment with these DAAs will hopefully obviate the need to use either interferon or ribavirin, and will allow physicians to cure their patients of HCV after as little as 8 weeks of treatment.

42. Several pharmaceutical companies have discovered and developed various potential DAAs, including those in the form of inhibitors of the non-structural proteins NSR, NS3, NS4A, NS4B, NS5A and NS5B. Of these, nucleotide and nucleoside polymerase inhibitors are considered the most powerful potential agents. HCV scientists often refer to nucleotide and nucleoside polymerase inhibitors as "Nucs." PSI-7977 is a Nuc.

43. These non-structural protein inhibitors combat HCV by suppressing the replication of viral RNA and directly interfering with the HCV life cycle. "Nucs," while

powerful, are also almost universally highly toxic at the concentrations necessary for effective disease treatment. PSI-7977, however, is not.

Pharmasset's Development of PSI-7977 (GS-7977) for Short Duration HCV Therapy

44. By no later than late 2010, Pharmasset's PSI-7977 had emerged as the leading Nuc in development by any pharmaceutical company. Different aspects of the compound and its use for treatment of HCV are protected by several United States patents, including U.S. Patent Nos. 7,964,580, 8,334,270, and 8,580,765.

45. Before being acquired by Gilead, Pharmasset spent many years of intensive effort and millions of dollars developing and testing PSI-7977 for use in the treatment of HCV. Well before any possible priority date of the fraudulent Abbott patents, Pharmasset recognized that 7977 could be used in an effective, short duration therapy, including in a short duration combination therapy.

46. No later than May 2009, for example, Pharmasset discussed internally that "small-molecule combination therapies" combining PSI-7851 with other compounds, may be able to suppress the HCV virus to undetectable levels and achieve "complete SVR" (sustained virological response) in as little as 12 weeks.

47. PSI-7851 is what is known as a "racemic" mixture. A racemic mixture is a mixture of two molecules in which each compound's three-dimensional structure is not superimposable upon its mirror image compound, much like our hands.. In this case, the so-called "enantiomers" that make up that racemic mixture PSI-7851 are PSI-7976 and PSI-7977.

48. On January 21, 2010, Pharmasset publicly announced its intention to conduct a 12-week Phase 2 clinical study of PSI-7977 in late 2010.

49. In August 2010, after receiving a "Fast track" designation from FDA, Pharmasset began "PROTON," a 12-week dosing study of PSI-7977 in treatment-naïve patients with HCV Genotypes 1, 2, and 3. According to the FDA, "Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier."

50. On January 10, 2011, Pharmasset and Bristol Myers-Squibb ("BMS") announced a clinical collaboration agreement for testing PSI-7977 in combination with BMS's BMS-790052 (Daclatasvir). BMS-790052, like Gilead's GS-5885, is an NS5A inhibitor.

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The addition of 12-week subgroups to the Pharmasset–BMS trials was publicly announced on November 4, 2011.

52. On September 6, 2011, Pharmasset released results from its Phase 2b PROTON study of PSI-7977 showing that it achieved a 90% SVR (i.e. it had reduced the virus to undetectable levels in 90% of patients) over a 12-week course of treatment.

53. Paragraphs 46-52 state just a few of the examples of Pharmasset's understanding of short duration therapies employing Sofosbuvir. Indeed, when FDA approved Sofosbuvir on December 6, 2013, it approved a labeled indication that includes a 12-week course of treatment for both HCV genotypes 1 and 2, the latter without any interferon. As such, Sofosbuvir is the first HCV treatment to be approved for use in patients for durations as short as 12 weeks.

54. Despite understanding the potency of Sofosbuvir, Pharmasset lacked the resources to develop it fully on its own. Accordingly, throughout its development and testing of PSI-7977, Pharmasset explored license agreements and/or partnerships with larger pharmaceutical companies that could help Pharmasset market and distribute its compound, or that could offer their own compounds to develop combination treatments with PSI-7977. As word spread about the promise of PSI-7977, several large pharmaceutical companies expressed strong interest in obtaining license rights to PSI-7977 or in acquiring Pharmasset.

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Gilead's HCV Drug Program and Development of GS-5885

72. For many years, Gilead has expended significant resources to discover and develop methods of treating HCV that have high SVR rates and low toxicity to patients. As part of this effort, Gilead sought to develop NS5A and NS5B inhibitors.

73. One compound that Gilead discovered and developed is the highly effective NS5A inhibitor, Ledipasvir (GS-5885). Gilead filed a patent application for compounds including GS-5885 on May 13, 2009. On January 3, 2012, the PTO issued U.S. Patent No. 8,088,368 ("the '368 patent") on GS-5885. The compound was not identified by the name GS-5885 in the patent, nor, on information and belief, was the structure of GS-5885 associated with the name GS-5885 in any public documents and/or disclosures until April, 2012.

74. In August 2010, Gilead conducted a Phase 1 clinical trial with GS-5885 in patients with chronic HCV GT 1. In October 2010, Gilead publicly announced results of the Phase 1 clinical trial with GS-5885, including favorable safety results and once daily dosing potential.

75. As of fall 2010, Gilead's HCV treatment pipeline included five compounds in clinical trials and two additional compounds slated to enter clinical trials in early 2011. One of these compounds included a nucleotide analog NS5B polymerase inhibitor of HCV GTs 1-6 called GS-6620, which was highly effective in in vitro tests as well as in in vivo tests in certain mammals.

76. Early in 2011, Gilead conducted a further Phase 1 three-day clinical trial to study the safety, pharmacokinetics and antiviral activity of GS-5885. The sustained viral response rate of the single drug treatment was 50 percent. By early 2011, Gilead had approved a plan to launch a Phase 2 study later in 2011, in which it would combine GS-5885 with its NS5B polymerase inhibitor, GS-6620, without pegylated interferon and both with and without ribavirin, to determine whether a 12-week course of treatment would be effective and tolerated in patients.

Gilead Acquires Pharmasset in Order to Develop a 12-Week Combination Therapy for HCV With GS-5885 and PSI-7977

77. On information and belief, by at least as early as June 2011, Gilead strongly believed that an all-oral regimen combining GS-5885 with PSI-7977 (eliminating interferon, and administered with or without ribavirin) for a duration of 12 weeks or less would successfully treat HCV patients, including GT 1 patients. Such a combination treatment would revolutionize the treatment of HCV, allowing for a much shorter duration of treatment and far fewer side effects.

78. Accordingly, Gilead's management recommended to its Board of Directors the acquisition of Pharmasset for the purpose of acquiring PSI-7977. Gilead's management believed that PSI-7977 would be the key component of its future HCV treatments across all genotypes and, in combination with GS-5885, would result in a highly effective, all-oral interferon-free and shorter duration HCV drug therapy.

79. Gilead pursued the acquisition of Pharmasset and sought to protect its intellectual property rights and significant anticipated financial investment in the combination.

80. While the discussions of the Gilead-Pharmasset acquisition were ongoing, Gilead filed a provisional patent application with the PTO on September 16, 2011. This application disclosed a method for treating HCV, including but not limited to GT 1, by administering, over a 12-week period, the combination of "Compound 6" and "Compound 10," with Compound 6 corresponding to the structure of GS-5885 and Compound 10 corresponding to the structure of PS-7977. The provisional application disclosed administering the "combination compounds" with and without ribavirin, but not interferon, to treat HCV.

81. On November 21, 2011, Gilead and Pharmasset jointly announced the acquisition of Pharmasset by Gilead for approximately $11 billion.

82. The main purpose of the acquisition, according to the press release issued jointly by Gilead and Pharmasset, was to advance Gilead's efforts to develop an all-oral regimen for the treatment of HCV, specifically with Pharmasset's "lead product candidate" PSI-7977. This press release, as well as an accompanying slide presentation detailing Gilead's plans for GS-5885 and PSI-7977, were exhibits to Gilead's November 21, 2011 Form 8-K filing with the Securities and Exchange Commission ("SEC"). A true and accurate copy of Gilead's Form 8-K filing dated November 21, 2011 (with accompanying exhibits) is attached as Exhibit E.

83. On November 21, 2011, M. Ian Somaiya and Do G. Kim, research analysts at Piper Jaffray & Co., commented on this acquisition in their analyst report: "[b]ased on strength of Phase II data, we expect Gilead to pursue Phase III trials in genotype 1 patients with PSI-7977 + ribavirin AND PSI-7977 + Gilead's NS5A and/or protease inhibitor +/- ribavirin."

84. Following the acquisition, PSI-7977 became known as GS-7977.

85. In January 2012, Gilead continued to evaluate the safety and efficacy of GS-5885 and GS-7977, including through clinical testing of the combination.

86. On February 2, 2012, Gilead held a public earnings call with stock analysts for the fourth quarter of 2011. During the call, Gilead's President and Chief Operating Officer, John F. Milligan, PhD, stated, "In keeping with our philosophy to develop best-in-class drugs, we acquired Pharmasset in order to bring PSI-7977 to our portfolio."

87. During the call, Norbert W. Bischofberger, Gilead's Chief Scientific Officer, commented specifically on Gilead's ongoing testing of the combination of GS-7977 and GS-5885.

88. Gilead stated that, "[a]s Gilead has pioneered in HIV, we expect to bring forward next generation single tablet regimens for the treatment of hepatitis C also. To that end, direct

[*sic*; drug-drug] interactions will be carried out with 7977 and GS 5885 and other internal candidates, which will be followed by Phase 2 clinical studies." Gilead publicly indicated that treatment was expected to last for 12 weeks.

89. In response to questions asked by analysts, Gilead stated, "so, we are currently pursuing a drug interaction study 7977, 5855. That will then be followed by a fairly small Phase II study to simply show that you can use together – the two together that you get reasonable SVR rates. And that would then lead to a Phase III study. And that's probably about six months behind 7977 by itself."

Defendants' Unlawful Scheme to Keep Gilead's Combination and Other Competitors' HCV Treatments from Reaching Patients

90. REDACTED In October 2011, Abbott reported that it was developing a 12-week interferon-free regimen to treat HCV using four separate compounds: the protease inhibitor ABT-450; ritonavir, an inhibitor of cytochrome P450; NS5A inhibitor ABT-267/ABT-072; and non-nucleoside polymerase inhibitor ABT-333.

91. On information and belief, Abbott's (now AbbVie's) proposed combination is inferior to the Gilead Combination that employs GS-7977. In contrast to the Gilead Combination, which comprises two drugs, the Abbott/AbbVie combination involves four drugs. A combination that requires more drugs per day is problematic for patient convenience and compliance, as well as increasing the potential drug-drug interactions and side effects.

92. On information and belief, Abbott was also concerned that its combination might also prove inferior to other companies' potential therapies. Other pharmaceutical companies that are attempting or have attempted to develop short-duration HCV treatments include, but are not limited to: Achillion, Alios BioPharma, Anadys, Avila, Arrow Therapeutics, BioCryst,

Boehringer-Ingelheim, BMS, Conatus, GlaxoSmithKline, Incivec, Inhibitex, InterMune, Janssen, Medivir, Merck, Novartis, Phenomix, Presidio, Roche, Schering-Plough, Tibotec, Vertex, ViraChem, and Virobay.

93. On information and belief, in 2011 if not earlier, Abbott determined to eclipse its competitors, not through innovation or the advancement of science, but through a carefully planned fraudulent scheme. The scheme was based on fraudulently seeking to procure patents on various combinations of its competitors' HCV treatment compounds. The ultimate goal for Abbott had nothing to do with the advancement of science or the welfare of individuals afflicted with HCV, but rather to delay, deter, and/or block competitors' superior treatments from entering the market and reaching patients.

94. In most, if not all, cases, the companies targeted by Abbott already had obtained or filed for patents on the individual compounds comprising their combination therapies. Thus, even if Abbott obtained a patent on a competitors' novel combination therapy, Abbott would not be able to make or sell that combination treatment without the permission/license of the owners of the patents to the individual compounds.

95. On information and belief, Abbott's intention was not to make or sell its competitors' combination therapies. Instead, Abbott merely sought to obtain patents on its competitors' inventions. Through such patents, Abbott intended to (1) block its competitors from obtaining patents on their own proprietary drug combinations and (2) make it commercially unfeasible for those competitors to continue to develop, test clinically, obtain regulatory approval for, and eventually market and sell their own combination drug therapies.

96. Abbott's first target was the Gilead Combination and any other therapy that employed PSI-7977. On information and belief, understanding that combinations with PSI-7977

would be superior to any Abbott combination, Abbott defrauded the United States Patent Office, Pharmasset, and Gilead by filing for patents that falsely claimed inventorship of the combination of PSI-7977 and GS-5885, the combination of PSI-7977 and any other NS5A inhibitor, and even the use of PSI-7977 as monotherapy.

97. As set forth in more detail below, Abbott's unlawful scheme included passing off Pharmasset's and Gilead's work as its own, and attempting to monopolize the compounds developed by Pharmasset and Gilead, as well as compounds developed by its other competitors.

1. Abbott's October 21, 2011 Provisional Patent Applications

98. A key step in Abbott's illicit plot was its filing of two provisional patent applications, No. 61/550,352 and No. 61/550, 360 with the PTO on October 21, 2011. These virtually identical provisional patent applications contained claims covering potentially thousands of combinations of HCV compounds invented by Abbott's competitors. Although Abbott met and spoke with investors and stock market analysts about its HCV regimen on that very day, it never mentioned its alleged invention of thousands of combination therapies (using its competitors' proprietary compounds) for the treatment of HCV.

99. Abbott's October 21, 2011 provisional patent filings recited virtually every DAA in development by all major Abbott competitors, including, without limitation, the following seventy (70) DAAs:

(1)	ACH-1095	Achillion	(10)	AZD-2836	Astra-Zeneca
(2)	ACH-1625	Achillion	(11)	AZD-7295	Astra-Zeneca
(3)	ACH-2684	Achillion	(12)	AVL-181	Avila
(4)	ACH-2928	Achillion	(13)	AVL-192	Avila
(5)	ALS-2158	Alios BioPharma/Vertex	(14)	BCX-4678	BioCryst
(6)	ALS-2200	Alios BioPharma/Vertex	(15)	BI-201335	Boehringer Ingelheim
(7)	ANA-598	Anadys	(16)	BI-207127	Boehringer Ingelheim
(8)	A-689	Arrow Therapeutics	(17)	BILB-1941	Boehringer Ingelheim
(9)	A-831	Arrow Therapeutics	(18)	BMS-650032	Bristol-Myers Squibb

(19)	BMS-790052	Bristol-Myers Squibb
(20)	BMS-791325	Bristol-Myers Squibb
(21)	BMS-824393	Bristol-Myers Squibb
(22)	GS-5885	Gilead
(23)	GS-6620	Gilead
(24)	GS-9132	Gilead
(25)	GS-9190	Gilead
(26)	GS-9256	Gilead
(27)	GS-9451	Gilead
(28)	GS-9669	Gilead
(29)	GL-59728	Glaxo
(30)	GL-60667	Glaxo
(31)	GSK-62336805	GlaxoSmithKline
(32)	GSK-625433	GlaxoSmithKline
(33)	IDX-102	Idenix
(34)	IDX-136	Idenix
(35)	IDX-184	Idenix
(36)	IDX-316	Idenix
(37)	IDX-320	Idenix
(38)	IDX-375	Idenix
(39)	Telaprevir	Incivek
(40)	INX-189	Inhibitex
(41)	ITX-4520	iTherX
(42)	ITX-5061	iTherX
(43)	TMC-64912	Medivir
(44)	boceprevir	Merck
(45)	MK-0608	Merck
(46)	MK-3281	Merck
(47)	MK-5172	Merck
(48)	Vaniprevir	Merck
(49)	NM-811	Novartis
(50)	alisporovir	Novartis/Debiopharm
(51)	PF-00868554	Pfizer
(52)	Filibuvir	Pfzier
(53)	PSI-7977	Pharmasset
(54)	PSI-938	Pharmasset
(55)	PHX-1766	Phenomix
(56)	PPI-1301	Presidio
(57)	PPI-461	Presidio
(58)	danoprevir	Roche
(59)	RG-7128	Roche
(60)	narlaprevir	Schering-Plough
(61)	SCY-635	Scynexis
(62)	TMC-435	Tibotec
(63)	TMC-647055	Tibotec
(64)	VX-222	Vertex
(65)	VX-500	Vertex
(66)	VX-813	Vertex
(67)	VX-985	Vertex
(68)	VCH-759	Vertex/ViraChem
(69)	VCH-916	Vertex/ViraChem
(70)	VBY-708	Virobay

100.

REDACTED

101. In the "Claims" section of the 61/550,352 and 61/550,360 provisional patent applications, Abbott represented that it had invented a method of treating HCV by administering at least two (and possibly more) DAAs with ribavirin for a duration of 12 weeks or less. As drafted, this broad claim attempted to encompass the invention of virtually thousands of combinations of the above seventy (70) DAAs. Although Abbott did not expressly mention the specific Gilead Combination, its claims in the '352 and '360 provisional applications were so broadly drafted that they included the combination of PSI-7977 and GS-5885, along with potentially thousands of other drug combinations.

102. While Abbott's '352 and '360 provisional patent applications provided the chemical structures of several of the above compounds, they did not provide the chemical structure of GS-5885. In fact, although the chemical structure of GS-5885 had been disclosed, along with the chemical structures of many other compounds, in the '368 patent, it had not been identified there with the Gilead research identifier GS-5885. Abbott's provisional application therefore did not contain the chemical structure of GS-5885, which Gilead had not made publicly available when Abbott filed the applications in October 2011.

103. The provisional patent applications, which were filed by REDACTED of Abbott's legal department on October 21, 2011, identified the following five individuals as inventors of the claims:

REDACTED

104.

REDACTED

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106.

107.

REDACTED

108. While Abbott's October 21, 2011 provisional patent applications provided clinical test data involving its own proprietary compounds, Abbott disclosed no data or other basis to support its claims regarding the combination of any of the 70 compounds of its competitors, including Gilead's GS-5885 and PSI-7977 (now GS-7977).

109. When it filed the October 21, 2011 provisional applications, Abbott knew that its subterfuge would be hidden from its competitors—including Gilead—as well as Abbott's shareholders and the general public, because provisional patent applications are unavailable publicly for up to 18 months under the federal patent laws.

110. Abbott's machinations extended beyond the PTO, reaching even the securities markets. Abbott was always careful to conceal its plot when answering questions about its HCV treatment pipeline and those of its competitors during its quarterly conference calls with stock analysts.

111. Abbott's management consistently stated that Abbott was relying on its internal pipeline to develop its HCV program, carefully avoiding any mention of its scheme to claim inventorship of treatment methods employing the use of thousands of combinations of its competitors' products

REDACTED

For example, during its Fourth Quarter 2011 earnings call with stock analysts on January 25, 2012, held after Abbott

filed its provisional patent application claiming combinations of Gilead's and other competitors' DAA compounds for the treatment of HCV, Abbott REDACTED stated:

> As we discussed in October, we made significant progress on our pipeline over the past several years . . . and successfully advancing internal programs. One of these internal programs is HCV where our data to-date have shown that we are in the running to have a leadership position in this category . . . we have all the types of assets we need.

2. Abbott's February 17, 2012 Provisional Patent Applications

112. Abbott's next major step in furtherance of its unlawful scheme occurred on February 17, 2012, shortly after Gilead announced its Phase 1, 2 and 3 clinical trials of the combination of GS-5885 and GS-7977 for 12-week HCV therapy in the February 2, 2012 quarterly conference call with stock analysts. On February 17, 2012, Abbott filed provisional patent application Nos. 61/600,276 and 61/600,468 with the PTO, titled "Methods for Treating HCV," which now increased the number of individuals named as inventors of the claims from five to eleven. They included:

REDACTED

113. REDACTED

114. The February 17, 2012 provisional patent applications falsely asserted in Claim 34 that Abbott invented the use of the Gilead Combination for treating HCV ("The method of claim 29, wherein said at least two DAAs comprise PSI-7977 and GS-5885.").

REDACTED

115. Like the October 21, 2011 provisional patent applications, the February 17, 2012 provisional patent applications were fraudulent in many material respects, including, without limitation, the following:

- They falsely represented that Abbott invented the use of the Gilead Combination to treat HCV;
- They falsely represented that Abbott invented the use of PSI-7977 to treat HCV;
- They did not provide the chemical structure of GS-5885, showing that Abbott did not even know the chemical composition of one of two Gilead Compounds comprising the combination treatment. In fact, GS-5885 was not commercially available and its chemical structure still was not publicly known;
- They failed to describe how to make GS-5885;
- REDACTED

- They included no working examples or data relating to the use of PSI/GS-7977 in combination with GS-5885 to treat patients suffering from HCV.

116. Rather than provide clinical data support for its alleged invention, Abbott instead allegedly relied on predictions regarding the SVRs of combinations of two and three DAAs allegedly derived from its so-called "mechanistic model."

3. Abbott's May 11, 2012 Provisional Application

117. The next major step in furtherance of Abbott's unlawful scheme was the filing of provisional patent application No. 61/645,696 titled "Solid Compositions" on May 11, 2012. This provisional patent application claimed the invention of PSI-7977 as well as Gilead's Combination in solid (pill) form, along with the solid forms of Abbott's other competitors HCV treatment compounds. The 61/645,696 provisional patent application is the first Abbott filing with the PTO to include the chemical structure of GS-5885, which, by that time, Gilead had made public.

118. The 61/645,696 provisional patent application was filed by attorney and listed two inventors REDACTED who are not listed as inventors of Abbott's other HCV treatment patents claiming the invention of Gilead's combination.

119. This was yet another flagrant act by which Abbott fraudulently claimed entitlement to PSI-7977 as well as the Gilead Combination.

4. Abbott's June 6, 2012 Provisional Patent Applications

120. The next major step in furtherance of Abbott's unlawful scheme was the filing of its June 6, 2012 provisional patent application Nos. 61/656,251 and 61/656,253. These applications listed REDACTED as inventors.

121. REDACTED

122. Abbott again included the chemical structure of GS-5885 in the provisional patent application.

123. Although Abbott and AbbVie claimed a priority date of October 21, 2011 for the '159 and '386 patents, its "mechanistic model" that purported to use clinical data generated by their competitors to predict the results of various combinations of drugs for HCV treatment was not described in any of its provisional applications until the filling of its provisional application Nos. 61/600,276 and 61/600,468 on February 17, 2012. The "mechanistic model" also was not applied to the Gilead Combination in any of the Abbott provisional applications until June 6, 2012, the date of filing of provisional application Nos. 61/656,251 and 61/656,253.

124. The Abbott/AbbVie model was dependent on data from Gilead's past clinical trial results for its "modeling" of the "predicted" performance of the Gilead Combination. Indeed, the model relied upon Gilead's published "[d]ata from Phase 1 and Phase 2 studies of GS-5885 and GS-7977 (PSI-7977)." '159 patent at col. 108, lines 56-60; '386 patent at col. 102. The Phase 1 and Phase 2 studies were studies that Gilead conducted on PSI-7977 and GS-5885.

125. During prosecution, Abbott and AbbVie relied on Gilead's clinical data, from later Gilead studies that were mentioned by Gilead in its earnings calls, to support their model and their claim to the use of the Gilead Combination to treat HCV. Neither Abbott nor AbbVie contributed any of their own clinical work on the Gilead Combination, despite their claims to have invented the combination.

126. While Abbott was trying to identify GS-5885 and decide how it could use Gilead's clinical data to obtain a patent on HCV treatment methods using the Gilead Combination, Gilead's HCV research and development teams were, at great expense, mounting a concerted clinical research initiative to test its Combination.

127. By the time Abbott filed provisional application Nos. 61/656,251 and 61/656,253, its "model" contributed nothing novel regarding the Gilead Combination or Sofosbuvir and was a sham.

5. The Abbott Inventors' False Declarations to the PTO

128. In August 2012, each of the 11 individuals named as inventors on the provisional patent applications claiming the Gilead Combination

REDACTED signed a declaration affirming that they (1) were the original and first and joint inventor of the subject matter claimed; (2) reviewed and understood the contents of all the claims; and (3) had a duty to disclose to the PTO all information known to be material to patentability as set forth in 37 C.F.R. § 1.56.

129. The alleged inventors further declared that all statements made on their own knowledge were true and acknowledged any willful false statements would be punishable by fine or imprisonment under 18 U.S.C. § 1001.

130. Finally, they acknowledged that any willful false statements may jeopardize the validity of the application or any patent issued based on the Application.

131. One or more of Abbott's alleged inventors willfully made material misrepresentations and omissions in their declarations.

132. Despite their affirmations, one or more of the alleged inventors knew, among other undisclosed facts, that (1) they were not the original, first, or joint inventor of the subject

matter claimed, e.g., the Gilead Combination and (2) they failed to disclose materials relevant to patentability about which they were keenly aware.

133.

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134. Thus, one or more of the alleged inventors willfully made material representations to the PTO and withheld material information from the PTO.

6. Abbott's September 4, 2012 Utility Patent Applications

135. On September 4, 2012, Abbott filed fraudulent utility patent applications, Nos. 13/603,022 and 13/603,006 ("the '022 application" and "the '006 application"), claiming the invention of the Gilead Combination in claims 18–21 and PSI-7977 in claims 29 and 30.

136. Seeking to obtain patent protection on the Gilead Combination as soon as it possibly could, Abbott requested that these utility applications proceed on a Track One, or expedited, basis, and the PTO granted its request.

137. The declarations referenced in paragraphs 128–133, above, were filed in support of these September 4, 2012 patent applications. The alleged inventors claimed benefit of, among others, Abbott provisional applications Nos. 61/550,352 and 61/550,360.

7. Abbott's October 19, 2012 Utility Patent Application

138. On October 19, 2012, Abbott filed another fraudulent utility patent application, No. 13/656,012 ("the '012 application"), again claiming the Gilead Combination. This new

application listed the same eleven inventors as the applications that were filed on September 4, 2012. The alleged inventors claimed benefit of, among other, Abbott provisional application No. 61/656,253.

139. On November 20, 2013, Abbott filed declarations of inventorship from the eleven alleged inventors. These declarations contained the very same false representations as the declarations described in paragraphs 128 to 133.

140. During prosecution of the ’012 application, Abbott broadened its claims, seeking patent coverage for a method of treating HCV for 12 weeks comprising the administration of PSI-7977 and any HCV NS5A inhibitor.

141.

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8. AbbVie’s Formation and Continuation of the Unlawful Scheme

142. On or around October 19, 2011, Abbott announced that it would separate into two publicly-traded companies, one in diversified medical products (Abbott) and the other in research-based pharmaceuticals (AbbVie). AbbVie was to absorb Abbott’s then-current portfolio of proprietary pharmaceuticals and biologics, including its HCV treatment pipeline.

143. On or around January 2, 2013, the announced separation of Abbott and AbbVie into two separate, publicly-traded companies took effect.

144.

REDACTED

145. On information and belief, REDACTED was fully knowledgeable of and instrumental in executing Abbott's scheme and continued to further that scheme on behalf of the newly formed AbbVie.

146. Shortly after the formation of AbbVie, the defendants continued to defraud the PTO.

147. On or around April 11, 2013, AbbVie stated under 37 CFR 3.73(b) that it was the owner to the entire right, title, and interest in Abbott's patent application Nos. 13/603,022 and 13/603,006. AbbVie attorney REDACTED signed the ownership statement, certifying that he was authorized to act on behalf of AbbVie.

148. On or around April 25, 2013, Abbott's (now AbbVie's) '022 and '006 patent applications were published by the PTO and thus, made publicly available for the first time.

149. Gilead learned of AbbVie's fraudulent '022 and '006 patent applications shortly after their publication.

150. On or around May 1, 2013, the day that the PTO issued its notice of allowance for AbbVie's first two patents, Gilead contacted REDACTED by email, attaching Gilead's PCT publication WO 2013/040492 A2 ("Gilead's PCT Publication"), entitled "Methods for Treating HCV," which has a priority date of September 16, 2011 and discloses the Gilead Combination of GS-7977 and GS-5885.

, was copied on the email. Gilead encouraged REDACTED to comply with 37 CFR 1.56 and disclose the reference to the PTO, given the close nature of Gilead's PCT Publication to Abbott/AbbVie's pending application. Neither REDACTED nor REDACTED , nor any other AbbVie representative, disclosed this reference to the PTO before

issuance of the '159 and '386 patents, despite Gilead informing them of the importance of the reference.

151. Gilead's PCT Publication was filed on September 14, 2012 and published on March 21, 2013. It claims priority to a provisional application (U.S.S.N. 61/535,885) ("Gilead's Provisional Application") filed September 16, 2011. Gilead's PCT application is prior art to the AbbVie Patents because the priority date of Gilead's PCT Publication is before the October 2011 filing of AbbVie's first provisional applications, before the February 2012 filing of AbbVie's first provisional applications to mention the Gilead Combination of GS-7977 and GS-5885, and before the June 2012 filing of AbbVie's first provisional applications to include the structure of GS-5885.

152. Gilead's PCT Publication and Provisional Application to which it claims priority disclose a method for treating HCV genotype 1 by administering the combination of "Compound 6" and "Compound 10":

> This invention relates to combinations of therapeutic molecules useful for treating hepatitis C virus infection. The present invention relates to methods, uses, dosing regimens, and compositions ….
> HCV is a genetically diverse virus. Within a single infected patient, many variant viruses can be identified, leading to the description of 'viral swarm', or viral quasispecies. Within the global human population, HCV is also genetically diverse, with at least 6 major 'genotypes' identified (Genotypes 1-6), and numerous subtypes (i.e., HCV Genotype 1a and 1b). HCV genotypes are defined by genomic phylogenetic analysis, and diagnosed (in a given patient) by HCV RNA sequence-based diagnostic assays ….
> Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 6 and further comprising a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10 and Compound 11 …. In one specific embodiment of the invention, the second compound may be Compound 10.

153. The structure of "Compound 6" is set forth on p. 8 of Gilead's PCT Publication and Provisional Application. This structure corresponds to the structure of GS-5885 set forth at cols. 83–84 of the '159 patent and cols. 79–80 of '386 patent.

154. The structure of "Compound 10" is set forth on p. 9 of Gilead's PCT Publication and Provisional Application This structure corresponds to the structure of PSI-7977 set forth at col. 80 of the '159 patent and col. 78 of the '386 patent.

155. Gilead's PCT Publication and Provisional Application define "combination compounds" as follows:

> As used herein the term "Combination Compounds" refers to Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10 and Compound 11.

156. Gilead's PCT Publication and Provisional Application disclose administering the "combination compounds" with ribavirin but not interferon to treat HCV:

> Combinations of Two or more of the Combination Compounds with Ribavirin but not Interferon
>
> As discussed above, some current HCV treatments include the administration of interferon, but this treatment typically produced unwanted side effects. Therefore it would be desirable to find effective HCV treatments that do not require the administration [of] interferon.
>
> One aspect of the present invention provides for compositions, methods, uses and the like for the treatment of HCV comprising administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, without administering one or more interferons. This aspect of the invention may be particularly useful because it allows for the effective treatment of HCV without the side effects associated with the administration of one or more interferon.

157. Gilead's PCT Publication and Provisional Application explain that using ribavirin is an option, but is not required. The PCT Publication and Provisional Application also contemplate the combination of Compounds 6 and 10 without ribavirin:

> The term "combination therapy" means combinations or methods or uses or the like that incorporate two or more of the Combination Compounds. Combination therapy may also incorporate other active ingredients in addition to the two or more of the Combination Compounds including, but not limited to, ribavirin.

158. Gilead's PCT Publication and Provisional Application disclose administering the treatment for 12 weeks:

> The course of treatment can extend, for example, from about 12 weeks to about 48 weeks or longer, for example, from about 12 weeks to about 24 weeks.

159. By letter dated May 2, 2013, Gilead again provided REDACTED with Gilead's PCT Publication WO 2013/040492 A2, noting its specific relevance to AbbVie's pending patent application Nos. 13/603,006, 13/656,012, 13/603,022, and 13/656,024, amongst others. Gilead copied REDACTED on the letter, in which Gilead, once again, encouraged AbbVie to comply with 37 CFR 1.56 and disclose the reference to the PTO. Neither REDACTED nor AbbVie responded to Gilead regarding this communication.

160. On May 2, 2013, just one day after the PTO issued its notice of allowance and despite AbbVie's awareness of the Gilead PCT Publication, AbbVie, nonetheless, paid the issue fee on the '022 application, further advancing its illegal scheme. The '159 patent issued from Application No. 13/603,022 on June 18, 2013. The '386 patent later issued from Application No. 13/603,006 on July 23, 2013, again with no disclosure of the Gilead PCT Publication and Provisional Application to the PTO.

161. On or around May 2, 2013, Gilead sent an email to REDACTED REDACTED, as well as REDACTED, citing Gilead's PCT application and describing, in detail, its relevance to (and impact on the validity of the claims relating to Gilead's Combination) in AbbVie's patent application No. 13/603,022. Gilead also noted that despite its previous

communication to AbbVie in which Gilead drew AbbVie's attention to Gilead's PCT application and its priority date of September 16, 2011, AbbVie had, nonetheless, subsequently paid the issue fee on its Applications.

162. In response to Gilead's email, REDACTED responded on behalf of AbbVie, stating not that she recognized the seriousness of AbbVie's duty to disclose Gilead's PCT application to the PTO, but rather, "Thank you for your email. Please direct your correspondence to my colleague REDACTED ."

163. On information and belief, despite its awareness of the Gilead PCT Publication (WO 2013/040492) and its obligation to disclose material information to the PTO, AbbVie never disclosed the Gilead PCT Publication, or any of Gilead's patent applications claiming Gilead's combination HCV treatment, as references to the PTO during prosecution of the '159 and '386 patents. In particular, REDACTED , who had a duty of candor and good faith to the PTO as a registered patent attorney and as the patent attorney prosecuting the AbbVie applications, paid the issue fee for the '159 and '386 AbbVie Patents without disclosing the Gilead PCT Publication despite having been personally informed of the Publication's existence and relevance on multiple occasions.

164. The disclosure described above in Paragraphs 152 to 158 is included in both Gilead's PCT Publication and the September 16, 2011 Provisional Application to which it claims priority. Thus, the Gilead PCT Publication qualifies as prior art under 35 U.S.C. § 102(e) against the AbbVie Patents' claims to the Gilead Combination (in particular, claims 13–16) because the subject matter of claims 13–16 "was described in an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent …."

165. The Gilead PCT Publication, and the Provisional Application to which it claims priority, is material to the claims of the AbbVie Patents. If the PTO examiner had been aware of the Gilead PCT Publication and Provisional Application during prosecution of the AbbVie Patents, the claims would not have issued because they are anticipated under 35 U.S.C. § 102(e).

166. Indeed, on December 9, 2013, the European Patent Office issued an examination report concluding that Abbott's pending European claims to a combination of PSI-7977 and GS-5885 lacked novelty over, among other things, the Gilead PCT Publication.

167. The materiality of the Gilead PCT Publication, which is entitled to priority to the Gilead Provisional Application, to claims 13–16 of the AbbVie Patents is demonstrated in the charts below. The Gilead PCT Publication and Provisional Application disclose each and every limitation of claims 13–16 of each patent.

REDACTED

The '159 Patent Claims	The Gilead PCT Publication and Provisional Application
13. A method of treatment for HCV, comprising administering at least two direct acting antiviral agents (DAAs) and ribavirin to an HCV patient infected with HCV genotype 1, wherein said treatment does not include administration of interferon to said patient,	"This invention relates to combinations of therapeutic molecules useful for treating hepatitis C virus infection. The present invention relates to methods, uses, dosing regimens, and compositions …. HCV is a genetically diverse virus. Within a single infected patient, many variant viruses can be identified, leading to the description of 'viral swarm', or viral quasispecies. Within the global human population, HCV is also genetically diverse, with at least 6 major 'genotypes' identified (Genotypes 1-6), and numerous subtypes (i.e., HCV Genotype 1a and 1b). HCV genotypes are defined by genomic phylogenetic analysis, and diagnosed (in a given patient) by HCV RNA sequence-based diagnostic assays …. Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 6 and further comprising a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10 and Compound 11 …. In one specific embodiment of the invention, the second compound may be Compound 10." Provisional Application at p. 1, lines 5–7 and 28–34; p. 17, lines 17–30. "As used herein the term "Combination Compounds" refers to Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10 and Compound 11." Provisional Application at p. 6, lines 4-6. "<u>Combinations of Two or more of the Combination Compounds with Ribavirin but not Interferon</u>

The '159 Patent Claims	The Gilead PCT Publication and Provisional Application
	As discussed above, some current HCV treatments include the administration of interferon, but this treatment typically produced unwanted side effects. Therefore it would be desirable to find effective HCV treatments that do not require the administration [of] interferon. One aspect of the present invention provides for compositions, methods, uses and the like for the treatment of HCV comprising administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, without administering one or more interferons. This aspect of the invention may be particularly useful because it allows for the effective treatment of HCV without the side effects associated with the administration of one or more interferon." Provisional Application at p. 60, lines 18–29.
wherein said at least two DAAs comprise PSI-7977 and GS-5885,	The structure of "Compound 6" is set forth at p. 7, line 15 to p. 8, lines 1–4 of the Provisional Application. This structure corresponds to the structure of GS-5885 set forth at cols. 83–84 of the '159 patent. The structure of "Compound 10" is set forth at p. 9, lines 8–10 of the Provisional Application. This structure corresponds to the structure of PS-7977 set forth at col. 80 of the '159 patent.
and wherein said treatment lasts for 12 weeks.	"The course of treatment can extend, for example, from about 12 weeks to about 48 weeks or longer, for example, from about 12 weeks to about 24 weeks." Provisional Application, at p. 60, lines 3–4.
14. The method of claim 13, wherein said patient is a treatment-naïve patient.	There are only two types of patients: treatment-naïve and treatment experienced. Because there are only two types of patients, a person of ordinary skill, reading the disclosure

The '159 Patent Claims	The Gilead PCT Publication and Provisional Application
	in the Gilead PCT Publication and Provisional Application of a treatment for "HCV infection," would understand this to mean that the treatment applied to both types of patients.
15. The method of claim 13, wherein said patient is infected with HCV genotype 1a.	"This invention relates to combinations of therapeutic molecules useful for treating hepatitis C virus infection. The present invention relates to methods, uses, dosing regimens, and compositions …. HCV is a genetically diverse virus. Within a single infected patient, many variant viruses can be identified, leading to the description of 'viral swarm', or viral quasispecies. Within the global human population, HCV is also genetically diverse, with at least 6 major 'genotypes' identified (Genotypes 1–6), and numerous subtypes (i.e., **HCV Genotype 1a** and 1b). HCV genotypes are defined by genomic phylogenetic analysis, and diagnosed (in a given patient) by HCV RNA sequence-based diagnostic assays." Provisional application at p. 1, lines 5–7 and 28–34.
16. The method of claim 14, wherein said patient is infected with HCV genotype 1a.	"This invention relates to combinations of therapeutic molecules useful for treating hepatitis C virus infection. The present invention relates to methods, uses, dosing regimens, and compositions …. HCV is a genetically diverse virus. Within a single infected patient, many variant viruses can be identified, leading to the description of 'viral swarm', or viral quasispecies. Within the global human population, HCV is also genetically diverse, with at least 6 major 'genotypes' identified (Genotypes 1–6), and numerous subtypes (i.e., **HCV Genotype 1a** and 1b). HCV genotypes are defined by genomic phylogenetic analysis, and diagnosed (in a given patient) by HCV RNA sequence-based diagnostic assays." Provisional Application at p. 1, lines 5–7 and 28–34

The '386 Patent Claims	The Gilead PCT Publication and Provisional Application
13. A method of treatment for HCV, comprising administering at least two direct acting antiviral agents (DAAs) to an HCV patient infected with HCV genotype 1,	"This invention relates to combinations of therapeutic molecules useful for treating hepatitis C virus infection. The present invention relates to methods, uses, dosing regimens, and compositions …. HCV is a genetically diverse virus. Within a single infected patient, many variant viruses can be identified, leading to the description of 'viral swarm', or viral quasispecies. Within the global human population, HCV is also genetically diverse, with at least 6 major 'genotypes' identified (Genotypes 1–6), and numerous subtypes (i.e., HCV Genotype 1a and 1b). HCV genotypes are defined by genomic phylogenetic analysis, and diagnosed (in a given patient) by HCV RNA sequence-based diagnostic assays …. Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 6 and further comprising a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10 and Compound 11 …. In one specific embodiment of the invention, the second compound may be Compound 10." Provisional Application at p. 1, lines 5–7 and 28–34; p. 17, lines 17–30. "As used herein the term "Combination Compounds" refers to Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10 and Compound 11." Provisional Application at p. 6, lines 4–6.
wherein said treatment does not include	The term "combination therapy" means

The '386 Patent Claims	The Gilead PCT Publication and Provisional Application
administration of either interferon or ribavirin to said patient,	combinations or methods or uses or the like that incorporate two or more of the Combination Compounds. Combination therapy ***may*** also incorporate other active ingredients in addition to the two or more of the Combination Compounds including, but not limited to, ribavirin. Provisional Application at p. 11, lines 16–19.
wherein said at least two DAAs comprise PSI-7977 and GS-5885,	The structure of "Compound 6" is set forth at p. 7, line 15 to p. 8, lines 1–4 of the Provisional Application. This structure corresponds to the structure of GS-5885 set forth at cols. 79–80 of the '386 patent. The structure of "Compound 10" is set forth at p. 9, lines 8-10 of the Provisional Application. This structure corresponds to the structure of PS-7977 set forth at col. 78 of the '386 patent.
and wherein said treatment lasts for 12 weeks.	"The course of treatment can extend, for example, from about 12 weeks to about 48 weeks or longer, for example, from about 12 weeks to about 24 weeks." Provisional Application, at p. 60, lines 3–4.
14. The method of claim 13, wherein said patient is a treatment-naïve patient.	There are only two types of patients: treatment-naïve and treatment experienced. Because there are only two types of patients, a person of ordinary skill, reading the disclosure in the Gilead PCT Publication and Provisional Application of a treatment for "HCV infection," would understand this to mean that the treatment applied to both types of patients.
15. The method of claim 13, wherein said patient is infected with HCV genotype 1a.	"This invention relates to combinations of therapeutic molecules useful for treating hepatitis C virus infection. The present invention relates to methods, uses, dosing regimens, and compositions …. HCV is a genetically diverse virus. Within a single infected patient, many variant viruses can be identified, leading to the description of 'viral swarm', or viral quasispecies. Within

The '386 Patent Claims	The Gilead PCT Publication and Provisional Application
	the global human population, HCV is also genetically diverse, with at least 6 major 'genotypes' identified (Genotypes 1–6), and numerous subtypes (i.e., **HCV Genotype 1a** and 1b). HCV genotypes are defined by genomic phylogenetic analysis, and diagnosed (in a given patient) by HCV RNA sequence-based diagnostic assays." Provisional Application at p. 1, lines 5–7 and 28–34.
16. The method of claim 14, wherein said patient is infected with HCV genotype 1a.	"This invention relates to combinations of therapeutic molecules useful for treating hepatitis C virus infection. The present invention relates to methods, uses, dosing regimens, and compositions …. HCV is a genetically diverse virus. Within a single infected patient, many variant viruses can be identified, leading to the description of 'viral swarm', or viral quasispecies. Within the global human population, HCV is also genetically diverse, with at least 6 major 'genotypes' identified (Genotypes 1–6), and numerous subtypes (i.e., **HCV Genotype 1a** and 1b). HCV genotypes are defined by genomic phylogenetic analysis, and diagnosed (in a given patient) by HCV RNA sequence-based diagnostic assays." Provisional Application at p. 1, lines 5–7 and 28–34

168. If REDACTED or anyone else acting on behalf of AbbVie had disclosed the Gilead PCT Publication and Provisional Application to the PTO, the Examiner would not have allowed at least claims 13–16 to issue because these claims are anticipated under 35 U.S.C. § 102(e). Thus, REDACTED and AbbVie knowingly failed to disclose material prior art.

169. A specific intent to deceive can be inferred because REDACTED REDACTED and AbbVie were specifically informed of the relevance of the Gilead PCT

Publication and Provisional Application to the AbbVie applications before they issued as the AbbVie Patents and still failed to disclose it.

170. On or around June 13, 2013, AbbVie management, including REDACTED —a named inventor on the '159 and '386 patents and REDACTED —presented at Goldman Sachs 45th Annual Global Healthcare Conference. When asked about AbbVie's progress on developing its HCV regimen as compared to Gilead's, stated, "I'll say that it is a very tight race and like I said we're executing extremely well and I think we've got a very good shot at being first, but it's close."

171. At the time of REDACTED statements, the PTO had already notified AbbVie of its Notices of Allowance for the '159 and '386 patents, which issued on June 18, 2013 and July 23, 2013, respectively.

172. AbbVie did not, however, disclose to investors or the public that it had secured patents covering the Gilead Combination.

173. AbbVie continued with its scheme of deception after the issuance of the '159 and '386 patents. On October 18, 2013, during prosecution of its European applications on the same GS-5885 / PSI -7977 combination, AbbVie, to support the patentability of its claims, argued that the "importance of the shortened treatment method continues to be underscored, even after the present invention was published and after it was quickly adopted by others – see Exhibit 1 hereto, page 1, last but one full paragraph (Press Release dated May 2, 2013, reporting on the LONESTAR study)." The attached press release related to Gilead's clinical studies on the GS-5885 / PSI-7977 combination. Thus, AbbVie told the European Patent Office that Gilead had "adopted" its claimed treatment method, despite AbbVie's knowledge that the situation was actually reversed, with AbbVie attempting to "adopt" Gilead's work for AbbVie's own patents.

As described in detail above, REDACTED and AbbVie REDACTED ,

REDACTED

174. It was not until September 2013, during prosecution of the ’012 application that has been allowed but not issued, that AbbVie finally disclosed the existence of the Gilead PCT Publication to the PTO. This disclosure was well after the ’159 and ’386 patents had already issued, and nearly a year into the prosecution of the ‘012 application.

175. Even though the Gilead PCT Publication was disclosed in prosecution of the ’012 application, AbbVie’s unclean hands from its earlier failure to disclose infects the later prosecution as well. The ’012 application descends from the same June 2012 provisional application as the ’386 patent and claims highly related subject matter. Indeed, the claims asserted in the ‘012 application are broader than the claims of the ’159 and ’386 patents, covering the use of PSI-7977 with any NS5A inhibitor rather than just its use with GS-5885.

176. Moreover, even though the Gilead PCT Publication was listed on an Information Disclosure Statement to the PTO in prosecution of the ‘012 patent application, AbbVie still continued with its deception. During the prosecution of the ‘012 patent application, AbbVie sought even broader claims, seeking to cover the use of PSI-7977 with any NS5A inhibitor, not just with GS-5885, for 12-week treatment, even though AbbVie itself has done no work with any PSI-7977 combination.

REDACTED

177. AbbVie has also continued to use Gilead’s clinical data to support these broad claims. On September 18, 2013, AbbVie attempted to support its claims to the use of PSI-7977

with any NS5A inhibitor without interferon for 12-week treatment of HCV by citing to Gilead data of 12-week clinical studies on PSI-7977 without interferon.

178. On November 20, 2013, two months after listing the Gilead PCT Publication on the Information Disclosure Statement, AbbVie's alleged inventors filed the declarations of inventorship discussed in paragraphs 128 to 134, falsely claiming that they were the original and first inventors of the claimed subject matter.

179. As discussed in paragraphs 128 to 134, these declarations were knowingly false. The submission of such false declarations to the PTO constitutes affirmative egregious misconduct.

180. AbbVie has obtained these patents on the Gilead Combination despite the fact that AbbVie itself would not be permitted to make, use, or sell the Gilead Combination without violating the U.S. Patent Law. Gilead Pharmasset LLC owns U.S. Patent No. 7,964,580, which covers PSI-7977, and U.S. Patent No. 8,088,368, which covers GS-5885. Any attempt by AbbVie to make, use, or sell the Gilead Combination would infringe both of these patents.

181. Despite Gilead's own patents, and despite its knowledge of Gilead's prior PCT application for the Gilead Combination, AbbVie has continued to assert, both before the U.S. PTO and in Europe, that it invented the Gilead Combination and other potential combinations that involved Sofosbuvir.

182. AbbVie willfully deceived the PTO, millions of HCV sufferers and its own investors as part of its scheme to prevent Gilead from bringing its HCV cure to market. AbbVie's pattern of deception constitutes affirmative egregious misconduct.

ADDITIONAL FACTS RELATED TO PRESENCE OF CASE OR CONTROVERSY

183. The AbbVie Patents claim as AbbVie's "invention," the Gilead Combination for the treatment of HCV GT1, with and without the use of ribavirin. Because this "invention"

covers only a product that would be marketed by Gilead, and because AbbVie would be prohibited from marketing such a product because of Gilead's own patents, there is no purpose to obtaining these patents except to either: a) attempt to block Gilead's product from the market; or b) extract royalties from Gilead through the litigation process or the threat of the litigation process.

184. The Gilead Compounds have, separately and as the Gilead Combination, been clinically tested in thousands of individuals in Phase 1, 2 and 3 clinical trials and have been shown to be generally safe and well tolerated, raising no serious safety issues and they have shown a high degree of efficacy in a variety of patients infected with a variety of HCV genotypes, including treatment naïve patients with HCV GT-1.

185. In particular, the Gilead Compounds and the Gilead Combination have been extensively and successfully tested in clinical trials of treatment-naïve HCV GT-1 patients with a treatment duration of twelve weeks or less, both with and without ribavirin. The same is true of the combination of Sofosbuvir and Gilead's next generation pan-genotypic NS5A inhibitor, GS-5816.

186. All of Gilead's Phase III clinical trials of the Gilead Combination necessary for seeking regulatory approval are completed or nearly completed.

187. Gilead is preparing to file, and has publicly announced that it plans to file, a New Drug Application ("NDA") submission to the FDA for the first quarter of 2014. Gilead expects that the FDA will act on its NDA within about eight months from the date it is filed.

188. Gilead has invested $11 billion to acquire Pharmasset, plus at least $200 million in the development of the Gilead Combination, and will expend millions of dollars and vast human resources during the final FDA review process and during preparation for launching these

drugs. Thus, Gilead has conspicuously engaged in meaningful preparation for making, selling and using the Gilead Combination.

189. On information and belief, AbbVie monitors the drug-development pipelines, clinical trials, and acquisitions of competitor pharmaceutical companies, including activities related to potential therapeutic products for the treatment of HCV infection. On information and belief, AbbVie has monitored and continues to monitor such activities as related to Gilead.

190. On information and belief, AbbVie has monitored and continues to monitor the progress and outcome of Gilead's clinical trials of the Gilead Combination. If approved, the Gilead NDA drug product comprising the Gilead Combination will directly compete against AbbVie's own all-oral DAA products that are the subject of AbbVie's own impending NDA in the HCV all-oral, interferon-free DAA market.

191. On information and belief, AbbVie has demonstrated a willingness to protect the market position of its proprietary drugs against competitors through patent infringement litigation. On October 25, 2013, REDACTED during a call with market analysts, stated "We certainly feel good about the patent portfolio that we have . . . . I believe it does and will provide a significant level of protection. And we certainly intend to enforce our patents and make sure no one violates those patents." Consistent with this, despite its relative short existence, on information and belief, AbbVie has been the plaintiff in eighteen patent cases filed in this judicial district, either those that it has filed itself or those in which it succeeded to Abbott's filing.

192. On information and belief, Abbott and AbbVie have sought patent protection on their competitors' proprietary developmental drugs so that they can assert those patents to eliminate competition for any AbbVie product.

193. On information and belief, AbbVie has a present intent to sue Gilead for infringement of the '159 and '386 patents. On information and belief, AbbVie secured issuance of those two patents on Track 1 status at the United States Patent Office for the specific purpose of enforcing them against Gilead.

LEGAL CLAIMS (FEDERAL LAW)

COUNT 1

(Declaratory Judgment – Invalidity of Claims 13-16 of the '159 Patent)

194. Gilead incorporates by reference the allegations contained in paragraphs 1–193 of this Complaint.

195. As a result of the acts described in the foregoing paragraphs, there exists an actual and justiciable controversy of sufficient immediacy and reality, within the meaning of the Federal Declaratory Judgment Act, 28 U.S.C. § 2201 *et seq.*, regarding the invalidity of claims 13–16 of the '159 patent.

196. Claims 13–16 of the '159 patent are invalid for failure to comply with one or more of the conditions for patentability set forth in 35 U.S.C. § 1, *et seq.*, including §§ 102(e), 102(f), 102(g)(2), 103, and 112.

197. Gilead is entitled to a judgment declaring that claims 13–16 of the '159 patent are invalid under 35 U.S.C. §§ 102(e), 102(f), 102(g)(2), 103, and 112.

198. This is an exceptional case entitling Gilead to an award of its attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285.

COUNT 2

(Declaratory Judgment – Unenforceability of the '159 Patent)

199. Gilead incorporates by reference the allegations contained in paragraphs 1–193 of this Complaint.

200. The ’159 patent is unenforceable due to inequitable conduct before the PTO. This conduct includes the submission of knowingly false declarations of original inventorship to claims 13–16 by REDACTED (collectively, the “Named AbbVie Inventors”) and the intentional failure of at least REDACTED to disclose material prior art—i.e., the Gilead PCT Publication and the Provisional Application to which the Gilead PCT Publication claims priority—to the PTO during prosecution of the ’159 patent with specific intent to deceive.

201. On or around August 15–29, 2012, each of the Named AbbVie Inventors signed declarations that declared that they believed each of them to be an original and first and joint inventor of the subject matter claimed in the ’159 patent, which includes the specific combination of GS-5885 and GS-7977, without interferon for 12 weeks, for the treatment of HCV genotype 1.

202. On information and belief, the Named AbbVie Inventors intentionally misrepresented to the PTO the identities of the true original inventors of claims 13–16 in the ’159 patent. This misrepresentation was material to patentability under 35 U.S.C. §§ 102(f), 111, and 115.

203. The inventors’ specific intent to deceive the PTO can be inferred from the facts described above and the fact that claims to the Gilead Combination do not appear in the application until after Gilead acquired Pharmasset and announced its intentions for 7977 and until after Gilead announced clinical trials were planned for the Gilead Combination. This intent to deceive can further be inferred from the fact that no AbbVie inventor had any knowledge of and/or access to any clinical data relating to the use of GS-7977 in combination with GS-5885 to treat patients suffering from HCV, as late as the filing date of Abbott/AbbVie’s

patent application number 61/656,251. The submission of such knowingly false declarations constitutes affirmative egregious misconduct before the PTO.

204. On information and belief, at least REDACTED intentionally failed to disclose the Gilead PCT Publication and the Provisional Application to which the Gilead PCT Publication claims priority to the PTO as prior art under 37 C.F.R. § 1.56. This misrepresentation and/or omission was material to patentability under 35 U.S.C. §§ 102(e) and 103.

205. An intent to deceive the PTO can be inferred from the fact that, on or around May 1, 2013 and May 2, 2013, prior to the issuance of the '159 patent, AbbVie received multiple instances of correspondence from Gilead encouraging AbbVie to disclose the Gilead PCT Publication to the PTO and bring it to the examiner's attention, but chose not to do so.

206. An intent to deceive the PTO can further be inferred from the fact that during the prosecution of the '159 patent, AbbVie relied on Gilead's clinical data to support its claim to the use of GS-5885 and GS-7977 to treat HCV in a March 6, 2013 Supplemental Response to the PTO, yet failed to disclose Gilead's patent applications to the PTO.

207. But for these misrepresentations and omissions to the PTO, claims 13–16 of the '159 patent would not have issued as detailed above.

208. As a result of the acts described in the foregoing paragraphs, there exists an actual and justiciable controversy of sufficient immediacy and reality, within the meaning of the Federal Declaratory Judgment Act, 28 U.S.C. § 2201 *et seq.*, regarding the unenforceability of the '159 patent.

209. The '159 patent is unenforceable due to Abbott/AbbVie's fraud on the PTO.

210. Gilead is entitled to a judgment declaring that the '159 patent is unenforceable due to Abbott/AbbVie's fraud on the PTO.

211. This is an exceptional case entitling Gilead to an award of its attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285.

COUNT 3

(Declaratory Judgment – Invalidity of Claims 13–16 of the '386 Patent)

212. Gilead incorporates by reference the allegations contained in paragraphs 1–193 of this Complaint.

213. As a result of the acts described in the foregoing paragraphs, there exists an actual and justiciable controversy of sufficient immediacy and reality, within the meaning of the Federal Declaratory Judgment Act, 28 U.S.C. § 2201 *et seq.*, regarding the invalidity of claims 13–16 of the '386 patent.

214. Claims 13–16 of the '386 patent are invalid for failure to comply with one or more of the conditions for patentability set forth in 35 U.S.C. § 1, *et seq.*, including §§ 102(e), 102(f), 102(g)(2), 103, and 112.

215. Gilead is entitled to a judgment declaring that claims 13–16 of the '386 patent are invalid under 35 U.S.C. §§ 102(e), 102(f), 102(g)(2), 103, and 112.

216. This is an exceptional case entitling Gilead to an award of its attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285.

COUNT 4

(Declaratory Judgment – Unenforceability of the '386 Patent)

217. Gilead incorporates by reference the allegations contained in paragraphs 1–193 of this Complaint.

218. The ’386 patent is unenforceable due to inequitable conduct before the PTO. This conduct includes the submission of knowingly false declarations of original inventorship to claims 13–16 by REDACTED (collectively, the “Named AbbVie Inventors”) and the intentional failure of at least REDACTED to disclose material prior art—i.e., the Gilead PCT Publication and the Provisional Application to which the Gilead PCT Publication claims priority—to the PTO during prosecution of the ’386 patent with specific intent to deceive.

219. On or around August 15–29, 2012, each of the Named AbbVie Inventors signed declarations that declared that they believed each of them to be an original and first and joint inventor of the subject matter claimed in the ’386 patent, which includes the specific combination of GS-5885 and GS-7977, without interferon for 12 weeks, for the treatment of HCV genotype 1.

220. On information and belief, the Named AbbVie Inventors intentionally misrepresented to the PTO the identities of the true original inventors of claims 13–16 in the ’386 patent. This misrepresentation was material to patentability under 35 U.S.C. §§ 102(f), 111, and 115.

221. The inventors’ specific intent to deceive the PTO can be inferred from the facts described above and the fact that claims to the Gilead Combination do not appear in the application until after Gilead acquired Pharmasset and announced its intentions for 7977 and until after Gilead announced clinical trials were planned for the Gilead Combination. This intent to deceive can further be inferred from the fact that no AbbVie inventor had any knowledge of and/or access to any clinical data relating to the use of GS-7977 in combination with GS-5885 to treat patients suffering from HCV, as late as the filing date of Abbott/AbbVie’s

patent application number 61/656,251. The submission of such knowingly false declarations constitutes affirmative egregious misconduct before the PTO.

222. On information and belief, at least REDACTED intentionally failed to disclose the Gilead PCT Publication, and the Provisional Application to which the Gilead PCT Publication claims priority, to the PTO as prior art under 37 C.F.R. § 1.56. This misrepresentation and/or omission was material to patentability under 35 U.S.C. §§ 102(e) and 103.

223. An intent to deceive the PTO can be inferred from the fact that, on or around May 1, 2013 and May 2, 2013, prior to the issuance of the ’386 patent, AbbVie, received multiple instances of correspondence from Gilead encouraging AbbVie to disclose the Gilead PCT Publication to the PTO and bring it to the examiner’s attention, but chose not to do so.

224. An intent to deceive the PTO can further be inferred from the fact that during the prosecution of the ’386 patent, AbbVie relied on Gilead’s clinical data to support its claim to the use of GS-5885 and GS-7977 to treat HCV in a March 6, 2013 Supplemental Response to the PTO, yet failed to disclose Gilead’s patent applications to the PTO.

225. But for Abbott and/or AbbVie’s misrepresentations and omissions to the PTO, claims 13–16 of the ’386 patent would not have issued.

226. As a result of the acts described in the foregoing paragraphs, there exists an actual and justiciable controversy of sufficient immediacy and reality, within the meaning of the Federal Declaratory Judgment Act, 28 U.S.C. § 2201 *et seq.*, regarding the unenforceability of the ’386 patent.

227. The ’386 patent is unenforceable due to Abbott/AbbVie’s fraud on the PTO.

228. Gilead is entitled to a judgment declaring that the '386 patent is unenforceable due to Abbott/AbbVie's fraud on the PTO.

229. This is an exceptional case entitling Gilead to an award of its attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285.

LEGAL CLAIMS (STATE LAW)

230. Gilead incorporates by reference the factual allegations contained in paragraphs 1–193 of this Complaint as if reproduced herein in full.

231. As described more fully in paragraphs 90-182 above, Abbott and AbbVie made knowing and intentional misrepresentations to the PTO, and intentionally failed to disclose material information to the PTO, all in support of their scheme to misappropriate and exploit the immense and years-long clinical research investment of Gilead and Pharmasset by fraudulently claiming the Gilead Combination and other combinations of GS/PSI-7977 with NS5A inhibitors as Abbott and AbbVie's own inventions. Pursuant to this deliberately planned and carefully executed scheme to defraud the PTO and damage Gilead, Abbott and AbbVie knowingly and affirmatively did the following:

a. Abbott supported its false claims of inventorship with unmistakably false affidavits of inventorship executed at Abbott's direction by the following persons acting within the course and scope of their employment by Abbott and conspiring with Abbott and later AbbVie to engage in the unlawful, unfair or fraudulent business acts described herein

REDACTED

. Also conspiring with AbbVie in the

commission of these unfair, unlawful or fraudulent acts or practices was AbbVie's employee and legal representative, REDACTED, who, acting in concert with Abbott/AbbVie, knowingly, willfully and deliberately caused these false affidavits to be filed with the PTO. Each of these individuals who, claiming to be an inventor of the inventions claimed in the AbbVie Patents, signed under oath an affidavit on a form prescribed by the PTO, or who caused such affidavits to be signed or filed (particularly, as noted hereinabove, the "inventors" REDACTED), were on notice that the making and filing of a false declaration to the PTO constitutes a violation of 18 U.S.C. § 1001(a), which provides, in pertinent part:

> * * * [W]hoever, in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States, knowingly and willfully—
>
> (1) falsifies, conceals, or covers up by any trick, scheme, or device a material fact;
>
> (2) makes any materially false, fictitious, or fraudulent statement or representation; or
>
> (3) makes or uses any false writing or document knowing the same to contain any materially false, fictitious, or fraudulent statement or entry;
>
> shall be fined under this title, imprisoned not more than 5 years * * *

b. Before each of the AbbVie Patents issued, Abbott and AbbVie knew that Gilead was the true inventor of the inventions related to GS-7977 and the combination of GS-7977 and GS-5885, and that Abbott and AbbVie and their assignors were not the true inventors, but Abbott and AbbVie nonetheless

knowingly and intentionally both misrepresented and withheld this information from the patent examiner. More specifically, Abbott and AbbVie knew that in its February 2, 2012, public earnings call, the written transcript of which was published on or about that same date, Gilead made a clear disclosure of the use of a combination of GS-7977 and GS-5885 in a twelve week treatment regimen that would assess efficacy in the absence of ribavirin and interferon in genotype 1 patients. This disclosure came just over two weeks before Abbott first filed its February 17, 2012, provisional application claiming for the first time the combination of these two Gilead Compounds, and over four months before Abbott first filed any provisional application disclosing the chemical structure of GS-5885 and applying the Abbott/AbbVie "model" to the GS-5885/GS-7977 combination.

c. Abbott and AbbVie also deceived the PTO and improperly exploited the fruits of Gilead's research investment in the course of prosecuting the AbbVie Patents. In the June 6, 2012 provisional patent application, and nine months later in a response to the patent examiner on March 6, 2013, Abbott and AbbVie relied on Gilead's clinical data to support their claims to the use of the Gilead Combination. That clinical data had been developed only through the expenditure of substantial sums of Gilead's money and the investment of extensive and costly clinical research by Gilead and its predecessor-in-interest Pharmasset into the combination of PSI/GS-7977 and GS-5885. Thus, Abbott and AbbVie misappropriated Gilead's idea for the Gilead Combination, having expended not one speck of their own financial or clinical research

resources in furtherance of clinical testing of the Gilead Combination, and exploited Gilead's enormous clinical research investment to help secure their ill-gotten patents.

d. In addition, with a specific intent to defraud the PTO, Abbott/AbbVie intentionally made a deliberate decision not to disclose to the PTO one or more material prior art references, including Gilead's PCT Publication WO 2013/040492, which AbbVie deliberately decided not to disclose to the PTO despite having received written notice from Gilead of said publication on two occasions prior to issuance of the AbbVie Patents. It was not until September 18, 2013, when, in connection with its then-pending application USSN 13/656,012, AbbVie finally filed an Initial Disclosure Statement with its Response to the Non-Final Rejection and Amended Claims citing Gilead's PCT Application (WO 2013/040492). This belated disclosure was, of course, too little and too late to reverse the effects of AbbVie's and Abbott's longstanding fraudulent conduct respecting their assertion of claims of inventorship regarding the Gilead Claims, and their claim to have invented the combination of GS-7977/Sofosbuvir and all NS5A inhibitors, which was also a clearly false and fraudulent assertion.

e. The foregoing fraudulent acts or omissions were each, and in combination with the others, material, in that the PTO would not have issued the AbbVie Patents but for the foregoing fraudulent acts or omissions.

232. As described more fully in Paragraphs 44–89, 194–198, and 212–216 above, Abbott and AbbVie's patent claims to GS/PSI-7977, GS-5885, and their various combinations are invalid, because these inventions were made by Gilead and Pharmasset, not Abbott/AbbVie:

a. Abbott and AbbVie derived the invention of the Gilead Claims from Gilead – it was Gilead, not AbbVie, that conceived the use of the Gilead Combination and Sofosbuvir itself to treat Genotype 1 HCV treatment naïve patients with a treatment duration of twelve weeks. Under 35 U.S.C. § 102(f), AbbVie's Gilead Claims are invalid.

b. The invention of the Gilead Claims and PSI/GS-7977 itself was made by Gilead and/or its predecessor-in-interest Pharmasset in the United States before the date Abbott/AbbVie purported to have invented it – *i.e.*, Gilead conceived of said invention and reduced it to practice before Abbott/AbbVie's purported date of invention, and Gilead did not, thereafter, abandon, suppress or conceal said invention. Quite the contrary: Gilead filed its '885 provisional application claiming the invention over a month before Abbott first filed any patent application even mentioning GS-5885 and PSI/GS-7977 and over five months before Abbott filed its first provisional application claiming the specific Gilead Combination on February 17, 2012. Gilead not only conceived of the invention of Abbott's Gilead Claims and GS-7977 itself, but reduced it to practice before Abbott's purported date of invention. Under these circumstances, Abbott's Gilead Claims are invalid pursuant to 35 U.S.C. § 102(g)(2).

c. The AbbVie Patents fail adequately to disclose sufficient information to teach persons skilled in the art how to make and use said invention without undue experimentation. Abbott did not even disclose the chemical structure of GS-5885 in any of this family of patent applications until it filed its provisional application Nos. 61/656,251 and 61/656,253 on June 6, 2012. Even then, Abbott based its invention of the Gilead Claims on a "mechanistic model" using past clinical trial data that would not enable a person skilled in the art to predict that the Gilead compound would be successful in curing Genotype 1 HCV patients with twelve weeks of treatment. Under 35 U.S.C. § 112(a), these failures render the patent invalid as to the Gilead Claims.

233. Abbott and AbbVie's fraudulent conduct before the PTO, and their efforts to obtain and assert spurious and invalid patent claims in order to block Gilead from bringing its life-saving anti-HCV combination therapy to market, have injured Gilead in violation of state law as described in Counts 5–8 below. Because these state law claims necessarily depend on the determination of the validity and enforceability of AbbVie's patents, they give rise to substantial, disputed questions of federal patent law and accordingly come within the subject matter jurisdiction of this Court pursuant to 28 U.S.C. § 1338(a).

COUNT 5

(Violation of 6 Del. Code § 2532. Deceptive Trade Practices)

234. Gilead incorporates by reference the factual allegations contained in paragraphs 1–233 of this Complaint as if reproduced herein in full.

235. 6 Del. Code § 2532 provides, in pertinent part:

(a) A person engages in a deceptive trade practice when, in the course of a business, vocation, or occupation, that person:

(2) Causes likelihood of confusion or of misunderstanding as to the source, sponsorship, approval, or certification of goods or services;

(3) Causes likelihood of confusion or of misunderstanding as to affiliation, connection, or association with, or certification by, another

(5) Represents that goods or services have sponsorship, approval, characteristics, ingredients, uses, benefits, or quantities that they do not have, or that a person has a sponsorship, approval, status, affiliation, or connection that the person does not have;

(8) Disparages the goods, services, or business of another by false or misleading representation of fact; [or]

(12) Engages in any other conduct which similarly creates a likelihood of confusion or of misunderstanding.

236. Abbott's and AbbVie's misrepresentations to the PTO and intentional failure to disclose material information to the PTO constitute deceptive trade practices under one or more of the foregoing provisions of 6 Del. Code §2532. Before each of the AbbVie Patents issued, Abbott and AbbVie knew that Gilead was the true inventor of the inventions related to GS-7977, the combination of GS-7977 and GS-5885 and that Abbott and AbbVie and their assignors were not the true inventors, but Abbott and AbbVie nonetheless knowingly and intentionally both misrepresented and withheld this information from the patent examiner. In doing so, Abbott and AbbVie and their assignors violated one or more of the above-quoted provisions of 6 Del. Code § 2532. Claiming to have invented the Gilead Combination in light of Abbott's and AbbVie's knowledge of the falsity of such claims likewise constituted a violation of one or more of the foregoing provisions of 6 Del. Code § 2532. Abbott's and AbbVie's prosecution of the AbbVie Patents was also deceptive and misleading in violation of one or more of the foregoing

provisions of 6 Del. Code § 2532 because, among other reasons, in the June 6, 2012 provision application and nine months later in a response to the patent examiner on March 6, 2013, Abbott and AbbVie relied on Gilead's clinical data to support their own claim to have invented the Gilead Combination. Thus, Abbott and AbbVie not only misappropriated Gilead's idea for the Gilead Combination, but also, having expended not one speck of their own financial or clinical research resources in furtherance of clinical testing of the Gilead Combination, exploited Gilead's enormous clinical research investment to help secure their ill-gotten patents. Doing so constituted a violation of one or more of the foregoing provisions of 6 Del. Code § 2532.

237. Abbott and AbbVie's fraudulent, inequitable, and unfair conduct before the PTO disparages Gilead's rightful claim to its HCV combination therapies, and creates a likelihood of confusion or misunderstanding as to Gilead's ability to bring these therapies to market. As a result, Gilead is likely to be damaged by Defendants' conduct.

238. AbbVie should be enjoined from asserting the AbbVie Patents.

239. In addition, Gilead is entitled to an award of triple the amount of actual damages proven at trial under any other state law cause of action based on the same facts alleged herein.

COUNT 6

(Slander of Title/Injurious Falsehood)

240. The factual allegations set forth in paragraphs 1–239 above are incorporated herein by reference as if reproduced in full.

241. Gilead is the owner of valuable property interests in (i) its issued patents on the compounds GS-5885/Sofosbuvir and PSI/GS-7977/Ledipasvir; (ii) its rights to the FDA-approved compound GS-7977 (Sofosbuvir); (iii) its rights to its impending New Drug Application seeking FDA approval of the Gilead Combination of Sofosbuvir and Ledipasvir for

treatment of, among others, treatment-naïve Genotype 1 HCV patients for durations of twelve weeks or less; and (iv) its pending patent application asserting the Gilead Claims.

242. More specifically, Gilead is the owner of and has a valuable property interest in issued patents covering each of the Gilead Compounds, as set forth in Paragraph 23 hereinabove, including, among others U.S. Patent No. 7,964,580 B2 ("the Gilead '580 patent") and U.S. Patent No. 8,088,368 B2 ("the Gilead '368 patent"). The Gilead '580 patent, which was originally issued to Pharmasset on June 21, 2011, covers the GS-7977/Sofosbuvir compound, and the Gilead '368 patent, which covers GS-5885/Ledipasvir, was issued to Gilead on January 3, 2012. The present value of Gilead's property interests in these issued patents on these particular compounds is based in significant part on the potential use of GS-5885/Ledipasvir in combination with GS-7977/Sofosbuvir for the treatment of, among other conditions, Genotype 1 HCV patients for a treatment duration of 12 weeks or less.

243. Sofosbuvir was approved by the FDA for use in combination with certain other drugs for treatment of patients with chronic HCV on December 6, 2013. Gilead is the owner of all rights to any and all current and future revenues flowing from the use by clinicians of Sofosbuvir, either alone or in combination with other drugs. Upon approval by the FDA of GS-5885/Ledipasvir, Gilead's rights will then include the right to any revenues generated by the use by clinicians of Sofosbuvir in combination with GS-5885/Ledipasvir. Part of the present value of Gilead's rights in the FDA-approved drug, Sofosbuvir is, necessarily, its value derived from its potential for use with GS-5885/Ledipasvir in the future. The safety and efficacy of the specific combination of Sofosbuvir and Ledipasvir for use in treating Genotype 1 treatment-naïve HCV patients has already been established in Phase 1–3 clinical trials and is the subject of Gilead's New Drug Application which will be filed in the very near future with the FDA.

244. Gilead's United States patent application relating to the Gilead Claims was published as PCT Publication WO 2013/040492 (the "Gilead PCT Publication"), entitled "Methods of Treating HCV", a true copy of which is filed herewith as Exhibit F and is incorporated herein by reference as if reproduced in full. Gilead's PCT Application was filed on September 14, 2012, was published on March 13, 2013, and claims priority to Gilead's provision application No. 61/535,885 ("Gilead's/the Gilead '885 Provisional Application") filed on September 16, 2011, over a month before Abbott's provisional application No. 61/550,360, was filed on October 21, 2011. The Gilead '885 Provisional Application and the Gilead PCT Publication claim methods of treatment of HCV using Compounds 6 and 10, which are identified by their respective chemical structures.

245. Gilead's property interests in these patent applications and patents are immensely valuable. In early 2012—about a month before Abbott filed its provisional application No. 61/600,267 on February 17, 2012, claiming for the first time the specific combination of GS-7977 and GS-5885—Gilead closed on its acquisition of Pharmasset, for which it paid over $11 billion, primarily to acquire the rights to PSI/GS-7977 (Sofosbuvir). As detailed in paragraphs 93–182 above, Abbott and AbbVie falsely claimed to have invented treatment methods for the treatment of HCV using the specific Gilead Combination and even using GS-7977 itself, when, in fact, Abbott and AbbVie had not done so, as part of a deliberately planned and careful scheme to defraud the PTO.

246. Under Delaware law, "slander of title" occurs when a person, without a privilege to do so, knowingly publishes a false statement that disparages or casts doubt upon another's title to a property interest, including intangible or personal property such as Gilead's property interests in the above-described Gilead patents and applications and the above-described FDA-

approved drug Sofosbuvir. By falsely claiming to have invented treatment methods for the treatment of HCV using the specific Gilead Combination when, in fact, Abbott and AbbVie had not done so for the reasons set forth hereinabove, Abbott and AbbVie committed knowing and willful acts and omissions that, separately and taken together, constitute a slander of title and were knowingly and willfully and maliciously committed by Abbott/AbbVie and its co-conspirators without any good faith privilege or justification to do so. Gilead has suffered and will continue to suffer damage as a result of Abbott and AbbVie's said knowing and willful acts and omissions.

247. Gilead asks that the Court remedy the aforementioned slander of title by Abbott and AbbVie by:

a. Declaring that Abbott's and AbbVie's claim to have invented treatment methods for the treatment of HCV using the specific Gilead Combination and/or Sofosbuvir itself, was false for the reasons set forth above, that Abbott's and AbbVie's acts or omissions set forth above were committed willfully and knowingly, and that, in fact, Abbott and AbbVie had not invented the Gilead Combination or Sofosbuvir;

b. Declaring that in willfully and knowingly making its false claim to have invented the Gilead Combination and/or Sofosbuvir itself, Abbott and AbbVie disparaged, slandered and cast a cloud over Gilead's property interests in the applications and patents described hereinabove, and did so without any justification or privilege, causing Gilead to sustain pecuniary loss and damage;

c. Awarding Gilead its damages; and

d. Enjoining AbbVie from asserting or enforcing any patent rights under the AbbVie Patents against Gilead or its affiliates, distributors, customers, or end users with respect to the Gilead Claims.

COUNT 7

(Tortious Interference with Prospective Business Relations)

(Delaware law)

248. The factual allegations set forth in paragraphs 1–247 above are incorporated herein by reference.

249. Gilead had a reasonable, valid expectation that, upon completion of clinical trials and FDA approval of its combination therapy of PSI/GS-7977 (Sofosbuvir) and GS-5885 (Ledipasvir), as well as any other combinations it might pursue involving PSI/GS-7977, it would enter into economically advantageous business relationships with various marketers, distributors, insurers, and health-care providers in order to manufacture, market, distribute, and provide the combination therapies to HCV patients.

250. Abbott and AbbVie were well aware of Gilead's valid business expectancies with respect to the Gilead Combination and other potential combination therapies, and have intentionally and wrongfully interfered with those business expectancies by filing fraudulent patent applications, supported by false declarations of inventorship, that wrongfully attempt to lay claim to Gilead's combinations of Gilead's own compounds. Abbott and AbbVie's intent in doing so was to prevent Gilead's therapies from competing with their own anti-HCV compounds, to the detriment not only of Gilead but of millions of HCV patients who could be denied access to these life-saving treatments.

251. Abbott and AbbVie's intentional acts of interference were independently wrongful and unlawful, insofar as they involved (1) false statements to the U.S. Patent Office in

violation of 18 U.S.C. § 1001(a), (2) slander of Gilead's property interest in its issued patents and pending patent applications, and (3) deceptive, unlawful, and unfair business practices in violation of the Delaware Deceptive Trade Practices Act, 6 Del. Code § 2532.

252. Abbott and AbbVie's conduct has in fact interfered with Gilead's reasonable expectations of prospective business relations, insofar as their spurious patent claims over the Gilead Combination and other anti-HCV combinations have hindered and will hinder Gilead's ability to form business relationships with third parties. Manufacturers, marketers, and distributors may be deterred from doing business with Gilead by the potential risk of liability for infringing AbbVie's patents. More importantly, if AbbVie enforces its patents so as to prevent Gilead from manufacturing, marketing, and distributing its combination therapies, then Gilead's prospective business relationships with health care providers and prescribers will be disrupted because Gilead will be unable to supply them with the treatments for the patients who need them and they will be unable to prescribe such combination therapies.

253. As a result of Abbott and AbbVie's intentional and unlawful acts of interference, Gilead has been, and, in reasonable probability, will continue to be, damaged in an amount to be proven at trial.

COUNT 8

REDACTED

254. The factual allegations set forth in paragraphs 1–253 above are incorporated herein by reference.

255.

REDACTED

REDACTED

256.

257.

258.

REDACTED

259.

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PRAYER FOR RELIEF

WHEREFORE, Plaintiffs Gilead respectfully request that this Honorable Court:

(1) Issue a declaratory judgment on Count 1 that claims 13–16 of the ’159 patent are invalid.

(2) Issue a declaratory judgment on Count 2 that the ’159 patent is unenforceable due to the inequitable misconduct of Defendants, who obtained the patent through fraud on the PTO.

(3) Issue a declaratory judgment on Count 3 that claims 13–16 of the ’386 patent are invalid.

(4) Issue a declaratory judgment on Count 4 that the ’386 patent is unenforceable due to the inequitable misconduct of Defendants, who obtained the patent through fraud on the PTO.

(5) Award Gilead its attorney’s fees incurred in connection with Counts 1 through 4.

(6) Enter judgment in favor of Gilead and against Defendants on Count 5 for violating 6 Del. Code § 2532, issue a permanent injunction barring Defendants from ever enforcing the AbbVie Patents, and award triple the amount of actual damages proven at trial under any other state law cause of action, as well as attorney’s fees.

(7) Enter judgment in favor of Gilead and against Defendants on Count 6 for Slander of Title, and award Gilead damages in an amount to be proven at trial.

(8) Enter judgment in favor of Gilead and against Defendants on Count 7 for Tortious Interference with Prospective Business Relations, and award Gilead damages in an amount to be proven at trial.

(9) REDACTED

(10) Enter such other relief as the Court may deem just and proper.

DEMAND FOR JURY TRIAL BY JURY

Pursuant to Federal Rule of Civil Procedure 38(b), Gilead hereby requests a trial by jury on all issues so triable.

Dated: December 18, 2013

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Exhibit A

US008466159B2

(12) **United States Patent**
Bernstein et al.

(10) **Patent No.: US 8,466,159 B2**
(45) **Date of Patent: *Jun. 18, 2013**

(54) **METHODS FOR TREATING HCV**

(75) Inventors: **Barry M. Bernstein**, Mequon, WI (US); **Rajeev M. Menon**, Buffalo Grove, IL (US); **Amit Khatri**, Waukegan, IL (US); **Sven Mensing**, Mannheim (DE); **Sandeep Dutta**, Gurnee, IL (US); **Daniel E. Cohen**, Wilmette, IL (US); **Thomas J. Podsadecki**, Chicago, IL (US); **Scott C. Brun**, Green Oaks, IL (US); **Walid M. Awni**, Green Oaks, IL (US); **Emily O. Dumas**, Libertyville, IL (US); **Cheri E. Klein**, Northbrook, IL (US)

(73) Assignee: **AbbVie Inc.**, North Chicago, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/603,022**

(22) Filed: **Sep. 4, 2012**

(65) **Prior Publication Data**

US 2013/0102525 A1 Apr. 25, 2013

Related U.S. Application Data

(60) Provisional application No. 61/550,352, filed on Oct. 21, 2011, provisional application No. 61/562,181, filed on Nov. 21, 2011, provisional application No. 61/587,225, filed on Jan. 17, 2012, provisional application No. 61/600,276, filed on Feb. 17, 2012, provisional application No. 61/619,870, filed on Apr. 3, 2012, provisional application No. 61/656,251, filed on Jun. 6, 2012.

(51) **Int. Cl.**

A61K 31/4965	(2006.01)
A61K 31/33	(2006.01)
A61K 31/505	(2006.01)
A61K 31/47	(2006.01)
A61K 31/415	(2006.01)
A61K 31/40	(2006.01)

(52) **U.S. Cl.**
USPC **514/255.05**; 514/183; 514/269; 514/314; 514/397; 514/309; 514/394; 514/422; 514/81

(58) **Field of Classification Search**
USPC 514/183, 269, 314, 397, 309, 394, 514/81, 274, 255.04, 422
See application file for complete search history.

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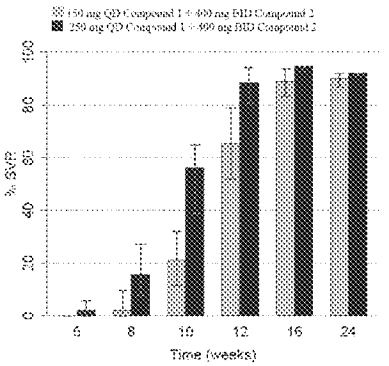
Primary Examiner — Shengjun Wang
(74) *Attorney, Agent, or Firm* — Xu Zhang

(57) **ABSTRACT**

The present invention features interferon-free therapies for the treatment of HCV. Preferably, the treatment is over a shorter duration, such as no more than 12 weeks. In one aspect, the therapies comprise administering at least two direct acting antiviral agents and ribavirin to a subject with HCV infection. For example, the therapies comprise administering to the subject effective amounts of therapeutic agent 1, therapeutic agent 2 (or therapeutic agent 3), an inhibitor of cytochrome P450 (e.g., ritonavir), and ribavirin.

16 Claims, 21 Drawing Sheets



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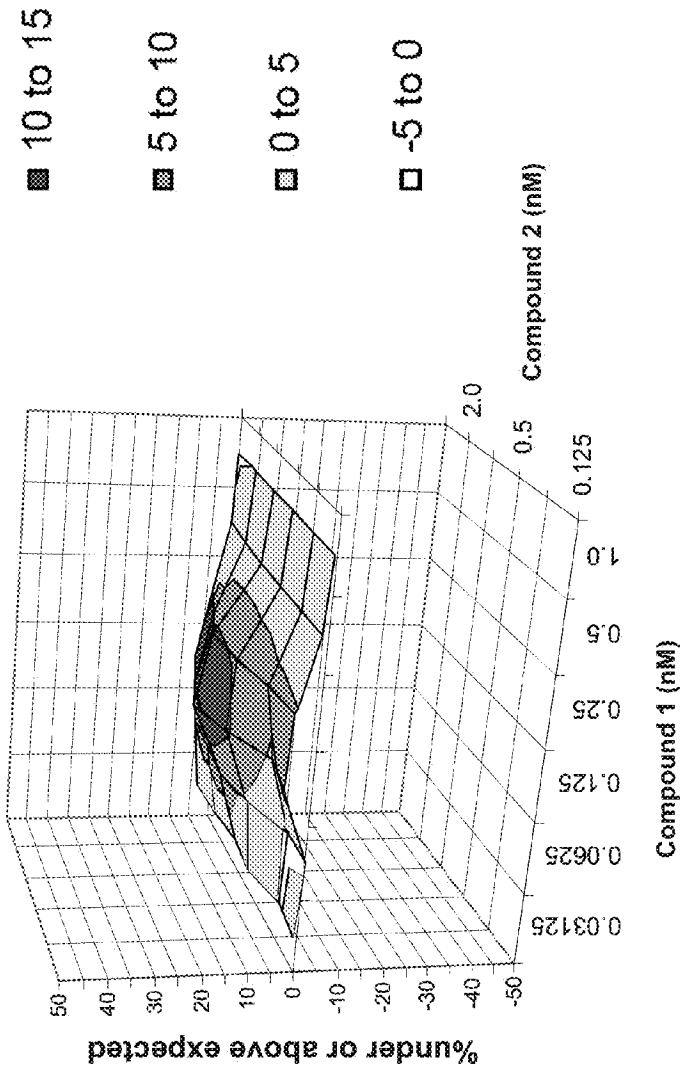

10 to 15
5 to 10
0 to 5
-5 to 0
Compound 2 (nM)
2.0
0.5
0.125
Compound 1 (nM)
1.0
0.5
0.25
0.125
0.0625
0.03125
%under or above expected
50
40
30
20
10
0
-10
-20
-30
-40
-50

Figure 1

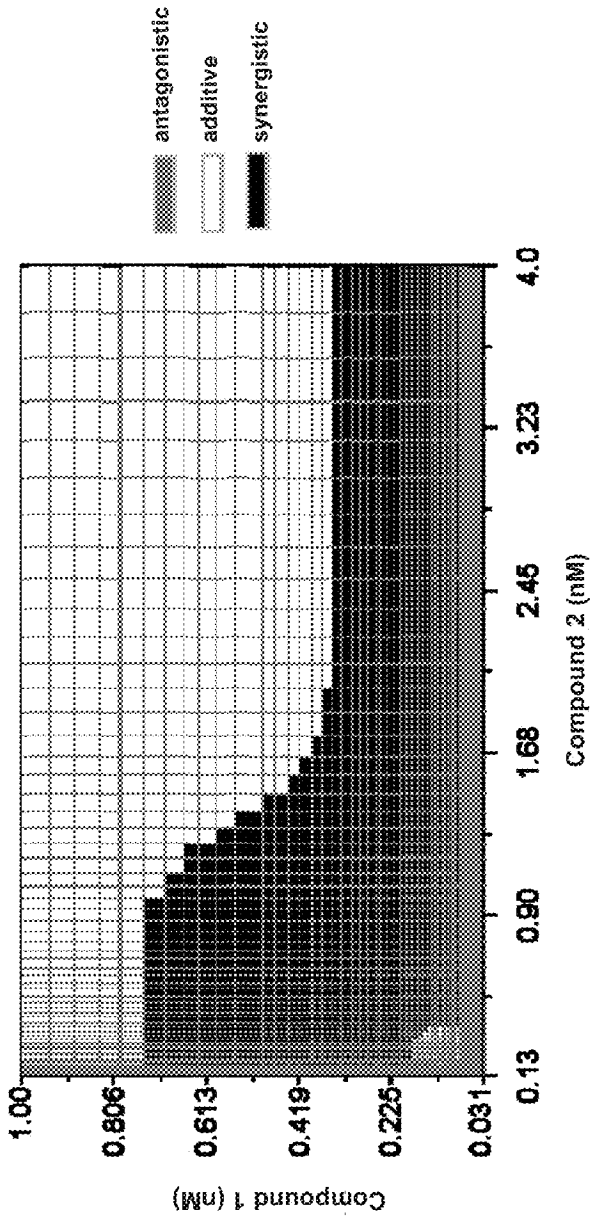

antagonistic
additive
synergistic
1.00
0.806
0.613
0.419
0.225
0.031
Compound 1 (nM)
0.13
0.90
1.68
2.45
3.23
4.0
Compound 2 (nM)

Figure 2

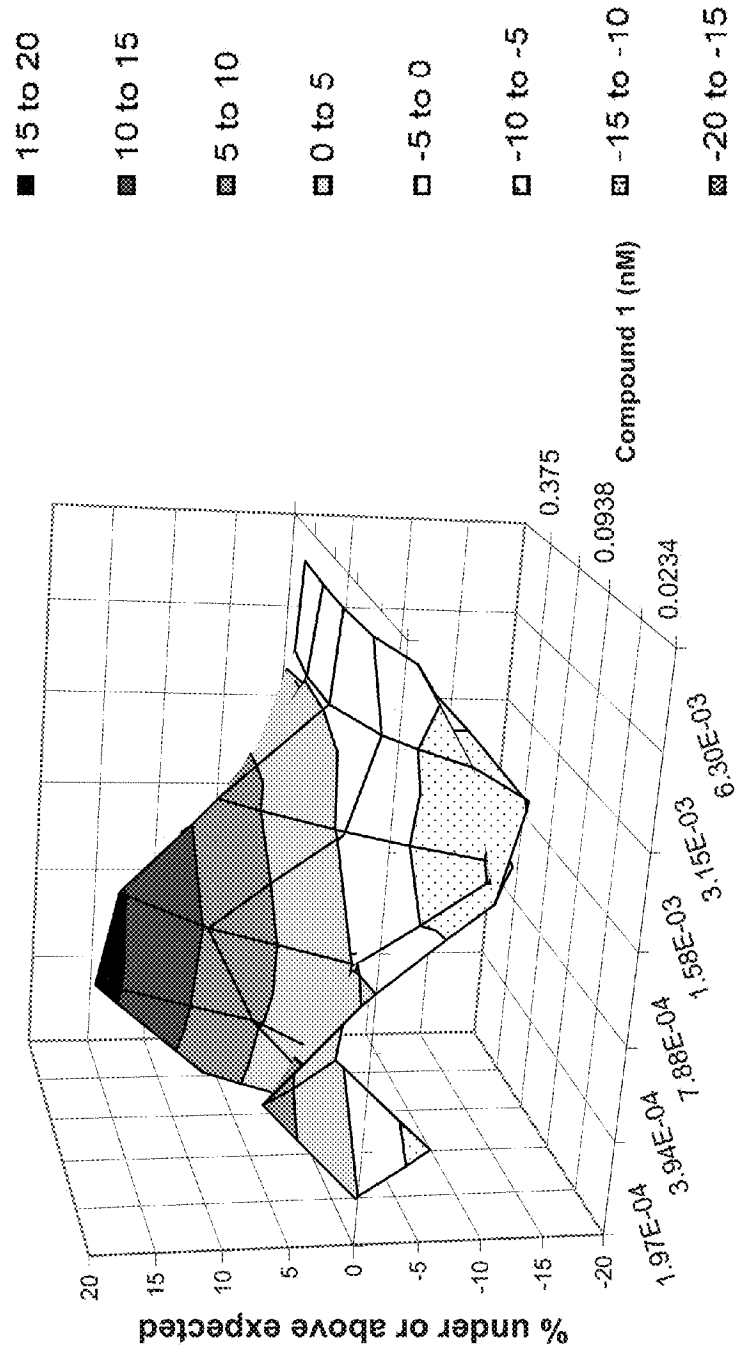

15 to 20
10 to 15
5 to 10
0 to 5
-5 to 0
-10 to -5
-15 to -10
-20 to -15
% under or above expected
20
15
10
5
0
-5
-10
-15
-20
Compound 4 (nM)
1.97E-04
3.94E-04
7.88E-04
1.58E-03
3.15E-03
6.30E-03
Compound 1 (nM)
0.0234
0.0938
0.375

Figure 3

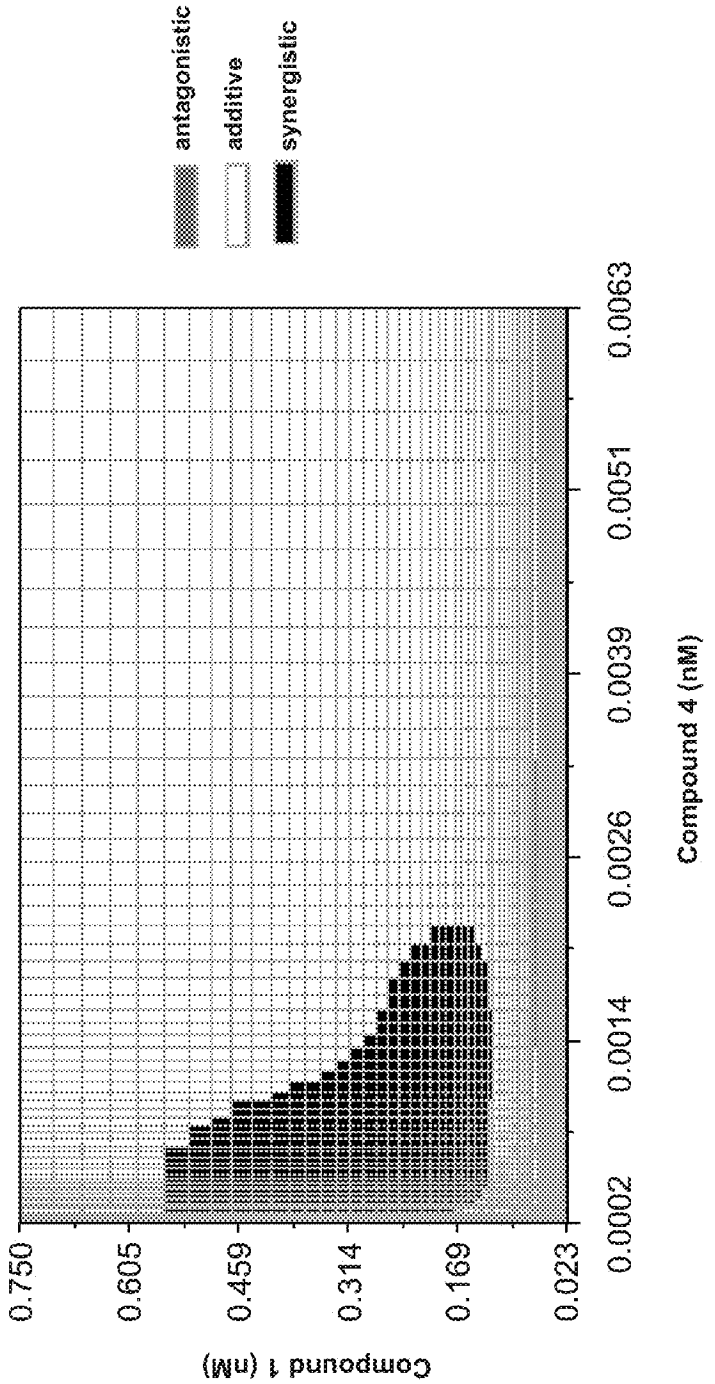

antagonistic
additive
synergistic
Compound 1 (nM)
0.750
0.605
0.459
0.314
0.169
0.023
0.0002
0.0014
0.0026
0.0039
0.0051
0.0063
Compound 4 (nM)

Figure 4

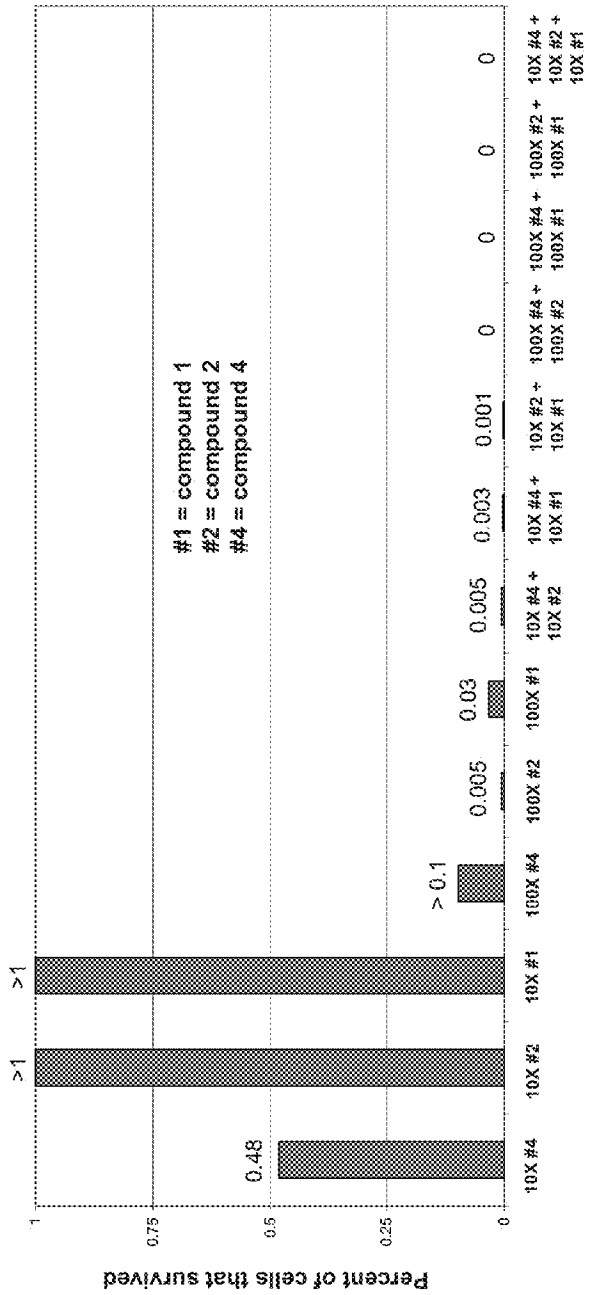

Percent of cells that survived
1
0.75
0.5
0.25
0
#1 = compound 1
#2 = compound 2
#4 = compound 4
0.48
>1
>1
>1
> 0.1
0.005
0.005
0.03
0.005
0.003
0.001
0
0
0
0
10X #4
10X #2
10X #1
100X #4
100X #2
100X #1
10X #4 + 10X #2
10X #4 + 10X #1
10X #2 + 10X #1
100X #4 + 100X #2
100X #4 + 100X #1
100X #2 + 100X #1
10X #4 + 10X #2 + 10X #1

Figure 5A

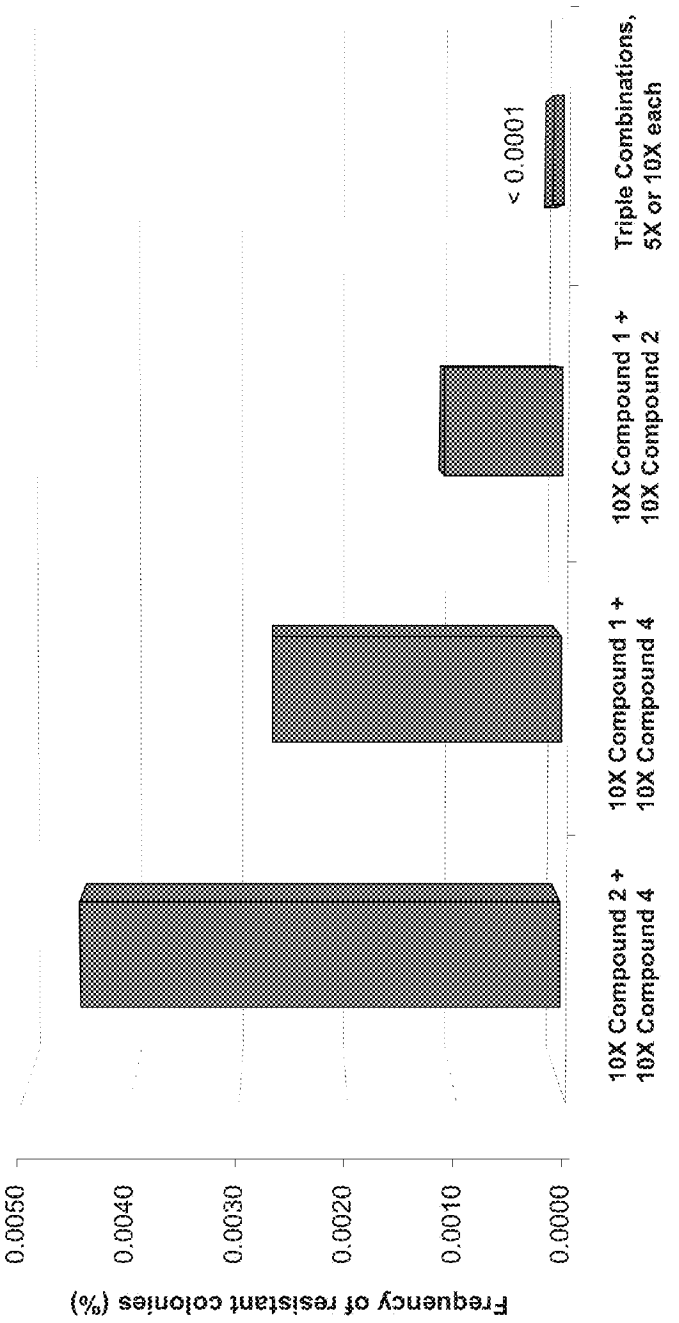

Frequency of resistant colonies (%)
0.0050
0.0040
0.0030
0.0020
0.0010
0.0000
< 0.0001
10X Compound 2 + 10X Compound 4
10X Compound 1 + 10X Compound 4
10X Compound 1 + 10X Compound 2
Triple Combinations, 5X or 10X each

Figure 5B

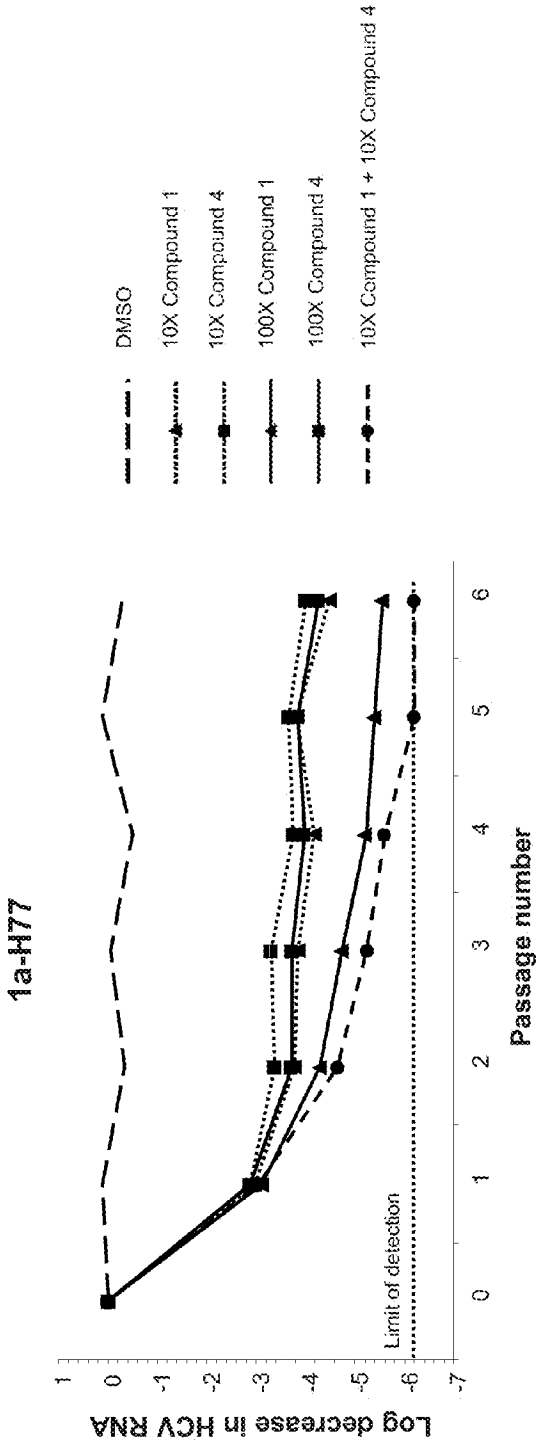

DMSO
10X Compound 1
10X Compound 4
100X Compound 1
100X Compound 4
10X Compound 1 + 10X Compound 4
1a-H77
Log decrease in HCV RNA
Passage number
Limit of detection
1
0
-1
-2
-3
-4
-5
-6
-7
0
1
2
3
4
5
6

Figure 5C

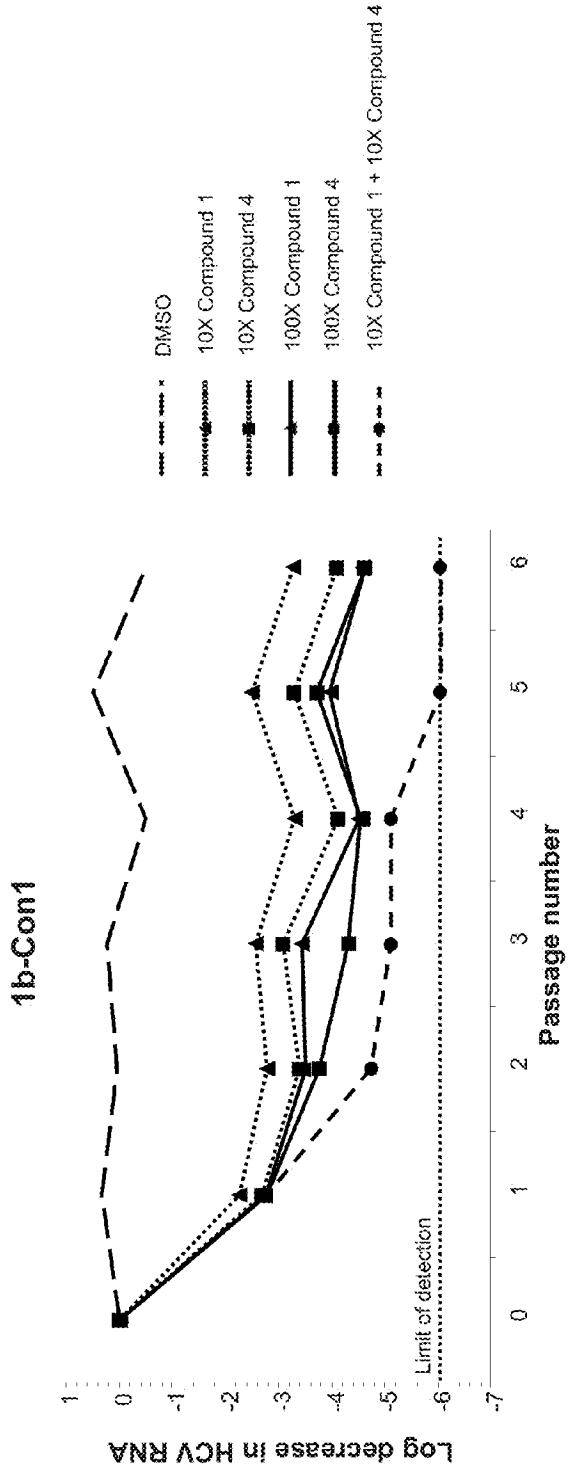

1b-Con1
DMSO
10X Compound 1
10X Compound 4
100X Compound 1
100X Compound 4
10X Compound 1 + 10X Compound 4
Log decrease in HCV RNA
1
0
-1
-2
-3
-4
-5
-6
-7
Limit of detection
0
1
2
3
4
5
6
Passage number

Figure 5D

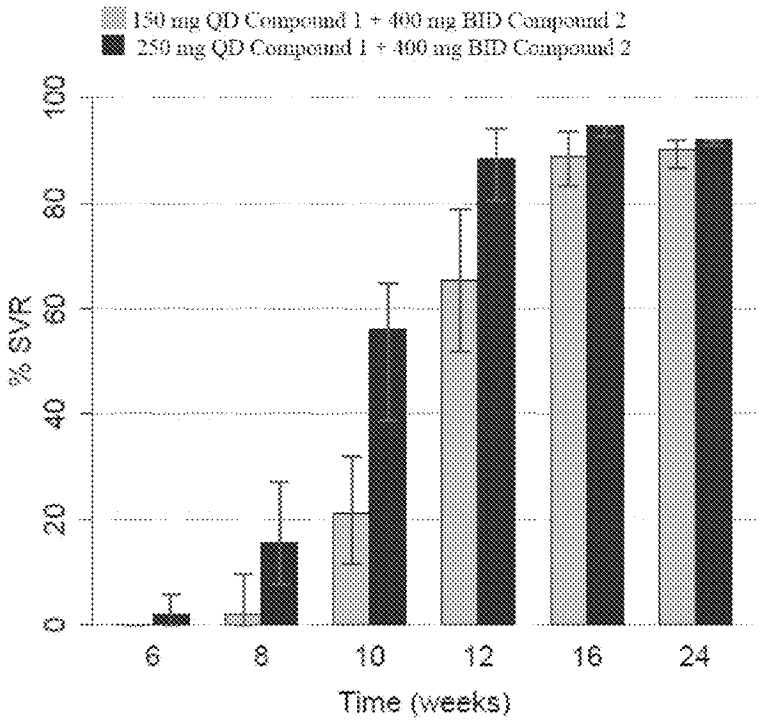

150 mg QD Compound 1 + 400 mg BID Compound 2
250 mg QD Compound 1 + 400 mg BID Compound 2
% SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 6A

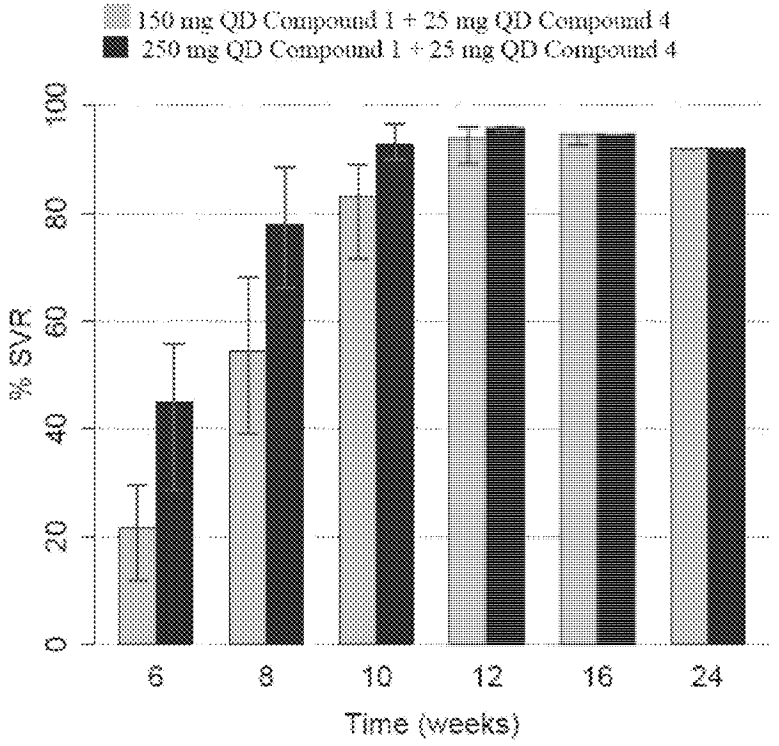

150 mg QD Compound 1 + 25 mg QD Compound 4
250 mg QD Compound 1 + 25 mg QD Compound 4
% SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 6B

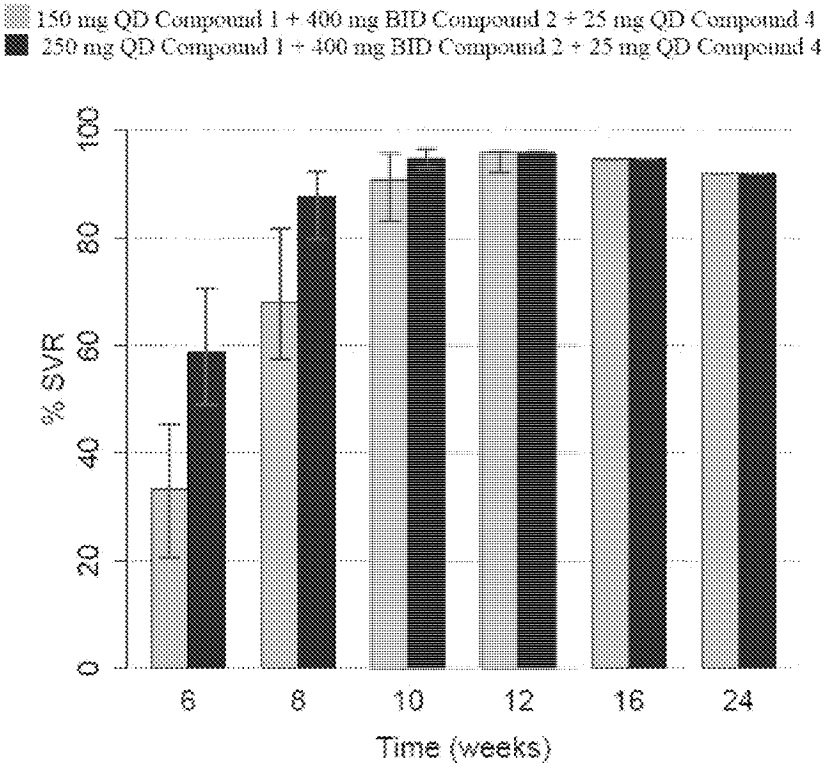

150 mg QD Compound 1 + 400 mg BID Compound 2 + 25 mg QD Compound 4
250 mg QD Compound 1 + 400 mg BID Compound 2 + 25 mg QD Compound 4
% SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 6C

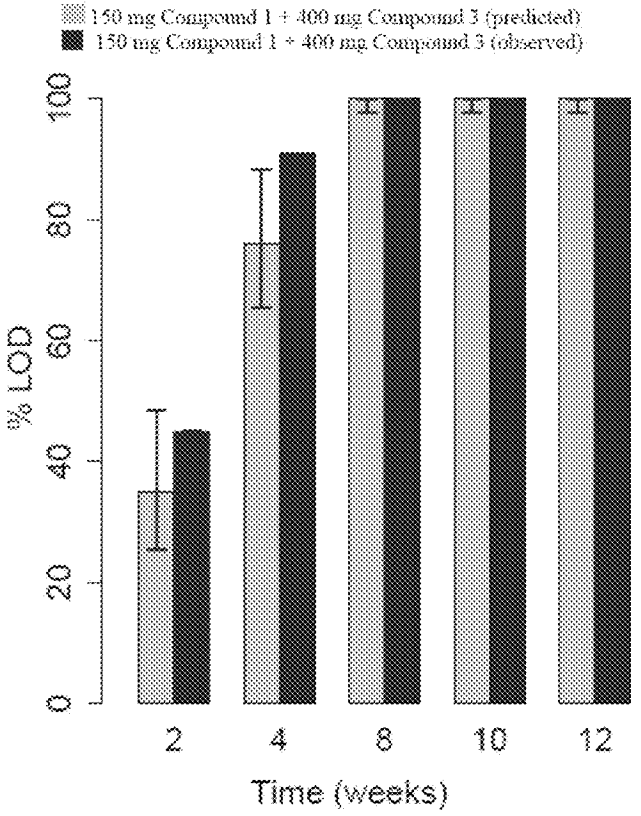

150 mg Compound 1 + 400 mg Compound 3 (predicted)
150 mg Compound 1 + 400 mg Compound 3 (observed)
% LOD
0
20
40
60
80
100
2
4
8
10
12
Time (weeks)

Figure 7

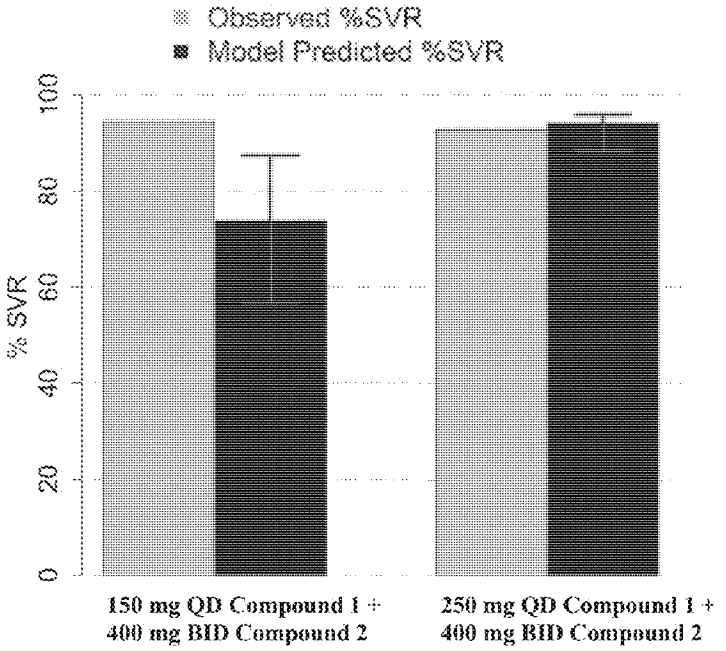

Observed %SVR
Model Predicted %SVR
% SVR
0
20
40
60
80
100
150 mg QD Compound 1 + 400 mg BID Compound 2
250 mg QD Compound 1 + 400 mg BID Compound 2

Figure 8

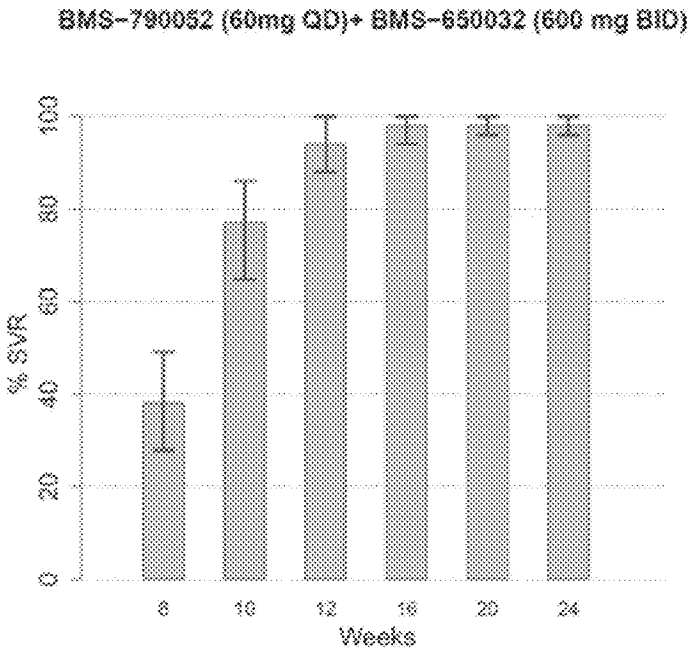

BMS-790052 (60mg QD)+ BMS-650032 (600 mg BID)
% SVR
0
20
40
60
80
100
8
10
12
16
20
24
Weeks

Figure 9

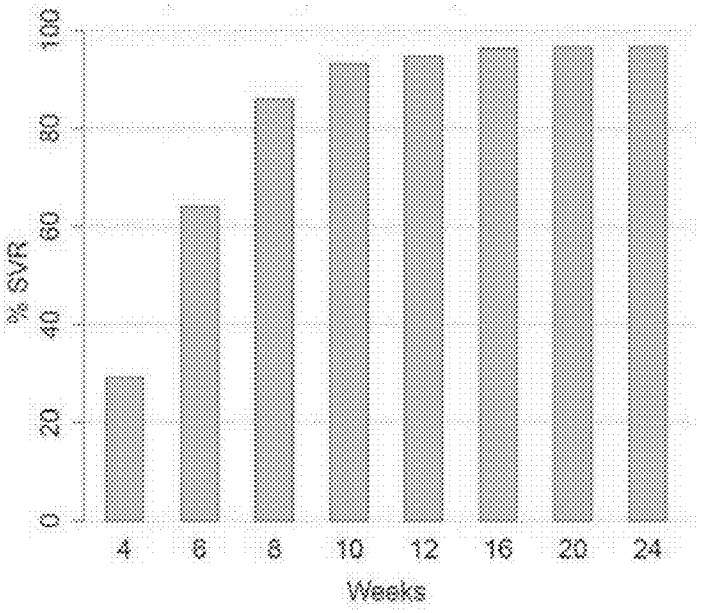


Figure 10

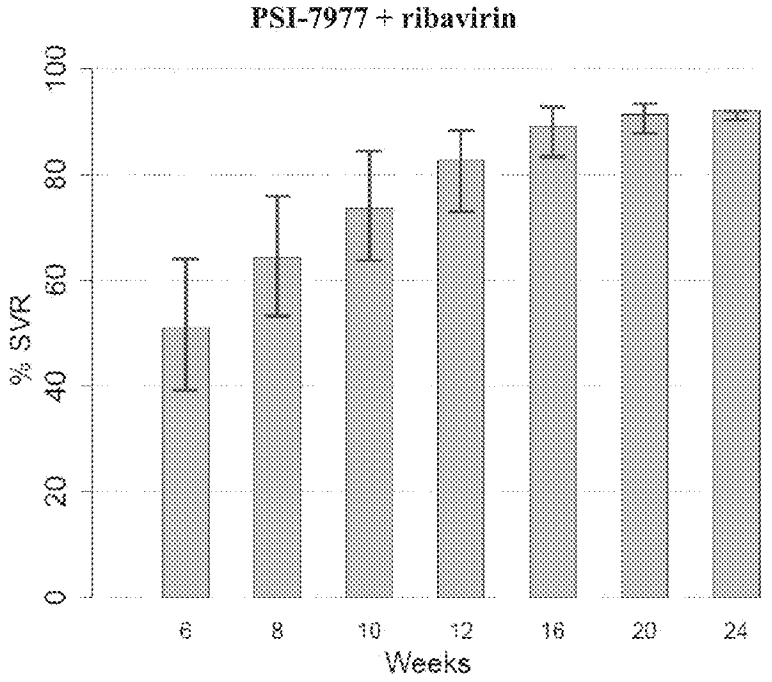


Figure 11

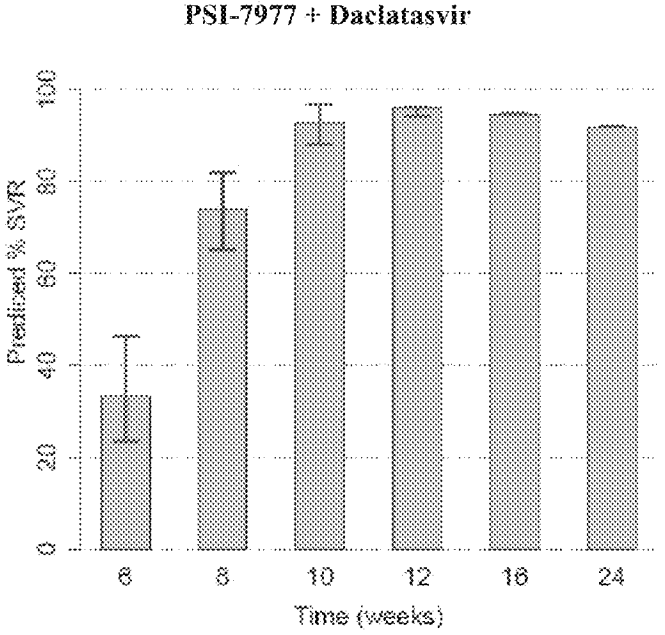

PSI-7977 + Daclatasvir
Predicted % SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 12

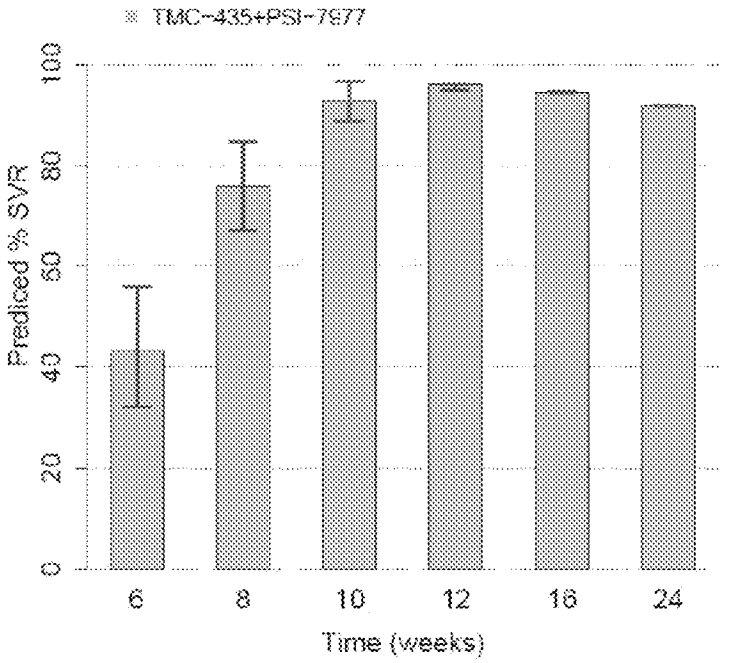

TMC-435+PSI-7977
Predicted % SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 13

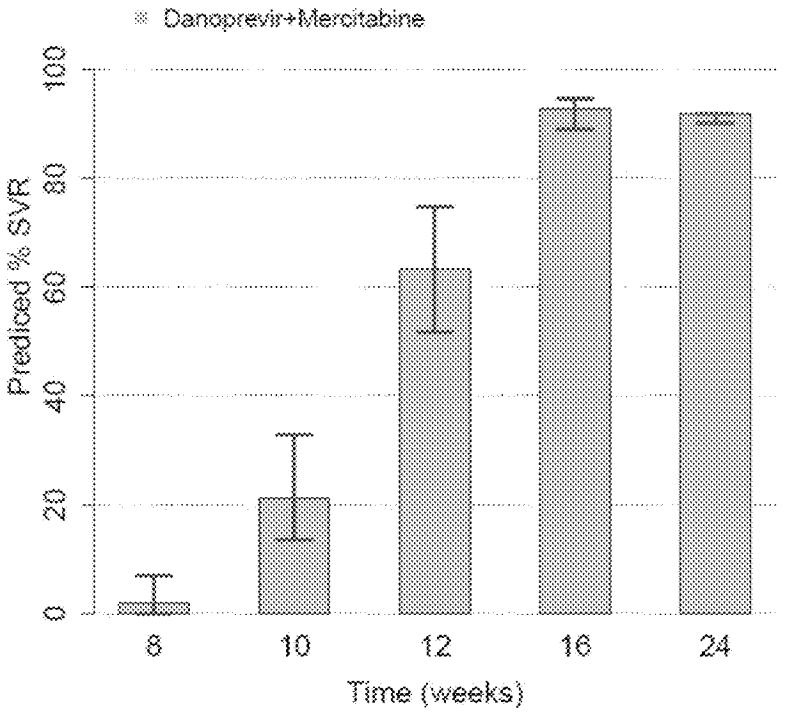

Danoprevir+Mercitabine
Predicted % SVR
0
20
40
60
80
100
8
10
12
16
24
Time (weeks)

Figure 14

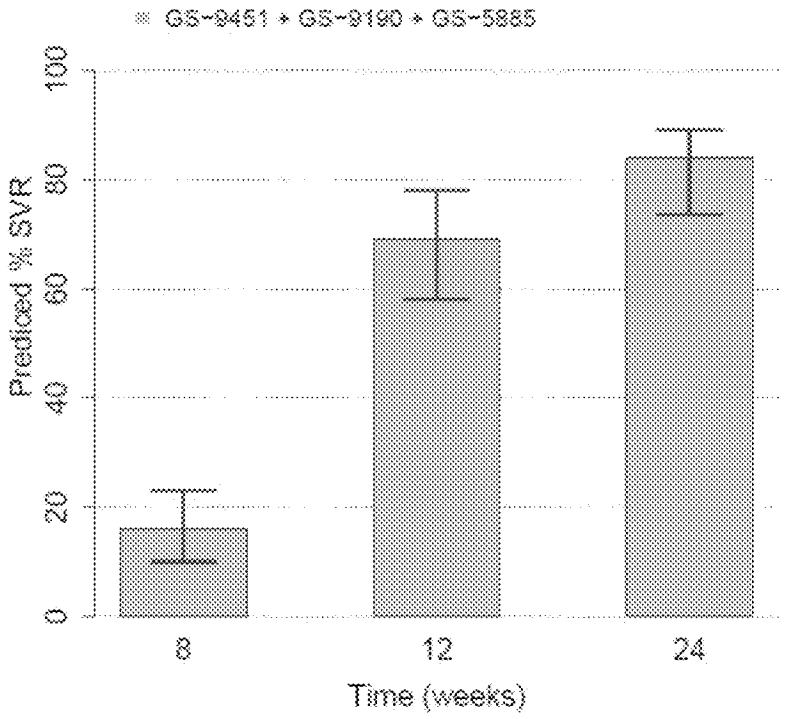

GS-9451 + GS-9190 + GS-5885
Predicted % SVR
0
20
40
60
80
100
8
12
24
Time (weeks)

Figure 15

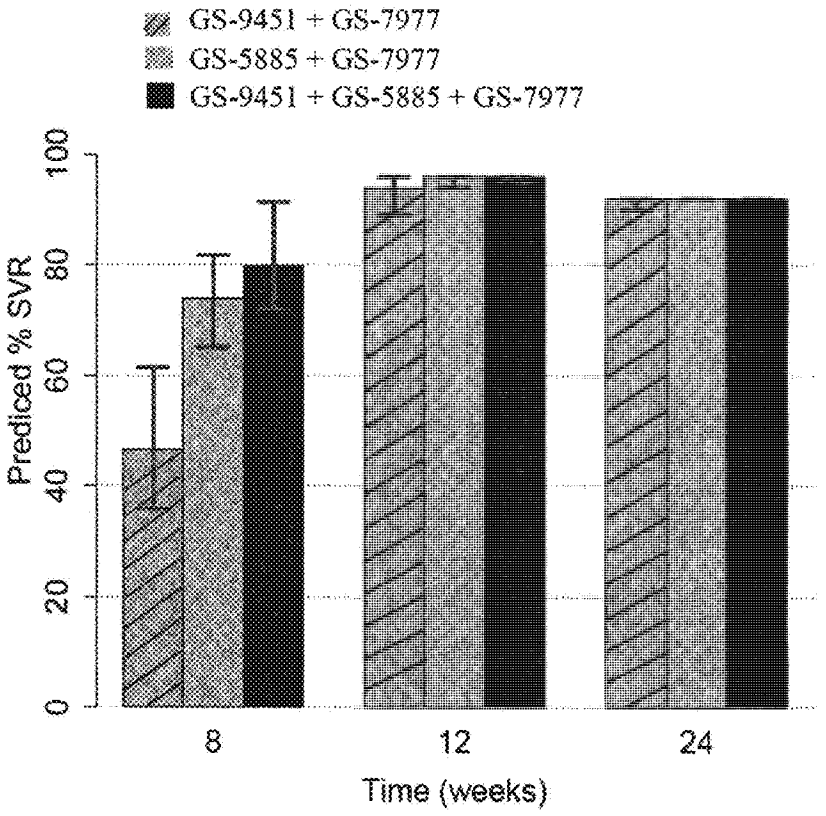

GS-9451 + GS-7977
GS-5885 + GS-7977
GS-9451 + GS-5885 + GS-7977
Predicted % SVR
0
20
40
60
80
100
8
12
24
Time (weeks)

Figure 16

METHODS FOR TREATING HCV

This application claims the benefit of U.S. Provisional Application No. 61/550,352 filed Oct. 21, 2011, U.S. Provisional Application No. 61/562,181 filed Nov. 21, 2011, U.S. Provisional Application No. 61/587,225 filed Jan. 17, 2012, U.S. Provisional Application No. 61/600,276 filed Feb. 17, 2012, U.S. Provisional Application No. 61/619,870 filed Apr. 3, 2012, and U.S. Provisional Application No. 61/656,251 filed Jun. 6, 2012.

FIELD OF THE INVENTION

The present invention relates to interferon-free treatment for hepatitis C virus (HCV).

BACKGROUND OF THE INVENTION

The HCV is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

Chronic HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often incomplete. Therefore, there is a need for new therapies to treat HCV infection.

BRIEF SUMMARY OF THE INVENTION

As one aspect of the present invention, methods for treating HCV infection in a subject are provided. The methods comprise administering at least two direct acting antiviral agents (DAAs) and ribavirin for a duration of no more than twelve weeks, or for another duration as set forth herein. Preferably, the duration of the treatment is twelve weeks. The duration of the treatment can also be no more than eight weeks. Preferably, the two or more direct acting antiviral agents (DAAs) and ribavirin are administered in amounts effective to provide a sustained virological response (SVR) or achieve another desired measure of effectiveness in a subject. The subject is not administered interferon during the treatment regimen. Put another way, the methods exclude the administration of interferon to the subject, thereby avoiding the side effects associated with interferon. In some embodiments, the methods further comprise administering an inhibitor of cytochrome P-450 (such as ritonavir) to the subject to improve the pharmacokinetics or bioavailability of one or more of the DAAs.

As another aspect, methods for treating HCV infection in a subject are provided. The methods comprise administering (a) therapeutic agent 1, (b) at least one polymerase inhibitor selected from the group consisting of therapeutic agent 2, therapeutic agent 3, and combinations thereof, (c) ribavirin and (d) an inhibitor of cytochrome P-450 to the subject for a duration of no more than twelve weeks, or for another duration as set forth herein (e.g., the treatment regimen can last a duration of for no more than 8 weeks). Preferably, therapeutic agent 1, the polymerase inhibitor(s), ribavirin and the inhibitor of cytochrome P-450 are administered in amounts effective to provide high rates of SVR or another measure of effectiveness in the subject. As non-limiting examples, therapeutic agent 1 and the inhibitor of cytochrome P-450 can be co-formulated and administered once daily, and the polymerase inhibitor(s) can be administered once daily or twice daily, and the treatment regimen preferably lasts for twelve weeks (the treatment regimen can also last, for example, for eight weeks).

As still another aspect, methods for treating a population of subjects having HCV infection are provided. The methods comprise administering at least two DAAs, together with ribavirin, to the subjects for a duration of no more than 12 weeks. Preferably, the at least two DAAs are administered to the subjects in amounts effective to result in SVR or another measure of effectiveness in at least about 50% of the population, preferably at least about 70% of the population.

In the foregoing methods as well as methods described hereinbelow, the DAAs can be selected from the group consisting of protease inhibitors, nucleoside or nucleotide polymerase inhibitors, non-nucleoside polymerase inhibitors, NS3B inhibitors, NS4A inhibitors, NS5A inhibitors, NS5B inhibitors, cyclophilin inhibitors, and combinations of any of the foregoing. For example, in some embodiments, the DAAs used in the present methods comprise or consist of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor. The HCV polymerase inhibitor can be a nucleotide or nucleoside polymerase inhibitor or a non-nucleoside polymerase inhibitor. The HCV polymerase inhibitor can also be a non-nucleotide polymerase inhibitor.

In some embodiments, the HCV protease inhibitor is therapeutic agent 1 (described below) and the HCV polymerase inhibitor is therapeutic agent 2 and/or therapeutic agent 3 (also described below). By way of example, therapeutic agent 1 can be administered a total daily dose of from about 100 mg to about 250 mg, or administered at least once daily at a dose of from about 150 mg to about 250 mg, and therapeutic agent 2 is administered in a total daily dose of from about 300 mg to about 1800 mg or administered at least twice daily at doses from about 200 mg to about 400 mg. For some embodiments, the HCV protease inhibitor is therapeutic agent 1 and the non-nucleoside HCV polymerase inhibitor is therapeutic agent 3. By way of example, therapeutic agent 1 can be administered at a total daily dose of about 100 mg, alternatively about 200 mg, or alternatively about 250 mg; and therapeutic agent 3 is administered at a total daily dose of about 400 mg. Ritonavir (or another cytochrome P-450 3A4 inhibitor) can be co-administered with therapeutic agent 1 to improve the pharmacokinetics and bioavailability of therapeutic agent 1.

In some embodiments, the at least two DAAs comprise at least one HCV protease inhibitor and at least one NS5A inhibitor. Preferably, the HCV protease inhibitor is therapeutic agent 1 and the NS5A inhibitor is therapeutic agent 4. By way of example, therapeutic agent 1 can be administered at a total daily dosage from about 100 mg to about 250 mg, and therapeutic agent 4 can be administered in a total daily dose from about 25 mg to about 200 mg. Ritonavir (or another cytochrome P-450 3A4 inhibitor) can be co-administered with therapeutic agent 1 to improve the pharmacokinetics and bioavailability of therapeutic agent 1.

In the foregoing methods as well as methods described herein, the DAAs and ribavirin can be administered in any effective dosing schemes and/or frequencies, for example, they can each be administered daily. Each DAA can be administered either separately or in combination, and each DAA can be administered at least once a day, at least twice a

day, or at least three times a day. Likewise, the ribavirin can be administered at least once a day, at least twice a day, or at least three times a day, either separately or in combination with one or more of the DAAs. In some preferred embodiments, therapeutic agent 3 is administered once daily (QD) or twice daily (BID), and therapeutic agent 1 is administered once daily.

In some aspects, the present technology provides a method for treating HCV infection comprising administering to a subject in need thereof at least two DAAs and ribavirin for a duration of no more than twelve weeks, wherein the subject is not administered with interferon during said duration. In some aspects, the at least two DAAs and ribavirin are administered in an amount effective to result in SVR. Some methods further comprise administering an inhibitor of cytochrome P450 to the subject. In some aspects, the duration is no more than eight weeks.

In some aspects of the present technology, the at least two direct acting antiviral agents comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, which is co-administered or co-formulated with ritonavir, and (ii) Compound 2 or a pharmaceutically acceptable salt thereof.

In other aspects, the at least two direct acting antiviral agents comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, which is co-administered or co-formulated with ritonavir, and (ii) Compound 3 or a pharmaceutically acceptable salt thereof.

In yet another aspect, the at least two direct acting antiviral agents comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, which is co-administered or co-formulated with ritonavir, and (ii) compound 4 or a pharmaceutically acceptable salt thereof.

In yet a further aspect, the at least two direct acting antiviral agents comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, which is co-administered or co-formulated with ritonavir, (ii) Compound 2 or a pharmaceutically acceptable salt thereof, and (iii) compound 4 or a pharmaceutically acceptable salt thereof.

In yet another aspect, the at least two direct acting antiviral agents comprises a drug combination selected from the group consisting of: a combination of PSI-7977 and PSI-938, a combination of BMS-790052 and BMS-650032, a combination of GS-5885 and GS-9451, a combination of GS-5885, GS-9190 and GS-9451, a combination of BI-201335 and BI-27127, a combination of telaprevir and VX-222, a combination of PSI-7977 and TMC-435, and a combination of danoprevir and R7128. In yet another aspect, the at least two direct acting antiviral agents comprises a combination of PSI-7977 and BMS-790052 (daclatasvir). In yet another aspect, the at least two direct acting antiviral agents comprises a combination of PSI-7977 and BMS-650032 (asunaprevir). In still another aspect, the at least two direct acting antiviral agents comprises a combination of PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir).

In other aspects, the present technology provides a method for treating HCV infection in a subject comprising administering (a) therapeutic agent 1, (b) at least one polymerase inhibitor selected from the group consisting of therapeutic agent 2, therapeutic agent 3 and combinations thereof, (c) ribavirin and (d) an inhibitor of cytochrome P450 to the subject and for a duration of no more than twelve weeks, wherein the therapeutic agent 1, the at least one polymerase inhibitor, the ribavirin and the inhibitor of cytochrome P450 are administered in amounts effective to result in sustained virological response (SVR) in the subject.

In yet another aspect, the present technology provides a method for treating a population of subjects having HCV infection, the method comprising administering at least two DAAs to the subjects for a duration of no more than 12 weeks, wherein the at least two DAAs are administered to the subjects in amounts and for a duration effective to provide a SVR in at least about 70% of the population.

In another aspect, the present technology features a combination of at least two DAAs for use in treating HCV infection, wherein the duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). The treatment comprises administering the at least two DAAs to a subject infected with HCV. Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon. The treatment may also include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder, a partial responder or a relapser), or not a candidate for interferon treatment.

In another aspect, the present technology features a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof) for use in treating HCV infection. The treatment comprises administering the DAAs to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon; and ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) is administered with Compound 1 (or the salt thereof) to improve the pharmacokinetics of the latter. Compound 1 (or the salt thereof) and Compound 2 (or the salt thereof) can be administered concurrently or sequentially. For example, Compound 1 (or the salt thereof) can be administered once daily, together with ritonavir or another CYP3A4 inhibitor (e.g., cobicistat), and Compound 2 (or the salt thereof) can be administered twice daily. For yet another example, Compound 1 (or the salt thereof) and ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat) are co-formulated in a single composition and administered concurrently (e.g., once daily). For yet another example, Compound 1 (or the salt thereof), co-formulated with ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat), is administered once daily, and Compound 2 (or the salt thereof) is administered twice daily. As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient

can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder infected (e.g., a null responder) with HCV genotype 1.

In another aspect, the present technology features a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 3 (or a pharmaceutically acceptable salt thereof) for use in treating HCV infection. The treatment comprises administering the DAAs to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon; and ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) is administered with Compound 1 (or the salt thereof) to improve the pharmacokinetics of the latter. Compound 1 (or the salt thereof) and Compound 3 (or the salt thereof) can be administered concurrently or sequentially. For example, Compound 1 (or the salt thereof) can be administered once daily, together with ritonavir or another CYP3A4 inhibitor (e.g., cobicistat), and Compound 3 (or the salt thereof) can be administered twice daily. For another example, Compound 1 (or the salt thereof) and Compound 3 (or the salt thereof) are administered once daily. For yet another example, Compound 1 (or the salt thereof) and ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat) are co-formulated in a single composition and administered concurrently (e.g., once daily). For yet another example, Compound 1 (or the salt thereof), ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat), and Compound 3 (or the salt thereof) are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the

subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In another aspect, the present technology features a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and compound 4 (or a pharmaceutically acceptable salt thereof) for use in treating HCV infection. The treatment comprises administering the DAAs to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon; and ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) is administered with Compound 1 (or the salt thereof) to improve the pharmacokinetics of the latter. Compound 1 (or the salt thereof) and compound 4 (or the salt thereof) can be administered concurrently or sequentially. For example, Compound 1 (or the salt thereof) can be administered once daily, together with ritonavir or another CYP3A4 inhibitor (e.g., cobicistat), and compound 4 (or the salt thereof) can be administered twice daily. For another example, Compound 1 (or the salt thereof) and compound 4 (or the salt thereof) are administered once daily. For yet another example, Compound 1 (or the salt thereof) and ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat) are co-formulated in a single composition and administered concurrently (e.g., once daily). For yet another example, Compound 1 (or the salt thereof), ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat), and compound 4 (or the salt thereof) are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In another aspect, the present technology features a combination of Compound 1 (or a pharmaceutically acceptable salt thereof), Compound 2 (or a pharmaceutically acceptable salt thereof), and compound 4 (or a pharmaceutically acceptable salt thereof) for use in treating HCV infection. The treatment comprises administering the DAAs to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon; and ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) is administered with Compound 1 (or the salt thereof) to improve the pharmacokinetics of the latter. Compound 1 (or the salt thereof), Compound 2 (or the salt thereof), and compound 4 (or the salt thereof) can be administered concurrently or sequentially. For example, Compound 1 (or the salt thereof) can be administered once daily, together with ritonavir or another CYP3A4 inhibitor (e.g., cobicistat), and compound 4 (or the salt thereof) can be administered once daily, and Compound 2 (or the salt thereof) can be administered twice daily. For yet another example, Compound 1 (or the salt thereof), compound 4 (or the salt thereof), and ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat) are co-formulated in a single composition and administered concurrently (e.g., once daily). For yet another example, Compound 1 (or the salt thereof), ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat), and compound 4 (or the salt thereof) are co-formulated in a single composition and administered concurrently (e.g., once daily), and Compound 2 (or the salt thereof) are administered twice daily. As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1.

In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In another aspect, the present technology features a combination of at least two DAAs for use in treating HCV infection, wherein said combination comprises a combination selected from:

a combination of PSI-7977 and PSI-938,
a combination of BMS-790052 and BMS-650032,
a combination of GS-5885 and GS-9451,
a combination of GS-5885, GS-9190 and GS-9451,
a combination of BI-201335 and BI-27127,
a combination of telaprevir and VX-222,
a combination of PSI-7977 and TMC-435, and
a combination of danoprevir and R7128.

The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon. The treatment may also include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In yet another aspect, the present technology features a combination of at least two DAAs for use in treating HCV infection, wherein said combination comprises a combination selected from:

a combination of PSI-7977 and BMS-790052
a combination of PSI-7977 and BMS-650032,
a combination of PSI-7977, BMS-790052 and BMS-650032,
a combination of INX-189 and BMS-790052
a combination of INX-189 and BMS-650032, or
a combination of INX-189, BMS-790052 and BMS-650032.

The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In still another aspect, the present technology features PSI-7977, or a combination of at least two DAAs, for use in treating HCV infection, wherein said combination comprises a combination selected from:

a combination of mericitabine and danoprevir,
a combination of INX-189, daclatasvir and BMS-791325, and
a combination of PSI-7977 and GS-5885.

The treatment comprises administering PSI-7977 or the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). For example, the duration of the treatment regimen is no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The

treatment includes administering ribavirin but does not include administering interferon. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In still another aspect, the present technology features PSI-7977, or a combination of at least two DAAs, for use in treating HCV infection, wherein said combination comprises a combination selected from:

a combination of mericitabine and danoprevir,

a combination of INX-189, daclatasvir and BMS-791325, and

a combination of PSI-7977 and GS-5885.

The treatment comprises administering PSI-7977 or the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In still another aspect, the present technology features a combination of at least two DAAs, for use in treating HCV infection, wherein said combination comprises a combination selected from:

a combination of tegobuvir and GS-9256,

a combination of BMS-791325, asunaprevir and daclatasvir, and

a combination of TMC-435 and daclatasvir.

The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In yet another aspect, the present technology features a combination of PSI-7977 and BMS-790052 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment can last, for example, no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2.

In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In yet another aspect, the present technology features a combination of PSI-7977 and TMC-435 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment includes administering ribavirin but does not include administering interferon. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In yet another aspect, the present technology features a combination of danoprevir and mercitabine for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than sixteen weeks (e.g., the duration being 16 weeks; or the duration being 14, 12 or 10 weeks). The duration of the treatment regimen may also be less than 10 weeks. The treatment includes administering ribavirin but does not include administering interferon. The treatment also includes co-administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) with danoprevir to improve the pharmacokinetics of danoprevir. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another

example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In yet another aspect, the present technology features a combination of INX-189, daclatasvir and BMS-791325 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than sixteen weeks (e.g., the duration being 16 weeks; or the duration being 14, 12 or 10 weeks). The duration of the treatment regimen may also be less than 10 weeks. The treatment includes administering ribavirin but does not include administering interferon. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In yet another aspect, the present technology features a combination of PSI-7977 and GS-5885 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than sixteen weeks (e.g., the duration being 16 weeks; or the duration being 14, 12 or 10 weeks). The duration of the treatment regimen may also be less than 10 weeks. The treatment includes administering ribavirin but does not include administering interferon. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV

genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In another aspect, the present invention features methods for treatment of HCV infection, wherein the methods comprise administering to a subject in need thereof at least two direct acting antiviral agents (DAAs) and ribavirin, and the treatment does not include administration of interferon to the subject. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In one embodiment of this aspect of the invention, the at least two DAAs comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, and (ii) Compound 2 or a pharmaceutically acceptable salt thereof, and said method further comprises administering ritonavir to the subject. Ritonavir improves the pharmacokinetics or drug exposure of Compound 1. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In another embodiment of this aspect of the invention, the at least two DAAs comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, and (ii) Compound 4 or a pharmaceutically acceptable salt thereof, and the method further comprises administering ritonavir to the subject to improve the pharmacokinetics or drug exposure of Compound 1. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In another embodiment of this aspect of the invention, the at least two DAAs comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, (ii) Compound 2 or a pharmaceutically acceptable salt thereof, and (iii) Compound 4 or a pharmaceutically acceptable salt thereof, and the method further comprises administering ritonavir to the subject to improve the pharmacokinetics or drug exposure of Compound 1. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV protease inhibitor and a HCV polymerase inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV protease inhibitor and a non-nucleoside or non-nucleotide HCV polymerase inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12

weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV protease inhibitor and a nucleoside or nucleotide HCV polymerase inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV protease inhibitor and a HCV NS5A inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV polymerase inhibitor and a HCV NS5A inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV non-nucleoside or non-nucleotide polymerase inhibitor and a HCV NS5A inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV nucleoside or nucleotide polymerase inhibitor and a HCV NS5A inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise PSI-7977 and TMC-435. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise PSI-7977 and daclatasvir. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise PSI-7977 and GS-5885. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise mericitabine and danoprevir. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise BMS-790052 and BMS-650032. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1b. As a non-limiting example, the subject being treatment is infected with HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise INX-189, daclatasvir and BMS-791325. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another aspect, the present invention features methods for treatment of a treatment-naïve subject with HCV genotype 1 infection, wherein the method comprises administering to said patient PSI-7977 and ribavirin, and the treatment does not include administration of interferon to the subject. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. Preferably, the subject being treated is infected with genotype 1a. More preferably, the subject being treated is a naïve patient infected with genotype 1. The subject being treated can also be a treatment-experienced patient or an interferon non-responder (e.g., a null responder), and/or is infected with HCV genotype 3. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with genotype 1. The present invention also features PSI-7977 or a pharmaceutical acceptable salt thereof for use in any treatment described in this aspect of the invention.

A treatment regimen of the present technology generally constitutes a complete treatment regimen, i.e., no subsequent interferon-containing regimen is intended. Thus, a treatment or use described herein generally does not include any subsequent interferon-containing treatment.

Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a 3-D surface plot illustrating deviations from expected inhibitory effects from varying concentrations of Compound 1 and Compound 2 in a genotype 1b HCV replicon assay.

FIG. **2** is a contour plot showing concentrations at which Compound 1 and Compound 2 exhibited syngeristic, additive, or antagonistic interactions in the genotype 1b HCV replicon assay.

FIG. **3** is a 3-D surface plot illustrating deviations from expected inhibitory effects from varying concentrations of Compound 1 and compound 4 in a genotype 1b HCV replicon assay.

FIG. **4** is a contour plot showing concentrations at which Compound 1 and compound 4 exhibited syngeristic, additive, or antagonistic interactions in the genotype 1b HCV replicon assay.

FIG. **5**A is a bar graph showing the percentage of cells containing HCV genotype 1a replicon constructs surviving after three weeks of exposure to therapeutic agent 1, therapeutic agent 2, therapeutic agent 4, or a combination of some or all of those therapeutic agents in the presence of G418.

FIG. **5**B is another bar graph showing the percentage of surviving 1a-H77 replicon cells grown in the presence of G418, and two or three DAA combinations, for approximately three weeks.

FIG. **5**C depicts the effect of Compound 1, Compound 2 and a combination thereof in long-term HCV RNA reduction assays in 1a-H77 replicon cell lines.

FIG. **5**D demonstrates the effect of Compound 1, Compound 2 and a combination thereof in long-term HCV RNA reduction assays in 1b-Con1 replicon cell lines.

FIG. **6**A shows the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen without ribavirin; the 2 DAAs include (i) Compound 1 with ritonavir (Compound 1/r) and (ii) Compound 2.

FIG. **6**B illustrates the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen without ribavirin; the 2 DAAs include (i) Compound 1 with ritonavir (Compound 1/r) and (ii) Compound 4.

FIG. **6**C depicts the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 3-DAA regimen without ribavirin; the 3 DAAs include (i) Compound 1 with ritonavir (Compound 1/r), (ii) Compound 2 and (iii) Compound 4.

FIG. **7** shows the exposure-response model predicted versus observed percentage of subjects with HCV RNA less than LOD over time in the clinical study described in Example 1.

FIG. **8** demonstrates the exposure-response model predicted versus observed percentage of subjects with SVR12 in the clinical study described in Example 2A.

FIG. **9** shows the predicted median and 90% confidence interval of SVR rates for different treatment durations of a 2-DAA regimen containing BMS-790052 and BMS-650032.

FIG. **10** shows the predicted median of SVR rates for different treatment durations of a 3-DAA regimen containing Compound 1/r, Compound 4 and PSI-7977.

FIG. **11** shows the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 1-DAA regimen containing PSI-7977 and ribavirin.

FIG. **12** depicts the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen containing daclatasvir (BMS-790052) 60 mg QD and PSI-7977 400 mg QD.

FIG. **13** shows the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen containing TMC-435 150 mg QD and PSI-7977 400 mg QD.

FIG. **14** illustrates the predicted median and 90% confidence interval of SVR percentage for different treatment

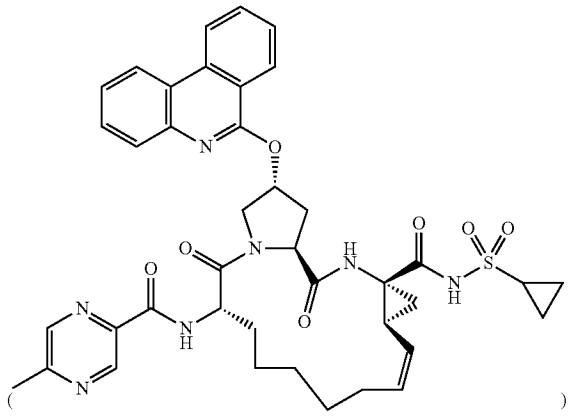
durations of a 2-DAA regimen containing danoprevir 100 mg BID and mercitabine 750 mg BID.

FIG. **15** depicts the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen containing GS-9190 (tegobuvir) 30 mg BID+GS-9451 200 mg QD+GS-5885 90 mg QD.

FIG. **16** shows the predicted median and 90% confidence interval of SVR percentage for different treatment durations of the following DAA combo regimens: (1) GS-9451 200 mg QD+GS-7977 (PSI-7977) 400 mg QD; (2) GS-5885 90 mg QD+GS-7977 (PSI-7977) 400 mg QD; and (3) GS-9451 200 mg QD+GS-5885 90 mg QD+GS-7977 (PSI-7977) 400 mg QD.

DETAILED DESCRIPTION OF THE INVENTION

The present methods can include administering therapeutic agent 1 to a subject. Therapeutic agent 1 is Compound 1

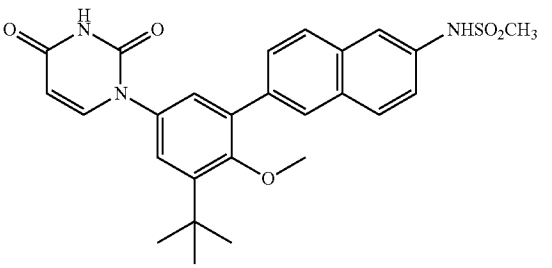


or a pharmaceutically acceptable salt thereof. Compound 1 is also known as (2R,6S,13aS,14aR,16aS,Z)—N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. Compound 1 is a potent HCV protease inhibitor. The synthesis and formulation of Compound 1 are described in U.S. Patent Application Publication No. 2010/0144608, U.S. Provisional Application Ser. No. 61/339,964 filed on Mar. 10, 2010, and U.S. Patent Application Publication No. 2011/0312973 filed on Mar. 8, 2011. All of these applications are incorporated herein by reference in their entireties. Therapeutic agent 1 includes various salts of Compound 1. Therapeutic agent 1 may be administered in any suitable amount such as, for example, in doses of from about 0.01 to about 50 mg/kg body weight, alternatively from about 0.1 to about 25 mg/kg body weight. As non-limiting examples, therapeutic agent 1 may be administered in a total daily dose amount of from about 50 mg to about 250 mg, preferably from about 100 mg to about 250 mg, and includes, but is not limited to, for example, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg and suitable amounts there between.

In preferred embodiments, ritonavir or another inhibitor of cytochrome P-450 is co-administered with therapeutic agent 1 to improve the pharmacokinetics of Compound 1.

The present methods can include administering therapeutic agent 2 to a subject. Therapeutic agent 2 is Compound 2 or a salt thereof.

Compound 2

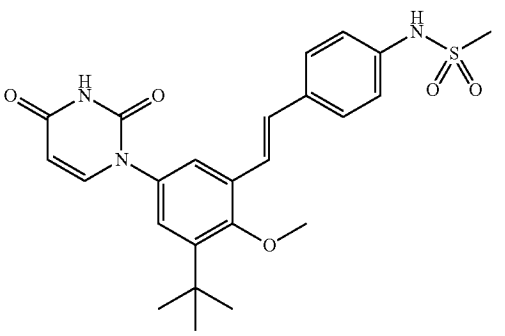


Compound 2 is also known N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl) naphthalen-2-yl)methanesulfonamide. As described in, for example, International Publication No. WO2009/039127, therapeutic agent 2 includes various salts of Compound 2, such as sodium salts, potassium salts, and choline salts. Therapeutic agent 2 also includes crystalline forms of Compound 2 and its salts such as solvate, hydrate, and solvent-free crystalline forms of Compound 2 and its salts. Compositions comprising therapeutic agent 2 can be prepared as described in, for example, International Publication No. WO2009/039127 which is incorporated by reference herein.

Therapeutic agent 2 may be administered as a free acid, salt or particular crystalline form of Compound 2. In some embodiments, therapeutic agent 2 is administered as a sodium salt. Therapeutic agent 2 may be administered in any suitable amount such as, for example, in doses of from about 5 mg/kg to about 30 mg/kg. As non-limiting examples, therapeutic agent 2 may be administered in a total daily dose amount of from about 300 mg to about 1800 mg, or from about 400 mg to about 1600 mg, or from about 600 mg to about 1800 mg, or from about 800 mg to about 1600 mg or any amounts there between. In some embodiments, the total daily dosage amount for therapeutic agent 2 is about 600 mg. In some embodiments, the total daily dosage amount for therapeutic agent 2 is about 800 mg. In some embodiments, the total daily dosage amount for therapeutic agent 2 is about 1200 mg. In some embodiments, the total daily dosage amount for therapeutic agent 2 is about 1600 mg.

The present methods can include administering therapeutic agent 3 or a salt thereof to a subject. Therapeutic agent 3 is Compound 3 or a salt thereof.

Compound 3



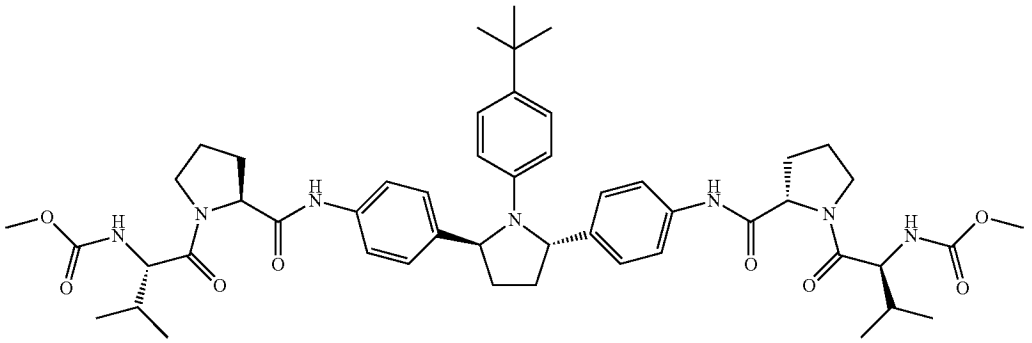
Compound 3 is also known as (E)-N-(4-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxystyryl) phenyl)methanesulfonamide. As described in, for example,

International Publication No. WO2009/039127, therapeutic agent 3 includes various salts of Compound 3, such as sodium salts, potassium salts, and choline salts. Therapeutic agent 3 also includes crystalline forms of Compound 3 and its salts such as solvate, hydrate, and solvent-free crystalline forms of Compound 3 and its salts. Compositions comprising therapeutic agent 3 can be prepared as described in, for example, International Publication No. WO2009/039127 which is incorporated by reference herein.

Therapeutic agent 3 may be administered as a free acid, salt or particular crystalline form of Compound 3. In some embodiments, Compound 3 is administered as a potassium salt. Therapeutic agent 3 may be administered in any suitable amount such as, for example, in doses of from about 0.5 mg/kg to about 15 mg/kg or from about 1 mg/kg to about 10 mg/kg. As non-limiting examples, therapeutic agent 3 may be administered in a total daily dose amount of from about 100 mg to about 600 mg. In some embodiments, the total daily dosage amount for therapeutic agent 3 is about 300 mg. In some embodiments, the total daily dosage amount for therapeutic agent 3 is about 320 mg. In some embodiments, the total daily dosage amount for therapeutic agent 3 is about 400 mg. In some embodiments, the total daily dosage amount for therapeutic agent 3 is about 600 mg.

The present methods can include administering therapeutic agent 4 or a salt thereof to a subject. Therapeutic agent 4 is compound 4 or a salt thereof.

Compound 4



Compound 4 is also known as dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5,diyl)bis(4,1-phenylene))bis(azane diyl)bis(oxomethylene) bis(pyrrolidine-2,1-diyl)bis(3-methyl-1-oxobutane-2,1-diyl) dicarbamate. Compound 4 can be prepared as described in, for example, U.S. Publication No. 2010/0317568, which is incorporated herein by reference.

Therapeutic agent 4 may be administered as a free acid, or a salt form. Therapeutic agent 4 may be administered in any suitable amount such as, for example, in doses of from about 0.1 mg/kg to about 200 mg/kg body weight, or from about 0.25 mg/kg to about 100 mg/kg, or from about 0.3 mg/kg to about 30 mg/kg. As non-limiting examples, therapeutic agent 4 may be administered in a total daily dose amount of from about 5 mg to about 300 mg, or from about 25 mg to about 200 mg, or from about 25 mg to about 50 mg or any amounts there between. In some embodiments, the total daily dosage amount for therapeutic agent 4 is about 25 mg.

The at least two DAAs may also be co-administered with ribavirin, or a pro-drug thereof, in the same or separate pharmaceutical compositions. Ribavirin may include any suitable form or formulation of ribavirin. Exemplary formulations of ribavirin include COPEGUS®, REBETOL® and RIBASPHERE®. An exemplary pro-drug of ribavirin is taribavirin having the chemical name of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamidine. Ribavirin and taribavirin may be administered in accordance with ribavirin and taribavirin administration well known in the art. In some embodiments, COPEGUS® or REBETOL® is administered in a daily dosage amount of from about 500 mg to about 1500 mg in one dose or in divided doses. In some embodiments, COPEGUS® or REBETOL® is administered in a daily dosage amount of about 800 mg. In some embodiments, REBETOL® is administered in a daily dosage amount of about 1000 mg. In some embodiments, COPEGUS® or REBETOL® is administered in a daily dosage amount of about 1200 mg. In some embodiments, REBETOL® is administered in a daily dosage amount of about 1400 mg. Suitable dosages of ribavirin are dependent on the weight of the subject, for example about 1000-1200 mg. Suitable total daily dosages of ribavirin include, but are not limited to about 400 mg to about 1400 mg a day, alternatively about 800 mg to about 1400 mg per day, alternatively about 400 mg to about 1200 mg, alternatively about 800 mg to about 1200 mg.

The current standard of care (SOC) for the treatment of HCV includes a course of treatment of interferon, e.g. pegylated interferon (e.g., pegylated interferon-alpha-2a or pegylated interferon-alpha-2b, such as PEGASYS by Roche, or PEG-INTRON by Schering-Plough) and the antiviral drug ribavirin (e.g., COPEGUS by Roche, REBETOL by Schering-Plough, or RIBASPHERE by Three Rivers Pharmaceuticals). The treatment often lasts for 24-48 weeks, depending on hepatitis C virus genotype. Other interferons include, but are not limited to, interferon-alpha-2a (e.g., Roferon-A by Roche), interferon-alpha-2b (e.g., Intron-A by Schering-Plough), and interferon alfacon-1 (consensus interferon) (e.g., Infergen by Valeant). Less than 50% of patients with chronic HCV infection with genotype 1 virus respond to this therapy. Further, interferon therapy has many side effects that hinder patient compliance and results in premature discontinuation of the treatment.

The interferon/ribavirin-based treatment may be physically demanding, and can lead to temporary disability in some cases. A substantial proportion of patients will experience a panoply of side effects ranging from a "flu-like" syndrome (the most common, experienced for a few days after the weekly injection of interferon) to severe adverse events including anemia, cardiovascular events and psychiatric problems such as suicide or suicidal ideation. The latter are exacerbated by the general physiological stress experienced by the patients. Ribavirin also has a number of side effects,

including, anemia, high pill burden (e.g. 5-6 pills a day split BID) and teratogenicity restricting use in women of child-bearing age.

The present methods provide effective treatment of HCV infection without the use of interferon and for a shorter period of time, such as a treatment duration of no more than twelve weeks, alternatively no more than eleven weeks, alternatively no more than ten weeks, alternatively no more than nine weeks, alternatively no more than eight weeks, alternatively no more than seven weeks, alternatively no more than six weeks, alternatively no more than five weeks, alternatively no more than four weeks, or alternatively, no more than three weeks.

In some embodiments, the present technology provides methods for treating HCV infection in a subject comprising administering at least two DAAs with ribavirin in the absence of interferon for a duration of no more than twelve weeks, alternatively no more than eight weeks. Put another way, the present methods exclude interferon, or the subject does not receive interferon for the duration of the treatment. The at least two DAAs can be co-administered or can be administered independently (with the same or different dosing frequencies) and can be administered once a day, alternatively twice a day, alternatively three times a day.

In some embodiments, the methods of treatment comprise daily administration of two or more DAAs, wherein a first DAA may be administered once a day, twice a day, or three times a day, and a second DAA may be administered once a day, twice a day, or three times a day. In some embodiments, a third DAA may be administered once a day, twice a day, or three times a day. The DAAs may be co-administered or administered at different times or frequencies. Preferably, in the methods, at least two DAAs and ribavirin are administered in effective amounts to provide a desired measure of effectiveness in the subject. Preferably, the treatment has reduced side effects as compared with interferon-containing treatments.

Various measures may be used to express the effectiveness of the present methods of HCV treatment. One such measure is rapid virological response (RVR), meaning that HCV is undetectable in the subject after 4 weeks of treatment, for example, after 4 weeks of administration of two or more of DAAs and ribavirin. Another measure is early virological response (EVR), meaning that the subject has >2 $\log_{10}$ reduction in viral load after 12 weeks of treatment. Another measure is complete EVR (cEVR), meaning the HCV is undetectable in the serum of the subject after 12 weeks of treatment. Another measure is extended RVR (eRVR), meaning achievement of RVR and cEVR, that is, HCV is undetectable at week 4 and 12. Another measure is the presence or absence of detectable virus at the end of therapy (EOT). Another measure is (SVR), which, as used herein, means that the virus is undetectable at the end of therapy and for at least 8 weeks after the end of therapy (SVR8); preferably, the virus is undetectable at the end of therapy and for at least 12 weeks after the end of therapy (SVR12); more preferably, the virus is undetectable at the end of therapy and for at least 16 weeks after the end of therapy (SVR16); and highly preferably, the virus is undetectable at the end of therapy and for at least 24 weeks after the end of therapy (SVR24). SVR24 is often considered as a functional definition of cure; and a high rate of SVR at less than 24 week post-treatment (e.g., SVR8 or SVR12) can be predictive of a high rate of SVR24. Likewise, a high rate of SVR at less than 12 week post-treatment (e.g., SVR4 or SVR8) can be predictive of a high rate of SVR12. A high rate of EOT (e.g., at week 8 or week 12) can also be indicative of a significant rate of SVR12 or SVR24.

In some embodiments, the amounts of the two or more DAAs and ribavirin, and/or the duration of the treatment regimen of the two or more DAAs and ribavirin, are effective to provide an RVR in a subject, or an EVR in a subject, or a cEVR in a subject, or an eRVR in a subject, or an absence of detectable virus at EOT in a subject. In some embodiments, the present methods comprise treating a population of subjects having HCV infection (e.g. treatment naïve subjects), and the methods comprise administering at least two DAAs and ribavirin to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein the at least two DAAs and ribavirin are administered to the subjects in amounts effective to provide an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment) in at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, alternatively about 100% of the population. In some embodiments, the present methods comprise treating a population of IFN experienced subjects (e.g., interferon non-responders) having HCV infection, and the methods comprise administering at least two DAAs and ribavirin to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein the at least two DAAs and ribavirin are administered to the subjects in amounts effective to provide an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment) in at least about 50% of the population, alternatively at least about 55% of the population, alternatively at least about 60% of the population, alternatively at least about 65% of the population. In other embodiments, the amount of DAAs and ribavirin and the duration of the treatment are effective to provide one or more of an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment), an RVR, an EVR, a cEVR, an eRVR, or an absence of detectable virus at EOT, in at least about 50% of the population, alternatively at least about 55%, in at least about 60% of the population, alternatively at least about 65% of the population, alternatively at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, alternatively about 100% of the population. For example, the present methods comprise administering at least two DAAs and ribavirin in amounts and for durations effective to provide an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment) in a subject. In some embodiments, the present technology provides for an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment) in at least about 50% of the population, alternatively at least about 55% of the population, in at least about 60% of the population, preferably in at least about 65% of the population, preferably in at least about 70% of the population, preferably at least about 75% of the patients treated by such methods herein described, more preferably in at least 80% of the population, and highly preferably in at least about 90% of the patients being treated. In some embodiments, a treatment of the present technology provides an RVR or undetectable level of HCV RNA in the bloodstream at four (4) weeks of treatment (preferably in addition to a SVR).

A DAA of the present technology includes, but is not limited to, a protease inhibitor, a HCV polymerase inhibitor, an HCV NS5A inhibitor, an HCV NS3B inhibitor, an HCV NS4A inhibitor, an HCV NS5B inhibitor, an HCV entry

inhibitor, a cyclophilin inhibitor, a CD81 inhibitor, or an internal ribosome entry site inhibitor. The HCV polymerase inhibitor may be a nucleoside polymerase inhibitor or a non-nucleoside polymerase inhibitor. The HCV polymerase inhibitor may be a nucleotide polymerase inhibitor or a non-nucleotide polymerase inhibitor.

In yet another example of this aspect of the technology, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir).

It was unexpectedly discovered that an interferon-free treatment using a combination of two or more DAAs, together with ribavirin, and for a duration of no more than 12 weeks, could achieve significant SVR. In many cases, such a treatment can achieve an SVR in at least about 75% of patients, and in some cases, such a treatment can achieve an SVR in at least about 85% of patients, and in certain cases, such a treatment can achieve an SVR in at least about 90% of patients. It was also surprising that such a treatment could achieve significant viral suppression even at 4 weeks of the treatment. In some embodiments, the interferon-free treatment using a combination of two or more DAAs, together with ribavirin, and for a duration of no more than 12 weeks, could achieve significant SVR in interferon non-responders, for example, treatment can achieve an SVR in at least about 50% of patients in the interferon non-responder population, preferably at least about 60% of patients in the interferon non-responder population, more preferably at least about 65% of patients in the interferon non-responder population.

Accordingly, in one aspect, the present technology features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 8 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs

comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 7 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet

another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 6 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-

435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 5 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combina-

tion of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 4 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more

DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 3 weeks (or even less, depending on the patient's condition) and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet

another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 24 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another

example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts from 13 to 23 weeks (e.g., the duration of the treatment is selected from 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 weeks) and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another

example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 12 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the com-

bination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 11 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more

DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 10 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes

danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts 9 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequency. The patient being treated can be an interferon naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes

PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs, together with an effective amount of ribavirin. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Ribavirin can be administered based on patient weight, and in many cases, 1000 to 1200 mg divided twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In another embodiment, the present technology provides interferon-free treatment comprising administering daily two DAAs with ribavirin, where the two DAAs include a HCV polymerase inhibitor, for example PSI-7977 and a NS5A inhibitor, for example BMS-790052 for a duration of no more than twelve weeks (e.g., no more than eleven weeks), preferably no more than eight weeks.

In some embodiments, the present technology provides a method of treating Hepatitis C virus infection in a subject comprising administering daily a HCV protease inhibitor and a HCV polymerase inhibitor to the subject in the absence of interferon for a duration of no more than twelve weeks, preferably no more than eight weeks. In some embodiments, ritonavir (or an equivalent thereof) is co-administered with one or more protease inhibitors to improve the pharmacokinetics of the protease inhibitor(s). The treatment further comprises administering ribavirin to the patient. In some embodiments, the HCV polymerase inhibitor is at least one nucleoside or nucleotide polymerase inhibitor or at least one non-nucleoside polymerase inhibitor. In some embodiments, both a nucleoside or nucleotide polymerase inhibitors and a non-nucleoside polymerase inhibitor may be administered.

The methods of the present technology as described herein may be used to treat a naïve patient or a treatment experienced patient. Treatment experienced patients include interferon non-responders, partial responders (patients whose HCV RNA levels declined but never became undetectable), and relapsers (patients who achieved undetectable levels of HCV RNA during therapy but rebound). Methods of the present technology may also be used to treat patients who are not candidates for interferon treatment. Patients who are not candidates for interferon treatment include, but are not limited to, one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon.

In some embodiments, a cytochrome P-450 inhibitor, e.g. ritonavir, is administered either in the same or separate pharmaceutical composition with the protease inhibitor (e.g. Compound 1 (or a pharmaceutically acceptable salt thereof)) to improve the pharmacokinetics. A cytochrome P450 inhibitor reduces the metabolism of some protease inhibitors, such as Compound 1, thereby improving the pharmacokinetics and bioavailability of the protease inhibitor, for example Compound 1. More preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is co-formulated with ritonavir in the same dosage form. Other cytochrome P450 inhibitors, such as cobicistat, may also be administered in lieu of ritonavir, to enhance the pharmacokinetics of Compound 1 (or a pharmaceutically acceptable salt thereof).

Inhibitors of cytochrome P450, such as ritonavir, may be co-administered with the DAAs, either sequentially or simultaneously, in the same or different compositions. In some embodiments, the cytochrome P450 inhibitors are administered in order to improve the pharmacokinetics of at least one of the DAAs. Not to be bound by any theory, but a cytochrome P450 inhibitor may also reduce the development of resistant strains of HCV when co-administered with a DAA, thus providing the effectiveness in a shorter treatment. In some embodiments, ritonavir is co-administered with therapeutic agent 1. In some embodiments, ritonavir is co-administered with therapeutic agent 1 in the same compositions.

In some embodiments, the present technology provides a method of treating HCV infection comprising administering at least one protease inhibitor and at least one HCV polymerase inhibitor with ribavirin in a course of treatment of no more than, or less than, eight weeks in the absence of interferon. In some embodiments, the HCV polymerase inhibitor is Compound 1 (or a pharmaceutically acceptable salt thereof).

In some embodiments, the present technology provides a method of treating HCV infection without using interferon, the method comprising administering at least two DAAs and ribavirin to a patient in need of such treatment, wherein the at least two DAAs include at least one protease inhibitor and at least one HCV polymerase inhibitor. In some embodiments, the at least two DAAs includes therapeutic agent 1 with at least one HCV polymerase inhibitor. In some embodiments, the HCV polymerase inhibitor is at least one non-nucleoside polymerase inhibitor. In some embodiments, the non-nucleoside polymerase inhibitor is therapeutic agent 2 or therapeutic agent 3 or a combination thereof.

In some embodiments, the present technology provides a method of treating HCV infection without using interferon, the method comprising administering a HCV protease inhibitor, preferably therapeutic agent 1, with at least one HCV NS5A inhibitor to a patient in need of such treatment. In some embodiments, the NS5A inhibitor is therapeutic agent 4.

In some embodiments of the present technology, a method of treating HCV infection without using interferon, the method comprises administering at least three DAAs and

ribavirin to a subject for no more than 8 weeks without administering interferon. The at least three DAAs can be at least one protease inhibitor, at least one HCV polymerase inhibitor, and at least one NS5A inhibitors. In a preferred embodiment, the at least one protease inhibitor is therapeutic agent 1, the at least one polymerase inhibitor is therapeutic agent 2 or therapeutic agent 3, and the at least one NS5A inhibitor is therapeutic agent 4.

Preferred HCV protease inhibitors include, but are not limited to, therapeutic agent 1, telaprevir (Vertex), boceprevir (Merck), BI-201335 (Boehringer Ingelheim), GS-9451 (Gilead), and BMS-650032 (BMS). Other suitable protease inhibitors include, but are not limited to, ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BMS-650032 (BMS), danoprevir (RG7227/ITMN-191, Roche), GS-9132 (Gilead), GS-9256 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir (Schering-Plough Corp), PHX-1766 (Phenomix), TMC-435 (Tibotec), vaniprevir (MK-7009, Merck), VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof.

Preferred non-nucleoside HCV polymerase inhibitors for use in the present technology include, but are not limited to, therapeutic agent 2, therapeutic agent 3, GS-9190 (Gilead), BI-207127 (Boehringer Ingelheim), and VX-222 (VCH-222) (Vertex & ViraChem). Preferred nucleotide HCV polymerase inhibitors include, but are not limited to, PSI-7977 (Pharmasset), and PSI-938 (Pharmasset). Other suitable and non-limiting examples of suitable HCV polymerase inhibitors include ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination thereof. A polymerase inhibitor may be a nucleoside polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination therefore. A polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as PF-00868554 (Pfizer), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof.

Preferred NS5A inhibitors include, but are not limited to, therapeutic agent 4, BMS-790052 (BMS) and GS-5885 (Gilead). Non-limiting examples of suitable NS5A inhibitors include GSK62336805 (Glaxo SmithKline), ACH-2928 (Achillion), AZD2836 (Astra-Zeneca), AZD7295 (Astra-Zeneca), BMS-790052 (BMS), BMS-824393 (BMS), GS-5885 (Gilead), PPI-1301 (Presidio), PPI-461 (Presidio) A-831 (Arrow Therapeutics), A-689 (Arrow Therapeutics) or a combination thereof.

Non-limiting examples of suitable cyclophilin inhibitors include alisporovir (Novartis & Debiopharm), NM-811 (Novartis), SCY-635 (Scynexis), or a combination thereof.

Non-limiting examples of suitable HCV entry inhibitors include ITX-4520 (iTherx), ITX-5061 (iTherx), or a combination thereof.

Specific examples of other DAA agents that are suitable for the present methods include, but are not limited to, AP-H005, A-831 (Arrow Therapeutics) (NS5A inhibitor), A-689 (Arrow Therapeutics) (NS5A inhibitor), INX08189 (Inhibitex) (polymerase inhibitor), ITMN-191 (Intermune/Roche) (NS3/4A Protease inhibitor), VBY-376 (Protease Inhibitor) (Virobay), ACH-1625 (Achillion, Protease inhibitor), IDX136 (Idenix, Protease Inhibitor), IDX316 (Idenix, Protease inhibitor), VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191 (Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), R7128 (Roche), PF-868554 (Pfizer) (non-nucleoside polymerase inhibitor), PF-4878691 (Pfizer), IDX-184 (Idenix), IDX-375 (Idenix, NS5B polymerase inhibitor), PPI-461 (Presidio), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), CTS-1027 (Conatus), GS-9620 (Gilead), PF-4878691 (Pfizer), RO5303253 (Roche), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), GSK62336805 (GlaxoSmithKline), or any combinations thereof.

In some embodiments, the present technology features methods for treating patients with genotype 1, such as 1a or 1b, HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks, preferably no more than 8 weeks, wherein the treatment does not include administration of interferon. Patients with genotype 1, such as 1a or 1b, infection can be treated with a combination of at least 2 DAAs without interferon where the at least two DAAs include therapeutic agent 1 and therapeutic agent 2 with ribavirin. Therapeutic agent 1 and therapeutic agent 2 with ribavirin can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) after a treatment duration of no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks). The patients may be treatment naïve patients or treatment experienced HCV patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than t 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 2 can be administered with therapeutic agent 1 in any of the dosages of therapeutic agent 1 described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, for example, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1500 mg, or 1800 mg. Suitably, ribavirin may be administered in connection with therapeutic agent 1 and therapeutic agent 2 at any of the dosages described above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example,

about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, but are not limited to, from about 50 mg to about 400 mg per day, preferably about 100 mg per day.

In some embodiments, the present technology features methods for treating patients with genotype 2 or 3 HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. Patients with genotype 2 or 3 HCV infection can be treated with a combination of at least 2 DAAs without interferon where the at least two DAAs include therapeutic agent 1 and therapeutic agent 2 with ribavirin. Therapeutic agent 1 and therapeutic agent 2 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) with a treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The patients may be treatment naïve HCV patients or treatment experienced HCV patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 300 mg. Therapeutic agent 2 can be administered in connection with therapeutic agent 1 in any of the dosages described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1500 mg, or 1800 mg. Suitably, ribavirin may be administered in connection with therapeutic agent 1 and therapeutic agent 2 in any combination of suitable dosages described above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day.

In some embodiments, the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 2 and ribavirin. Suitably, the patient may be a treatment naïve patient, a treatment experienced patient or an interferon non-responder. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. In some embodiments, the patient is infected with HCV genotype 1b. In some embodiments, the patient is infected with HCV genotype 2 or 3, such as 2a or 2b. In some other embodiments, the patient is infected with HCV genotype 3a. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The treatment duration can be for no more than 12 weeks, preferably no more than 8 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. Therapeutic agent 1 and therapeutic agent 2 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR 16, or SVR 24) after treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 2 can be administered with therapeutic agent 1 in any of the dosages described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, for example, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg. Suitably, ribavirin may be administered in connection with therapeutic agent 1 and therapeutic agent 2 at any combination of the dosages described above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg.

In some embodiments, the present technology features methods for treating patients with HCV infection who are not candidates for interferon treatment. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. Patients who are not candidates for interferon treatment include, but are not limited to, one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon. A non-candidate for interferon treatment can be infected with HCV genotype 1 or 2, for example, genotype 1a or 1b. A non-candidate for interferon treatment can be infected with HCV genotype 2, for example, genotype 2a or 2b. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. In some embodiments, non-candidate for interferon treatment patients can be treated with a combination of at least 2 DAAs without interferon and with ribavirin for a treatment duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The at least two DAAs include at least one HCV protease inhibitor and at least one HCV polymerase inhibitor. Suitably, the at least one HCV protease inhibitor can be therapeutic agent 1 and the at least one HCV polymerase inhibitor can be therapeutic agent 2. Therapeutic agent 1 and therapeutic agent 2 can be administered in therapeutically effective amounts to provide a SVR after a treat-

ment duration of no more than 12 weeks, preferably no more than 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 2 can be administered with therapeutic agent 1 with therapeutic agent 1 administered at any of the dosages described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, for example, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg. Suitably, ribavirin may be administered in connection with therapeutic agent 1 and therapeutic agent 2 at any of the dosages described above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg.

In another aspect, the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 2, therapeutic agent 4 and ribavirin. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks or the duration being 8 weeks. Therapeutic agent 1, therapeutic agent 2, and therapeutic agent 3 can be provided in effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) after a treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 300 mg. Therapeutic agent 2 can be administered with therapeutic agent 1 with therapeutic agent 1 being administered in any of the dosages described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, for example, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg. Therapeutic agent 4 can be provided in combination with therapeutic agent 1 and therapeutic agent 2 in which therapeutic agent 1 and therapeutic agent 2 are administered in any combination of the dosages for therapeutic agent 1 and therapeutic agent 2 described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1 and therapeutic agent 2 in a total daily dose of therapeutic agent 4 of an amount from about 5 mg to about 350 mg, preferably about 5 mg to about 300 mg, more preferably about 25 mg to about 200 mg. The total daily dosage of therapeutic agent 4 can be, but are not limited to, for example, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, or about 100 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. Suitably, ribavirin may be administered in connection with therapeutic agent 1, therapeutic agent 2, and therapeutic agent 4 in which therapeutic agent 1, therapeutic agent 2, and therapeutic agent 4 are administered in any combination of the dosages described above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg. Suitably, in some embodiments, the patient may be a treatment naïve patient, a treatment experienced patient, or an interferon nonresponder.

In some embodiments, the present technology features methods for treating patients with genotype 1, such as genotype 1a or 1b, HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 3 and ribavirin. The treatment duration may be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 3 can be administered in connection with therapeutic agent 1 with therapeutic agent 1 being administered at any of the dosages of described above. Therapeutic agent 3 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 3 can be, but is not limited to, for example, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg. Ribavirin can be administered either at the same time or at a separate time than therapeutic agent 1 and therapeutic agent 3; and therapeutic agent 1 and therapeutic agent 3 can be administered in any of the suitable dosages of therapeutic agent 1 or therapeutic agent 3 recited above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day.

In some embodiments, the present technology features methods for treating patients with genotype 2 or 3, such as

genotype 2a, 2b or 3a, HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 3 and ribavirin. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. Therapeutic agent 1 and therapeutic agent 3 and ribavirin can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16 or SVR24) in a treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 3 can be administered with therapeutic agent 1 with therapeutic agent 1 being administered at any of the dosages described above. Therapeutic agent 3 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 3 can be, but is not limited to, for example, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg. Ribavirin can be administered either at the same time or at a separate time than therapeutic agent 1 and therapeutic agent 3; and therapeutic agent 1 and therapeutic agent 3 can be administered in any combination of dosage of therapeutic agent 1 or therapeutic agent 3 recited above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day.

In some embodiments, the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 3 and ribavirin. Suitably, the patient may be a treatment naïve patient, a treatment experienced patient or an interferon non-responder. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. In some embodiments, the patient is infected with HCV genotype 1b. In some other embodiments, the patient is infected with HCV genotype 2 or 3, such as 2a or 2b. In some other embodiments, the patient is infected with HCV genotype 3a. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 3 can be administered in connection with therapeutic agent 1 with therapeutic agent 1 being administered at any of the dosages described above. Therapeutic agent 3 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 3 can be, but is not limited to, for example, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg. Ribavirin can be administered either at the same time or at a separate time than therapeutic agent 1 and therapeutic agent 3; and therapeutic agent 1 and therapeutic agent 3 can be administered in any combination of the suitable dosages recited above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day.

In some embodiments, the present technology features methods for treating patients with HCV infection who are not candidates for interferon treatment. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 3 and ribavirin. Patients who are not candidates for interferon treatment include, but are not limited to, one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. In some embodiments, the patient is infected with HCV genotype 1b. In some other embodiments, the patient is infected with HCV genotype 2 or 3, such as 2a or 2b. In some other embodiments, the patient is infected with HCV genotype 3a. The treatment according to this aspect of the technology can also be effec-

tive against other HCV genotypes. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably patients who are more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 week, or the duration being 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 3 can be administered with therapeutic agent 1 with therapeutic agent 1 being administered at any of the dosages described above. Therapeutic agent 3 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 3 can be, but is not limited to, for example, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg. Ribavirin can be administered either at the same time or at a separate time than therapeutic agent 1 and therapeutic agent 3; and therapeutic agent 1 and therapeutic agent 3 can be administered in any combination of dosages of therapeutic agent 1 and therapeutic agent 3 recited above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day.

In some embodiments, the present technology features methods for treating patients with HCV genotype 1, such as 1a or 1b, infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 4 and ribavirin. Patients with genotype 1a or 1b infection can be treated with a combination of at least 2 DAAs without interferon in which the at least two DAAs include therapeutic agent 1 and therapeutic agent 4 with ribavirin. Therapeutic agent 1 and therapeutic agent 4 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) in a treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered in connection with therapeutic agent 1 where therapeutic agent 1 is administered in any of the dosages described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1 in a total daily dose of therapeutic agent 4 of from about 25 mg to about 200 mg. The total daily dosage of therapeutic agent 4 can be, but is not limited to, for example, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1 and therapeutic agent 4 are administered once a day. Suitably, ribavirin may be administered in connection with therapeutic agent 1 and therapeutic agent 4 where therapeutic agent 1 and therapeutic agent 4 are administered in any combination of the suitable dosages detailed above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg.

In some embodiments the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 4 and ribavirin. The patients may be treatment naïve patients or treatment experienced patients. The treatment can be administered for a duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The patient can have HCV genotype 1, such as HCV genotype 1a or 1b. In other embodiments, the patient may have HCV genotype 1b. In some embodiments, it is contemplated to treat other HCV genotypes. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered in connection with therapeutic agent 1 in any of the dosages described above. Therapeutic agent 4 can be provided alone or in combination with therapeutic agent 1. The total daily dosage of therapeutic

agent 4 can be, but is not limited to, for example, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1 and therapeutic agent 4 are administered once a day. In some embodiments, therapeutic agent 1 and therapeutic agent 4 are administered with ribavirin. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg.

In some embodiments, the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 4 and ribavirin. The patients may be treatment naïve patients or treatment experienced patients. The treatment can be administered for a duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The patient can have HCV genotype 2 or 3, such as HCV genotype 2a. In some embodiments, the patient may have HCV genotype 2b. In other embodiments the patient may have HCV genotype 3a. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered in connection with therapeutic agent 1 in which therapeutic agent 1 is administered in any of the dosages described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 4 can be, but is not limited to, for example, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1 and therapeutic agent 4 are administered once a day. In some embodiments, therapeutic agent 1 and therapeutic agent 4 are administered with ribavirin. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg.

In some embodiments, the present technology features methods for treating patients with HCV infection who are not candidates for interferon treatment. The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. The combination comprises therapeutic agent 1, therapeutic agent 4 and ribavirin. Patients who are not candidates for interferon treatment include, but are not limited to one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. In some embodiments, the patient is infected with HCV genotype 1b. In some other embodiments, the patient is infected with HCV genotype 2 or 3, such as 2a or 2b. In some other embodiments, the patient is infected with HCV genotype 3a. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. Therapeutic agent 1 and therapeutic agent 4 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16 or SVR24) after treatment of no more than 12 weeks, preferably no more than 8 weeks. The interferon non-responder patients include partial interferon responders and interferon rebound patients. See Guidance for Industry—Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment (FDA, September 2010, draft guidance) for the definitions of naive, partial responder, responder relapser (i.e., rebound), and null responder patients. The interferon non-responder patients also include null responder patients. The treatment can be administered for a duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered with therapeutic agent 1 where therapeutic agent 1 is administered in any of the dosages described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 4 can be, but is not limited to, for example, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240

mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1 and therapeutic agent 4 are administered once a day. Suitably, ribavirin may be administered in connection with therapeutic agent 1 and therapeutic agent 4 where therapeutic agent 1 and therapeutic agent 4 are administered in any combination of suitable dosages as described above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg.

In some embodiments, the present technology features methods for treating patients with HCV infection who are interferon non-responders (e.g., null responders). The methods comprise administering to such a patient a combination of at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon. Interferon nonresponder patients can be treated with a combination of at least 2 DAAs without interferon with ribavirin wherein the two DAAs include therapeutic agent 1 and therapeutic agent 4 with ribavirin. Therapeutic agent 1 and therapeutic agent 4 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16 or SVR24) after treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The interferon non-responder patients include partial interferon responders and interferon rebound patients. The interferon nonresponder patient may have HCV genotype 1, such as 1a. The interferon nonresponder patient may have HCV genotype 1b. The interferon nonresponder patient can have HCV genotype 2 or 3, such as HCV genotype 2a. In some embodiments, the patient may have HCV genotype 2b. In other embodiments the patient may have HCV genotype 3a. In some embodiments, it is contemplated to treat other HCV genotypes. The treatment can be administered for a duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered with therapeutic agent 1 wherein therapeutic agent 1 is administered in any of the dosages described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 4 can be, but is not limited to, for example, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1 and therapeutic agent 4 are administered once a day. Suitably, ribavirin may be administered in connection with therapeutic agent 1 and therapeutic agent 4 wherein therapeutic agent 1 and therapeutic agent 4 are administered in any combination of suitable dosages as described above. Suitable total daily dosages of ribavirin can be based on the weight of the patient and include, but are not limited to, from about 800 mg to about 1200 mg, including, for example, about 1000 mg per day for a patient <75 kg or about 1200 mg per day for a patient ≧75 kg.

Accordingly, in some embodiments, the present technology features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs, together with an effective amount of ribavirin. The treatment lasts no more than 12 weeks, alternatively no more than 11 weeks, alternatively no more than 10 weeks, alternatively no more than 9 weeks, preferably no more than 8 weeks, alternatively no more than 7 weeks, alternatively no more than 6 weeks, alternatively no more than 5 weeks, alternatively no more than 4 weeks, alternatively no more than 3 weeks and does not include administration of any interferon. The DAAs and ribavirin can be administered at the same or different dosing frequencies. The patient being treated can be an HCV-treatment naïve patient or HCV-treatment experienced patient, including, interferon non-responders, interferon partial responders (patients whose HCV RNA levels declined but never became undetectable when treated with interferon), or relapsers (patients who achieved undetectable levels of HCV RNA during therapy but rebound) or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotypes 1 or 2. In some embodiments are preferably genotypes 1a or 1b. In other embodiments, the HCV genotype is 2 or 3. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors.

For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor).

For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. In an example, the combination of two or more DAAs comprises GS-5885 (an NS5A inhibitor), and GS-9451 (a protease inhibitor or an NS3 protease inhibitor). In some examples, GS-5885 is provided in a daily dose from about 3 mg to about 200 mg, alternatively from about 3 mg to about 100 mg, alternatively from about 30 mg to about 90 mg, including, but not limited to, for example, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160

mg, about 170 mg, about 180 mg, about 190 mg, or about 200 mg. GS-9451 can be administered in combination with any of the daily dosages of GS-5885 described above. GS-9451 can be administered in a total daily dose from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, for example, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, or about 500 mg. Suitably examples include total daily dosages of about 30 mg GS-5885 and about 200 mg GS-9451; alternatively about 60 mg GS-5885 and about 200 mg GS-9451; alternatively about 90 mg GS-5885 and about 200 mg GS-9451.

In another instance, the present technology provides the at least two DAAs comprise at least two HCV polymerase inhibitors. In some embodiments, the at least two HCV polymerase inhibitors comprise at least one nucleoside or nucleotide analog polymerase inhibitor. In some embodiments, the at least two HCV polymerase inhibitors comprise at least two nucleoside or nucleotide analog polymerase inhibitors. Suitable nucleotide analog polymerase inhibitors include PSI-7977 (Pharmasset) and PSI-938 (Pharmasset). Suitable daily dosages of the at least one nucleoside or nucleotide analog polymerase inhibitor include from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, for example, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, or about 500 mg. For example, a suitable combination includes a total daily dose of PSI-7977 of about 400 mg and a total daily of PSI-938 of about 300 mg, alternatively a total daily dose of about 200 mg PSI-7977 and a total daily dose of about 300 mg PSI-938. Suitably, ribavirin can be administered with the at least two DAAs, preferably in an amount based on weight of the subject, in a total daily dose of from about 400 mg to about 1400 mg, suitably about 1000 mg or about 1200 mg per day. For example, a suitable ribavirin daily treatment is weight based, for example, 1000 mg/day<75 kg and 1200 mg/day≧75 kg, divided twice daily (BID). In yet another instance, the combination of two or more DAAs comprises at least one HCV protease inhibitor and at least one HCV polymerase inhibitor. In some embodiments, the at least one protease inhibitor is TMC-435 (Medivir) and the at least one polymerase inhibitor is a nucleotide/nucleoside analog polymerase inhibitor, for example PSI-7977. Suitably, the at least one protease inhibitor, e.g. TMC-435, is provided in a total daily dosage from about 25 mg to about 250 mg, alternatively from about 25 mg to about 200 mg, alternatively from about 50 mg to about 200 mg, alternatively from about 75 mg to about 150 mg, for example, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg; and the at least one polymerase inhibitor (e.g. PSI-7977) is provided in a total daily dose from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, for example, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, or about 500 mg. For example, a combination can be a total daily dosage of about 75 mg TMC-435 and about 400 mg PSI-7977, alternatively about 100 mg TMC-435 and about 400 mg PSI-7977, alternatively about 150 mg TMC-435 and about 400 mg PSI-7977, alternatively about 100 mg TMC-435 and about 400 mg PSI-7977, alternatively about 75 mg TMC-435 and about 200 mg PSI-7977, alternatively about 150 mg TMC-435 and about 200 mg PSI-7977, alternatively about 100 mg TMC-435 and about 200 mg PSI-7977, alternatively about 75 mg TMC-435 and about 100 mg PSI-7977, alternatively about 100 mg TMC-435 and about 100 mg PSI-7977, alternatively about 150 mg TMC-435 and about 100 mg PSI-7977, and can include other suitable combinations. Suitably, in some embodiments, ritonavir or a suitable equivalent can be added to the at least two DAAs comprising at least one protease inhibitor, suitably in an amount from about 100 mg to about 400 mg per day, preferably about 100 mg per day. Suitable ribavirin can be administered with the at least two DAAs, preferably in an amount based on weight of the subject, suitably about 1000 mg or about 1200 mg per day. For example, a suitable ribavirin daily treatment is weight based, for example, 1000 mg/day<75 kg and 1200 mg/day≧75 kg, divided twice daily (BID). In alternative embodiments, the at least one protease is BI-201335 (NS3/4A protease inhibitor) and the at least one HCV polymerase inhibitor is a non-nucleoside polymerase inhibitor, e.g. BI-207127. In some examples, the BI-201335 is provided in a total daily dose from about 100 mg to about 400 mg, alternatively from about 120 mg to about 240 mg, including about 100 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 275 mg, about 300 mg, about 320 mg, about 330 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, or about 400 mg; and BI-207127 can be administered in a total daily dose from about 300 mg to about 3600 mg, preferably from about 1200 mg to about 2100 mg, including, but not limited to, for example, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 750 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, about 2100 mg, about 2200 mg, about 2400 mg, about 2500 mg, about 2600 mg, about 2700 mg, about 2800 mg, about 3000 mg, about 3200 mg, about 3400 mg, or about 3600 mg. Suitable examples, include, but are not limited to, a combination of a total daily dose of about 120 mg BI-201335 and about 1200 mg BI-207127, alternatively about 120 mg BI-201335 and about 1500 mg BI-207127, alternatively about 120 mg BI-201335 and about 1800 mg BI-207127, alternatively about 120 mg BI-201335 and about 2100 mg BI-207127, alternatively about 240 mg BI-201335 and about 1200 mg BI-207127, alternatively about 240 mg BI-201335 and about 1500 mg BI-207127, alternatively about 240 mg BI-201335 and about 1800 mg BI-207127, alternatively about 240 mg BI-201335 and about 2100 mg BI-207127. Suitably, in some embodiments, ritonavir or a suitable equivalent can be added to the at least two DAAs comprising at least one protease inhibitor, suitably in an amount of about 100 mg per day. Suitably, in some embodiments, ritonavir or a suitable equivalent can be added to the at least two DAAs comprising at least one protease inhibitor, suitable in an amount from about 100 mg to about 400 mg per day, preferably about 100 mg per day. Suitable ribavirin can be administered with the at least two DAAs, preferably in an amount based on weight of the subject, suitably from about 400 mg to about 1400 mg per day, for example, about 1000 mg or about 1200 mg per day. For example, a suitable ribavirin daily treatment is weight based, for example, from 400 mg to about 1400 mg, preferably about 1000 mg/day<75 kg and 1200 mg/day≧75 kg, divided twice daily (BID). In yet another example, the combination of two or more DAAs comprises telaprevir (VX-950, protease inhibitor) and VX-222 (non-nucleoside polymerase inhibitor). In some examples, the telaprevir is provided in total daily doses from about 1000 mg to about 2500 mg, alternatively from about 2000 mg to about 2500 mg, including, but not limited to, for example, about

1000 mg, about 1200 mg, about 1300 mg, about 1500 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, about 2100 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2400 mg, about 2500 mg. VX-222 can be administered with telaprevir in any combination with the dosage amounts of telaprevir provided above. VX-222 can be provided in a total daily dosage from about 100 mg to about 1000 mg, alternatively from about 200 mg to about 800 mg, including, but not limited to, for example, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg. In some examples, telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 100 mg, alternatively telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 200 mg, alternatively telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 400 mg, alternatively telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 600 mg, alternatively telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 800 mg, alternatively telaprevir can be a total daily dose of about 1500 mg and VX-222 can be a total daily dose of about 200 mg, alternatively telaprevir can be a total daily dose of about 1500 mg and VX-222 can be a total daily dose of about 400 mg, alternatively telaprevir can be a total daily dose of about 1500 mg and VX-222 can be a total daily dose of about 800 mg. Suitably, telaprevir can be administered three times a day (TID), for example 3 times a day with 750 mg per dose. Other suitable daily dosage of telaprevir is 1125 mg twice a day (BID). Suitably, in some embodiments, ritonavir or a suitable equivalent can be added to the at least two DAAs comprising at least one protease inhibitor, suitably in an amount of about 100 mg to about 400 mg per day, preferably about 100 mg per day. Suitable ribavirin can be administered with the at least two DAAs, preferably in an amount based on weight of the subject, from about 400 mg to about 1400 mg, suitably about 1000 mg or about 1200 mg per day. For example, a suitable ribavirin daily treatment is weight based, for example, 1000 mg/day<75 kg and 1200 mg/day≧75 kg, divided twice daily (BID).

In yet another example, the combination of two or more DAAs includes danoprevir (protease inhibitor) and R7128 (nucleoside polymerase inhibitor). In some embodiments, danoprevir can be administered in a total daily dosage from about 100 mg to about 2000 mg, alternatively from about 200 mg to about 1800 mg, alternatively from about 400 mg to about 1800 mg, including, but not limited to, for example, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, and other amounts therebetween. R7128 can be administered in a total daily dose from about 100 mg to about 2000 mg, alternatively from about 200 mg to about 2000 mg, alternatively from about 1000 mg to about 2000 mg, including, but not limited to, for example, about 150 mg, about 200 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, or about 2000 mg. In some examples, the total daily dose of the danoprevir is about 200 mg and the total daily dose of R7128 is about 200 mg, alternatively the total daily doses of the danoprevir is about 400 mg and the total daily dose of R7128 is about 200 mg, alternatively, the total daily dose of the danoprevir is about 1000 mg and the total daily dose of R7128 at about 200 mg, alternatively the total daily dose of the danoprevir is about 1800 mg and the total daily dose of R7128 is about 200 mg, alternatively the total daily dose of the danoprevir is about 2000 mg and the total daily dose of R7128 is about 200 mg, alternatively the total daily dose of the danoprevir is about 400 mg and the total daily dose of R7128 is about 400 mg, alternatively, the total daily dose of the danoprevir is about 1000 mg and the total daily dose of R7128 is about 400 mg, alternatively the total daily dose of the danoprevir is about 2000 mg and the total daily dose of R7128 is about 400 mg, alternatively the total daily dose of the danoprevir is about 1800 mg and the total daily dose of R7128 is about 400 mg, alternatively the total daily dose of the danoprevir is about 400 mg and the total daily dose of R7128 is about 1000 mg, alternatively, the total daily dose of the danoprevir is about 1000 mg and the total daily dose of R7128 is about 1000 mg, alternatively the total daily dose of the danoprevir is about 2000 mg and the total daily dose of R7128 is about 1000 mg, alternatively the total daily dose of the danoprevir is about 1800 mg and the total daily dose of R7128 is about 1000 mg, alternatively the total daily dose of the danoprevir is about 400 mg and the total daily dose of R7128 is about 2000 mg, alternatively, the total daily dose of the danoprevir is about 1000 mg and the total daily dose of R7128 is about 2000 mg, alternatively the total daily dose of the danoprevir is about 2000 mg and the total daily dose of R7128 is about 2000 mg, alternatively the total daily dose of the danoprevir is about 1800 mg and the total daily dose of R7128 is about 2000 mg. In suitable embodiments, danoprevir and R7128 can be administered with ritonavir, suitably in an amount of about 100 mg to about 400 mg per day, preferably about 100 mg per day. Suitable ribavirin can be administered with the at least two DAAs, preferably in an amount based on weight of the subject, from about 400 mg to about 1400 mg, suitably about 1000 mg or about 1200 mg per day. For example, a suitable ribavirin daily treatment is weight based, for example, 1000 mg/day<75 kg and 1200 mg/day≧75 kg, divided twice daily (BID).

In some other instances of the present technology, the combinations of two or more DAAs may be at least one protease inhibitor and at least one NS5A inhibitor. In some examples, the at least one protease inhibitor is an NS3 protease inhibitor. In some embodiments, the at least one protease inhibitor and at least one NS5A inhibitor comprises BMS-650032 (BMS) and BMS-790052 (BMS) respectively. In suitable embodiments, BMS-650032 can be administered in a total daily dose from about 300 mg to about 1500 mg, alternatively from about 500 mg to about 1500 mg, including, but not limited to, for example, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, and about 1500 mg, and BMS-790052 (BMS) can have a total daily dose from about 10 mg to about 200 mg, alternatively from about 50 mg to about 100 mg, including, but not limited to, for example, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, or about 200 mg. In suitable examples, BMS-650032 (BMS) total daily dose is about 1200 mg and BMS-790052 (BMS) total daily dose is about 60 mg, alternatively BMS-650032 (BMS) total daily dose is about 300 mg and BMS-790052 (BMS) total daily dose is about 60 mg. Suitable ribavirin can be administered with the at least two DAAs, preferably in an amount based on weight of the subject, from about 400 mg to about 1400 mg, suitably about 1000 mg or about 1200 mg per day. For example, a suitable

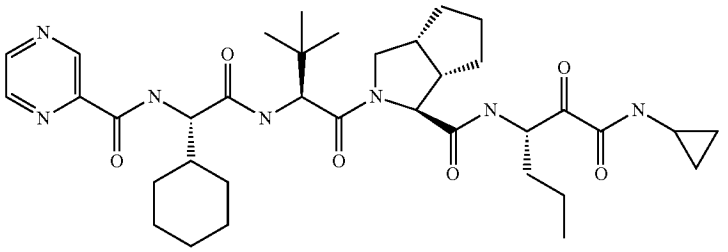
ribavirin daily treatment is weight based, for example, 1000 mg/day<75 kg and 1200 mg/day≧75 kg, divided twice daily (BID).

In some other instances of the present technology, the combinations of two or more DAAs may be at least one nucleoside or nucleotide polymerase inhibitor, at least one protease inhibitor, and at least one NS5A inhibitor. In some examples, the at least one protease inhibitor is an NS3 protease inhibitor. In some embodiments, the at least one nucleoside or nucleotide polymerase inhibitor is INX-189, the at least one protease inhibitor is BMS-650032 (asunaprevir), and the at least one NS5A inhibitor comprises is BMS-790052 (daclatasivr). Such embodiments are especially contemplated for treating a patient infected with HCV genotype 1, such as genotype 1a or 1b (particularly genotype 1a), as well as patients infected with other HCV genotypes, such as genotypes 2 or 3. In suitable embodiments, INX-189 can be administered in a total daily dose from about 5 mg to about 400 mg, alternatively from about 25 mg to about 200 mg, including but not limited to, for example, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. In suitable embodiments, BMS-650032 can be administered in a total daily dose from about 300 mg to about 1500 mg, alternatively from about 500 mg to about 1500 mg, including, but not limited to, for example, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, and about 1500 mg, and BMS-790052 (BMS) can have a total daily dose from about 10 mg to about 200 mg, alternatively from about 50 mg to about 100 mg, including, but not limited to, for example, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, or about 200 mg. In suitable examples, BMS-650032 (BMS) total daily dose is about 1200 mg and BMS-790052 (BMS) total daily dose is about 60 mg, alternatively BMS-650032 (BMS) total daily dose is about 300 mg and BMS-790052 (BMS) total daily dose is about 60 mg. Suitable ribavirin can be administered with the at least two DAAs, preferably in an amount based on weight of the subject, from about 400 mg to about 1400 mg, suitably about 1000 mg or about 1200 mg per day. For example, a suitable ribavirin daily treatment is weight based, for example, 1000 mg/day<75 kg and 1200 mg/day≧75 kg, divided twice daily (BID).

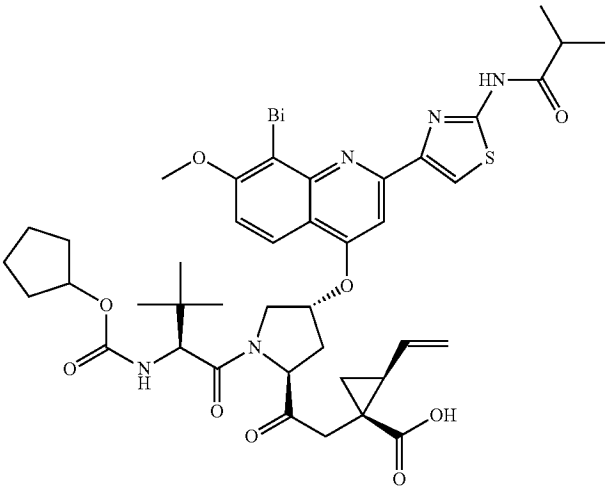
For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In an example, the combination of two or more DAAs comprises GS-5885 (an NS5A inhibitor), GS-9190 (tegobuvir, a non-nucleoside polymerase inhibitor), and GS-9451 (a protease inhibitor or a NS3 protease inhibitor). In some examples, GS-5885 is provided in a daily dose from about 3 mg to about 200 mg, alternatively from about 3 mg to about 100 mg, alternatively from about 30 mg to about 90 mg, including, but not limited to, for example, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, or about 200 mg, and GS-9190 is provided in a daily dose from about 10 mg to about 100 mg, alternatively from about 30 mg to about 90 mg, including, but not limited to, for example, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg; and GS-9451 can be administered in a daily dose from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, or about 500 mg. Suitably examples include about daily amounts of about 30 mg GS-5885, about 60 mg GS-9190 and about 200 mg GS-9451; alternatively about 60 mg GS-5885, about 60 mg GS-9190, and about 200 mg GS-9451; alternatively about 90 mg GS-5885, about 60 mg GS-9190, and about 200 mg GS-9451. In some embodiments the GS-9190, GS-9451, and GS-5885 is administered with ritonavir or a suitable equivalent, suitably in an amount of about 100 mg to about 400 mg per day, preferably about 100 mg per day. Suitable ribavirin can be administered with the at least two DAAs, preferably in an amount based on weight of the subject, from 400 mg to about 1400 mg, suitably about 1000 mg or about 1200 mg per day. For example, a suitable ribavirin daily treatment is weight based, for example, 1000 mg/day<75 kg and 1200 mg/day≧75 kg, divided twice daily (BID). For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor.

In another embodiment, the present technology provides interferon-free treatment comprising administering daily two DAAs with ribavirin, where the two DAAs include a HCV polymerase inhibitor, for example PSI-7977 and a NS5A inhibitor, for example BMS-790052 for a duration of no more than eleven weeks, preferably no more than eight weeks. PSI-7977 and BMS-790052 are administered in an effective amount to provide an SVR (for example, an SVR8, SVR12, SVR16, or SVR24) with a treatment duration of no more than eleven weeks, no more than ten weeks, no more than nine weeks, no more than eight weeks, no more than seven weeks, no more than six weeks, no more than five weeks, no more than four weeks or no more than three weeks. The patients can be treatment naïve patients or treatment experienced patients. In some embodiments, the patients can have HCV genotype 1, such as 1a or 1b. In some embodiments, the patients can have genotype 2 or 3, such as 2a, 2b or 3a. PSI-7977 can be provided in a total daily dose of from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, for example, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg. BMS-790052 can be administered in combination with PSI-7977 at any daily dose of PSI-7977 provided above. BMS-790052 (BMS) can have a total daily dose of from about 10 mg to about 200 mg, alternatively from about 50 mg to about 100 mg, including, but not limited to, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, or about 200 mg. In one suitable example, PSI-7977 is administered in a total daily dose of 400 mg and BMS-790052 is administered in a total daily dose of 60 mg.

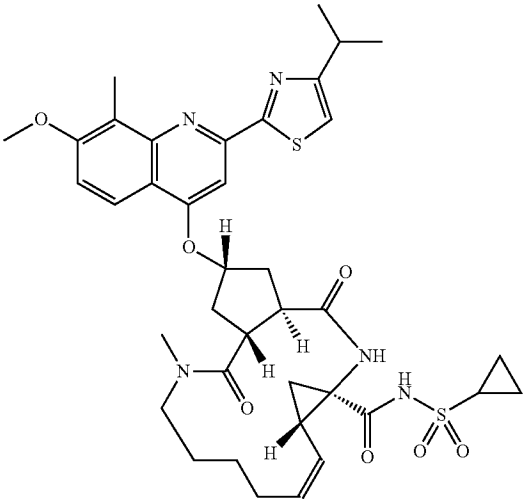
The chemical structures of some of these HCV inhibitors as reported by numerous sources are provided below:



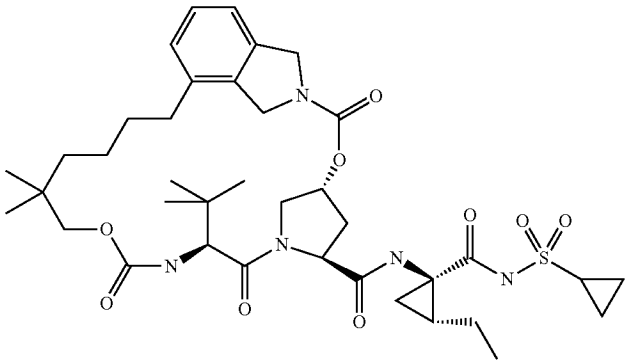
Telaprevir



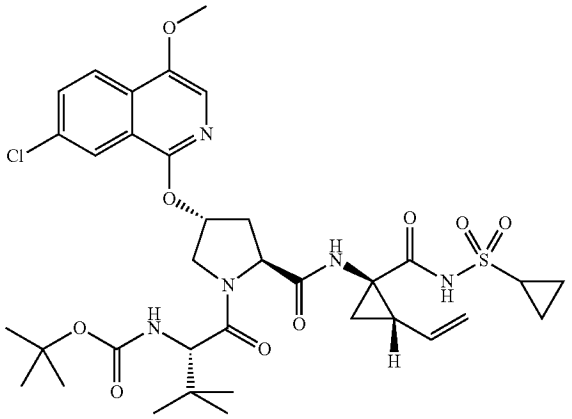
BI-201335



TMC-435 (TMC-435350)

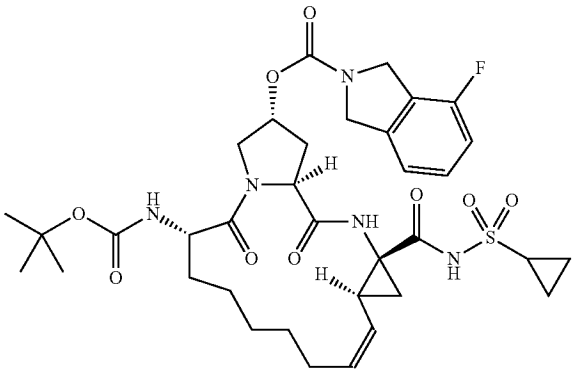


Vaniprevir, MK-7009

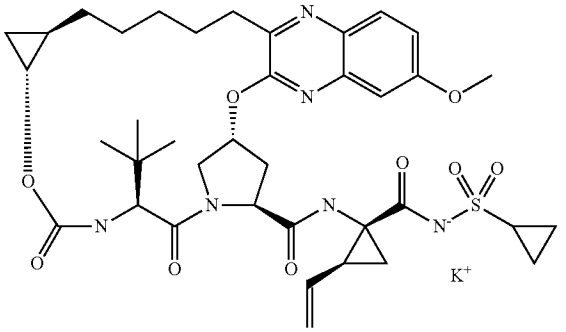


BMS-650032 (Asunaprevir)

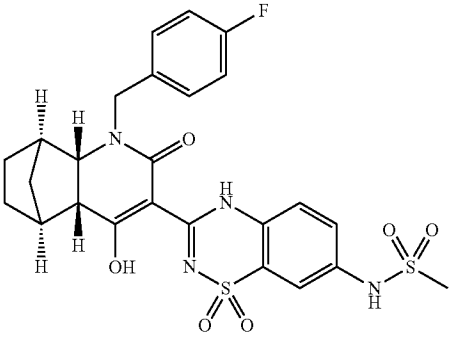
-continued



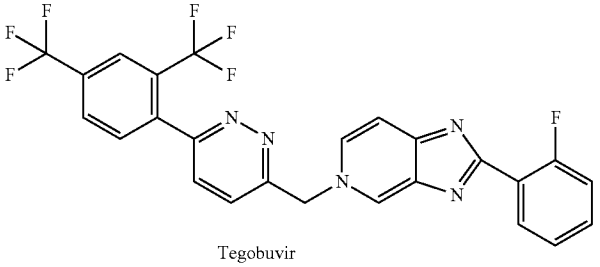
danoprevir



MK-5172

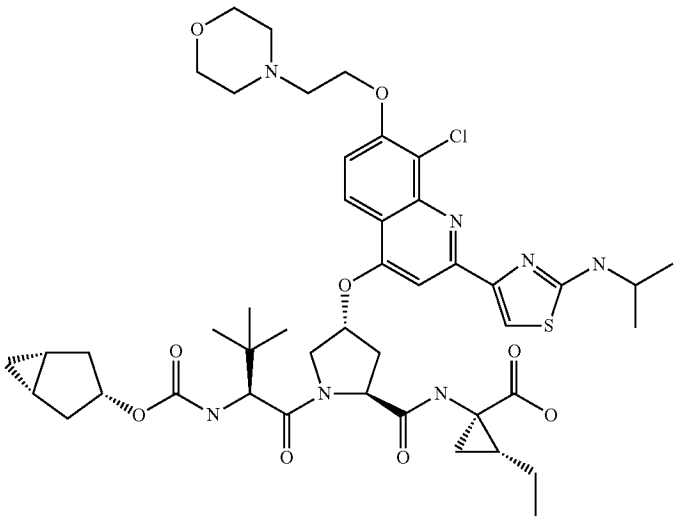


ANA-598 (Setrobuvir)



Tegobuvir

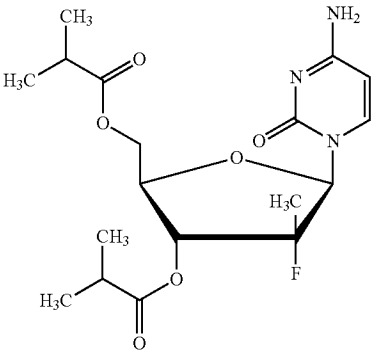
GS-333126 (GS-9190 or tegobuvir)



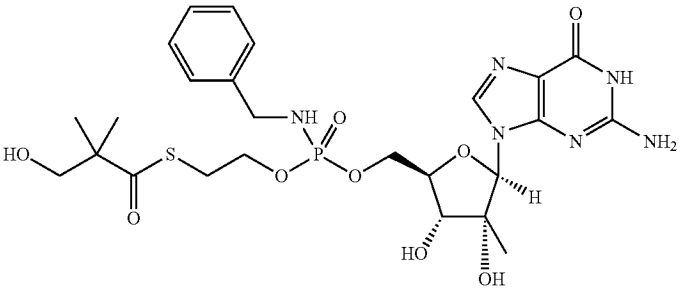
GS-9451

GS-9451

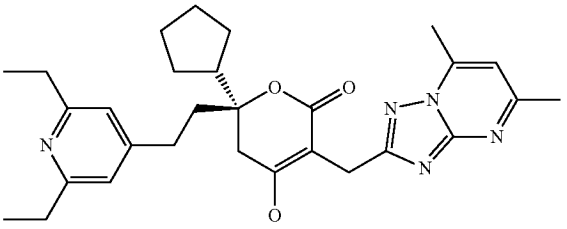
-continued



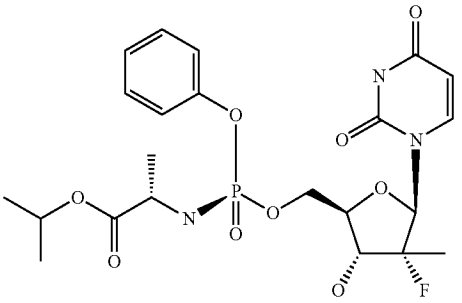
Mericitabine (R-4048 or RG7128 or R7128)



IDX-184

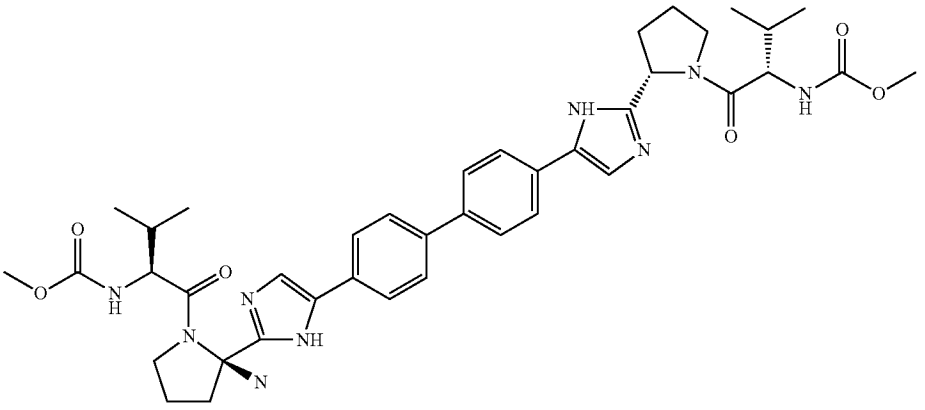


filibuvir (PF-00868554)



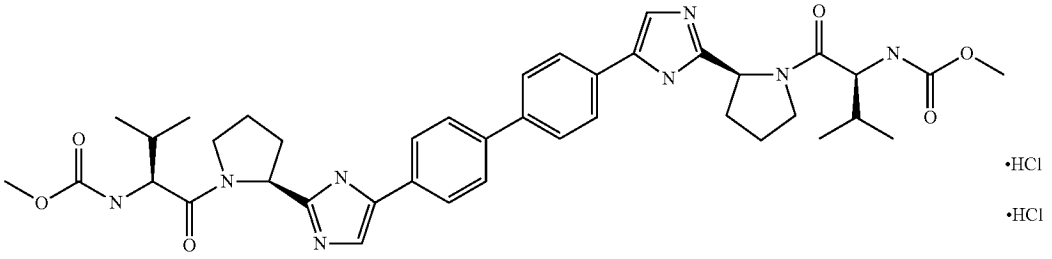
PSI-7977

PSI-7977 (GS-7977)



BMS-790052 (daclatasvir)

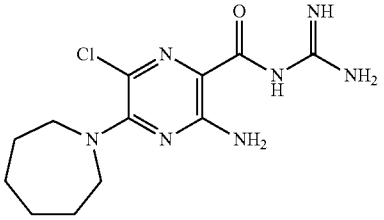
-continued



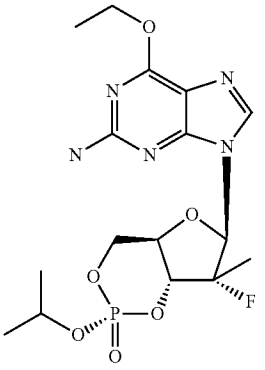
•HCl

•HCl

Daclatasvir dihydrochloride

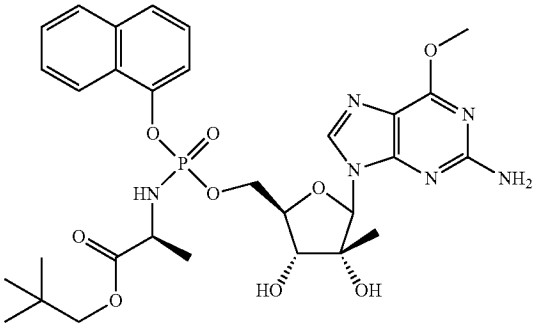


BIT-225

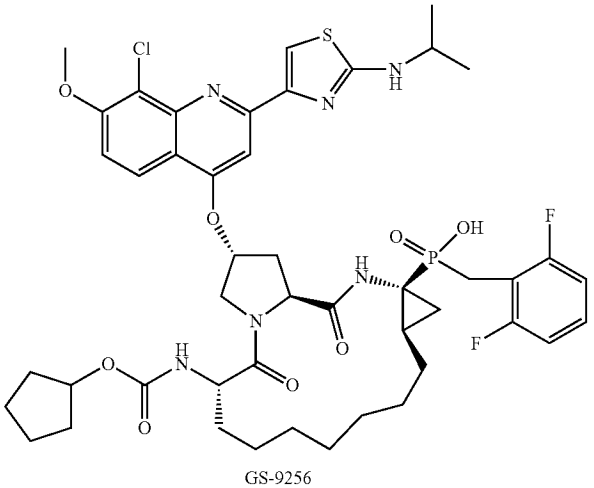


PSI-352938

PSI-352938



INX-189



GS-9256

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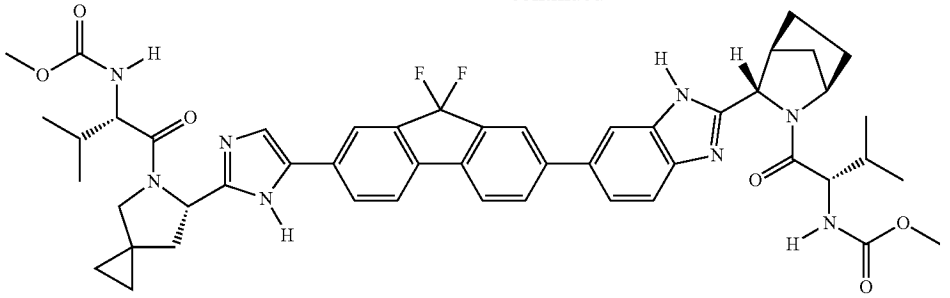
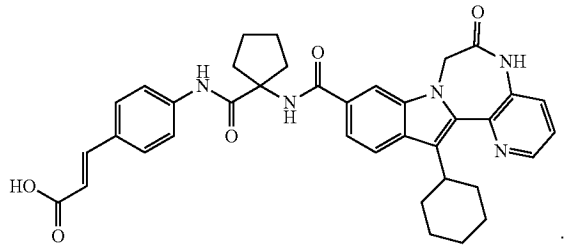


GS-5885

It has also been reported that BMS-791325 has the following structure:



See also publications at http://www1.eas1.eu/eas12011/program/Posters/Abstract680.htm; and http://clinicaltrials.gov/show/NCT00664625. For GS-5885, see publications at http://www.natap.org/2011/EASL/EASL_68.htm; http://www1.eas1.eu/eas12011/program/Posters/Abstract1097.htm; and http://clinicaltrials.gov/ct2/show/NCT01353248.

Any HCV inhibitor or DAA described herein encompasses its suitable salt forms when it is used in therapeutic treatments or pharmaceutical formulations.

The following table lists non-limiting examples of the treatment regimens of the present technology. In each treatment regimen, the at least two DAA with or without ritonavir, are administered daily to an HCV patient under such treatment. Each treatment is interferon-free. Administration of ribavirin is included in each regimen. Each treatment regimen may also optionally comprise administering one or more other additional DAAs to the patient. The duration of each treatment regimen may last, for example and without limitation, no more than 12 weeks, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, no more than 8 weeks, alternatively no more than 7 weeks, alternatively no more than 6 weeks, alternatively no more than 5 weeks, alternatively no more than 4 weeks and may depend on the patient's response. In any given regimen described below, the drugs can be, for example and without limitation, co-formulated in a single solid dosage form when each has the same dosing frequency.

For instance, two or more drugs in a regimen can be co-formulated in amorphous forms or molecularly dispersed in a matrix comprising a water-soluble polymer and optionally a surfactant; for another instance, therapeutic agent 1 and ritonavir (RTV) are formulated in an amorphous form or molecularly dispersed in a matrix comprising a water-soluble polymer and optionally a surfactant, and therapeutic agent 3 is combined with amorphous Compound 1 and RTV in a single solid dosage form. For yet another instance, Compound 1 and RTV are formulated in a different dosage form than that of therapeutic agent 3.

TABLE 1

Non-Limiting Examples of Interferon-free Treatment Regimens with two or more DAAs (with ribavirin** and with or without ritonavir)

Regimen	Drugs Used in Treatment	Suitable total daily dosages
1	Therapeutic Agent 1*+	150 to 250 mg (pref. 150, 200, 250 mg)
	Therapeutic Agent 4	5 mg to 300 mg (pref. 25 mg)
2	Therapeutic Agent 1*+	150 to 250 mg (pref. 150, 200, 250 mg)
	Therapeutic Agent 4+	5 mg to 300 mg (pref. 25 to 200 mg)
	Therapeutic Agent 2	300 to 1800 mg (pref. 400 mg or 800 mg)
3	Therapeutic Agent 1*+	150-250 mg (pref. 150 mg or 250 mg)
	Therapeutic Agent 3+	50 mg-1000 mg (pref. 400 mg)
	Therapeutic Agent 4	5 mg-300 mg (pref. 25 mg-200 mg, more pref. 25 mg)
4	Therapeutic Agent 1*+	150-250 mg (150 mg, 200 mg or 250 mg)
	Therapeutic Agent 2	300-1800 mg (pref. 200 mg, 800 mg)
5	Therapeutic Agent 1*+	50 mg to 250 mg (pref. 50 mg or 250 mg)
	Therapeutic Agent 3	50 mg to 1000 mg (pref. 400 mg to 800 mg)
6	PSI-7977+	100 mg to 500 mg (pref. 200, 400 mg)
	PSI-938	100 mg to 500 mg (pref. 300 mg)
7	BMS-790052+	10 mg to 200 mg (pref. 60 mg)
	BMS-650032	300 mg to 1500 mg (pref. 1200 mg)
8	GS-5885+	3 mg to 200 mg (pref. 30 mg to 90 mg)
	GS-9190+	30 mg to 90 mg (pref. 60 mg)
	GS-9451	100 mg to 500 mg (pref. 200 mg)
9	GS-5885+	3 mg to 200 mg (pref. 30 to 90 mg)
	GS-9451	100 mg to 500 mg (pref. 200 mg)
10	BI-201335+	100 mg to 400 mg (pref. 120 mg or 240 mg)
	BI-207127	300 mg to 3600 mg (pref. 1200 mg to 2100 mg)
11	PSI-7977+	100 mg to 500 mg (pref. 400 mg)
	TMC-435	25 mg to 200 mg (pref. 75 mg to 150 mg)
12	telaprevir+	1000 mg to 2500 mg (pref. 2250 mg)
	VX-222	200 mg to 800 mg
13	Danoprevir*+	100 mg to 2000 mg (pref. 200 mg or 400 mg)
	R7128	100 mg to 2000 mg (pref. 200 mg, 400 mg, 1000 mg or 2000 mg)
14	Danoprevir+	100 mg to 2000 mg (pref. 800 mg or 1000 mg, or 1800 mg or 2000 mg)
	R7128	100 mg to 2000 mg (pref. 200 mg, 400 mg, 1000 mg or 2000 mg)
15	PSI-7977+	100 mg to 500 mg (pref. 400 mg)
	daclatasvir (BMS-790052)	10-200 mg (pref. 60 mg)

TABLE 1-continued

Non-Limiting Examples of Interferon-free Treatment Regimens with two or more DAAs (with ribavirin** and with or without ritonavir)

Regimen	Drugs Used in Treatment	Suitable total daily dosages
16	PSI-7977+	100 mg to 2000 mg (pref. 1800 mg or 2000 mg)
	asunaprevir (BMS-650032)	300-1500 mg (pref. 1200 mg)
17	PSI-7977+	100 mg to 500 mg (pref. 400 mg)
	daclatasvir (BMS-790052)	10-200 mg (pref. 60 mg)
	asunaprevir (BMS-650032)	300-1500 mg (pref. 1200 mg)

*ritonavir or a suitable equivalent can be added to any one of these treatments as described and may be added to any of these treatments at a daily total dosage as described in the present technology; preferably ritonavir is co-formulated with therapeutic agent 1 or danoprevir; the dose of ritonavir preferably is 100 mg. Pref. = preferred
**in each regimen, ribavirin preferably is used in a weight based amount from 400 mg to 1400 mg (pref. 1000 to 1200 mg)

Additional non-limiting examples of interferon-free treatment regimens with two or more DAAs, with ribavirin and with or without ritonavir or a suitable equivalent, including the following: (a) Therapeutic Agent 1 at a total daily dose of 5 mg to 150 mg (pref. 5 mg, 25 mg, 50 mg, or 100 mg) with ritonavir or a suitable equivalent, and Therapeutic Agent 4 at a total daily dose of 5 mg to 150 mg (pref. 5 mg, 25 mg, 50 mg, or 100 mg); (b) Therapeutic Agent 1 at a total daily dose of 5 mg to 200 mg (pref. 5 mg, 25 mg, 50 mg, 100 mg) with ritonavir or a suitable equivalent, Therapeutic Agent 4 at a total daily dose of 5 mg to 200 mg (pref. 25 mg or 100 mg), and Therapeutic Agent 2 at a total daily dose of 200 mg to 800 mg (pref. 400 mg or 800 mg); (c) Therapeutic Agent 1 at a total daily dose of 5 mg to 150 mg (pref. 5 mg, 25 mg, 50 mg, or 100 mg) with ritonavir or a suitable equivalent, Therapeutic Agent 3 at a total daily dose of 100 mg to 600 mg (pref. 400 mg), and Therapeutic Agent 4 at a total daily dose of 5 mg to 300 mg (pref. 25 mg to 200 mg, more pref. 25 mg); (d) Therapeutic Agent 1 at a total daily dose of 5 mg to 150 mg (pref. 5 mg, 25 mg, 50 mg, 100 mg) with ritonavir or a suitable equivalent, and Therapeutic Agent 2 at a total daily dose of 200-800 mg; (e) GS-5885 at a total daily dose of 3-200 mg (pref. 30-90 mg). GS-9190 at a total daily dose of 30-90 mg (pref. 60 mg), and GS-9451 at a total daily dose of 100-500 mg (pref. 200 mg); (f) GS-5885 at a total daily dose of 3 mg to 200 mg (pref. 30 mg, 60 mg, or 90 mg), and GS-9451 at a total daily dose of 100 mg to 500 mg (pref. 200 mg); (g) BI-201335 at a total daily dose of 100 mg to 400 mg (pref. 120 mg, 240 mg), and BI-207127 at a total daily dose of 300 mg to 3600 mg (pref. 1200 or 1500 mg, 1800 mg or 2100 mg); (h) PSI-7977 at a total daily dose of 100 mg to-500 mg (pref. 100, 200 mg), and TMC-435 at a total daily dose of 25 mg to 200 mg (pref. 75 mg, 100 mg, or 150 mg); (i) telaprevir at a total daily dose of 1000 mg to 2500 mg (pref. 1500 mg or 2250 mg), and VX-222 at a total daily dose of 100 mg to 800 mg (pref. 100 mg, 200 mg, 400 mg, 600 mg or 800 mg); (j) INX-189 at a total daily dose of 5 mg to 400 mg (pref. 50 mg, 100 mg or 200 mg), and daclatasvir (BMS-790052) at a total daily dose of 10 mg to 200 mg (pref. 60 mg); (k) INX-189 at a total daily dose of 5 mg to 400 mg (pref. 50 mg, 100 mg or 200 mg), and asunaprevir (BMS-650032) at a total daily dose of 300 mg to 1500 mg (pref. 1200 mg); and (l) INX-189 at a total daily dose of 5 mg to 400 mg (pref. 50 mg, 100 mg or 200 mg), daclatasvir (BMS-790052) at a total daily dose of 10 mg to 200 mg (pref. 60 mg), and asunaprevir (BMS-650032) at a total daily dose of 300 mg to 1500 mg (pref. 1200 mg). In any of these examples, ritonavir or a suitable equivalent can be added to any one of these treatments as described and may be added to any of these treatments at a daily total dosage as described in the present technology; preferably ritonavir is co-formulated with therapeutic agent 1 or danoprevir; the dose of ritonavir preferably is 100 mg. In these examples, ribavirin preferably is used in a weight based amount from 400 mg to 1400 mg (pref. 1000 to 1200 mg).

The treatments of the present technology may be effective in treating HCV infection against HCV genotypes 1, 2, 3, 4, 5, 6, including subgenotypes, such as 1a, 1b, 2a, and 3a.

In general and depending on patients' conditions, the total daily dose of the DAAs of the present technology may be administered (either as a single or divided dose) in amounts from about 0.001 mg/kg to about 200 mg/kg, or from about 0.001 mg/kg to about 30 mg/kg, or from about 0.001 mg/kg to about 30 mg/kg, or from about 0.01 mg/kg, to about 10 mg/kg (i.e. mg of the compound or salt per kg body weight), and include any amounts or ranges there between, including, but not limited to increments of 0.001 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.05 mg/kg, and multiple factors thereof (e.g. 0.25×, 0.5×, 1×, 2×, 3×, 5×, 10×, 100×, etc.). Suitable dosages of the DAAs of the present technology include, but are not limited to, from about 25 mg to about 2000 mg, from about 25 mg to about 1500 mg, from about 25 mg to about 1600 mg, from about 25 mg to about 1000 mg, from about 25 mg to about 800 mg, from about 25 mg to about 500 mg, from about 25 mg to about 250 mg, from about 50 mg to about 2000 mg, from about 50 mg to about 1500 mg, from about 50 mg to about 1600 mg, from about 50 mg to about 1000 mg, from about 50 mg to about 800 mg, from about 50 mg to about 500 mg, from about 50 mg to about 250 mg, and include, but are not limited to, for example, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 80 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 165 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 250 mg, and includes any increments there between, including increments of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 10 mg, about 15 mg, about 20 mg, about 25, and multiples thereof (e.g. 0.25×, 0.5×, 1×, 2×, 3×, 5×, 10×, 100×, etc.). It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the disease undergoing therapy.

The cytochrome P-450 inhibitor may be administered in any suitable amount such as, for example, in doses of from about 0.3 mg/kg to about 2 mg/kg or from about 0.6 mg/kg to about 1.5 mg/kg. As non-limiting examples, the cytochrome P-450 inhibitor may be administered in a total daily dose amount of from about 25 mg to about 300 mg, or from about 50 mg to about 250 mg, or from about 100 mg to about 200 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose of about 100 mg to about 400 mg, preferably about 100 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 25 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 50 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 75 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 100 mg. In some embodiments, the

cytochrome P-450 inhibitor is administered in a total daily dose amount of about 125 mg.

The one or more DAAs and ribavirin can be administered, for example and without limitation, concurrently or sequentially, and at the same or different frequencies. For instance, For example, one DAA can be administered immediately before or after the administration of another DAA. A short delay or time gap may exist between the administration of one DAA and that of another DAA. The frequency of administration may also be different. For example, a first DAA may be administered once a day and a second DAA may be administered twice or three times a day. For example, a first DAA with or without ritonavir may be administered once daily, and a second DAA may be administered twice daily.

The DAAs of the present technology can be co-formulated in a single dosage form. Non-limiting examples of suitable dosage forms include liquid or solid dosage forms. For example, a dosage form of Compound 1 as a solid dosage form is described in U.S. Patent Application Publication No. 2011/0312973, filed Mar. 8, 2011 and entitled "Solid Compositions", the entire content of which is incorporated herein by reference. More preferably, the dosage form is a solid dosage form in which at least one of the DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. The other DAAs can also be in an amorphous form or molecularly dispersed in the matrix, or formulated in different form(s) (e.g., in a crystalline form).

The DAAs of the present technology can be formulated in different dosage forms. It will be understood that the total daily dosage of the compounds and compositions to be administered will be decided by the attending physician within the scope of sound medical judgment.

In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 150 mg once a day (QD), therapeutic agent 2 at a dose of 400 mg or 800 mg twice a day (BID), ritonavir at a dose of 100 mg once a day (QD), and an effective amount of ribavirin (for example, 1000 mg or 1200 mg, or an amount based on the weight of the subject) QD, for 12 weeks. At the end of treatment, the subject has no detectable virus.

In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 50 mg QD, Therapeutic agent 2 at a dose of 400 mg or 800 mg BID, ritonavir at a dose of 100 mg QD, and an effective amount of ribavirin (for example, 1000 mg or 1200 mg, or an amount based on the weight of the subject) QD, for 12 weeks. At the end of treatment, the subject has no detectable virus.

In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 250 mg QD, Therapeutic agent 2 at a dose of 400 mg BID, ritonavir at a dose of 100 mg QD, and an effective amount of ribavirin (for example, 1000 mg or 1200 mg, or an amount based on the weight of the subject) QD, for 12 weeks. At the end of treatment, the subject has no detectable virus.

In another embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 150 mg QD, Therapeutic agent 2 at a dose of 400 mg BID, ritonavir at a dose of 100 mg QD, and an effective amount of ribavirin (for example, 1000 mg or 1200 mg, or an amount based on the weight of the subject) QD, for 12 weeks. At the end of treatment, the subject has no detectable virus.

In yet another embodiment, a method for treating a peginterferon+ribavirin (P/RBV) non-responder comprises administering Therapeutic agent 1 at a dose of 150 mg QD, Therapeutic agent 2 at a dose of 400 mg BID, ritonavir at a dose of 100 mg QD, and an effective amount of ribavirin (for example, 1000 mg or 1200 mg, or an amount based on the weight of the subject) QD, for 12 weeks. At the end of treatment, the subject has no detectable virus.

In yet another embodiment, a method for treating a peginterferon+ribavirin (P/RBV) non-responder comprises administering Therapeutic agent 1 at a dose of 50 mg QD, Therapeutic agent 2 at a dose of 400 mg BID, ritonavir at a dose of 100 mg QD, and an effective amount of ribavirin (for example, 1000 mg or 1200 mg, or an amount based on the weight of the subject) QD, for 12 weeks. At the end of treatment, the subject has no detectable virus.

In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a total daily dose of 150 mg QD, Therapeutic agent 3 at a total daily dose of 400 mg QD, ritonavir at a dose of 100 mg QD, and an effective amount of ribavirin (for example, 1000 mg or 1200 mg, or an amount based on the weight of the subject) QD, for 12 weeks. At the end of treatment, the subject has no detectable virus.

In another embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a total daily dose of 100 mg or 200 mg QD, Therapeutic agent 4 at a total daily dose of 25 mg QD, ritonavir at a dose of 100 mg QD, and an effective amount of ribavirin (for example, 1000 mg or 1200 mg, or an amount based on the weight of the subject) QD, for 12 weeks. At the end of treatment, the subject has no detectable virus.

In yet another embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a total daily dose of 100 mg or 150 mg QD, Therapeutic agent 2 at a total daily dose of 400 mg BID, Therapeutic agent 4 at a total daily dose of 25 mg QD, ritonavir at a dose of 100 mg QD, and an effective amount of ribavirin (for example, 1000 mg or 1200 mg, or an amount based on the weight of the subject) QD, for 12 weeks. At the end of treatment, the subject has no detectable virus.

It should be understood that the above-described embodiments and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

Example 1

Use of 2-DAA Combination with Ribavirin (RBV) to Treat Treatment-Naïve Subjects Infected with HCV Genotype 1

Previously untreated subjects having HCV infection were treated with a protease inhibitor (in combination with ritonavir), a polymerase inhibitor, and ribavirin. The treatment was without interferon.

Subjects included 11 treatment naïve, non-cirrhotic HCV genotype 1-infected subjects between the ages of 18 and 65.

All subjected had IL28B CC genotype. All subjects completed 12 weeks of therapy with Compound 1 and ritonavir (Compound 1/r) dosed in combination with Compound 3 and ribavirin (RBV). Compound 1 (150 mg once daily (QD)) was dosed with 100 mg QD ritonavir, 400 mg QD Compound 3, and weight-based amounts of RBV (1,000-1,200 mg/day dosed twice daily) in treatment naïve subjects infected with genotype (GT) 1 HCV.

HCV RNA levels were measured by TaqMan assay. Five of the eleven subjects had hepatitis C ribonucleic acid (HCV RNA) <25 IU/mL (i.e., below the limit of quantification) at 2 weeks. Another five subjects had undetectable levels of HCV RNA at 2 weeks. At week 3, three of the eleven subjects had HCV RNA levels of less than 25 IU/mL, and eight subjects had undetectable levels of HCV RNA. Ten of the eleven subjects had undetectable levels of HCV RNA at 4 weeks, and one subject had an HCV RNA level of less than 25 IU/mL. All eleven subjects had undetectable levels of HCV RNA at 5 weeks. HCV RNA levels remained undetectable in all subjects at week 6, 7, 8, 9, 10, 11 and 12. All subjects had undetectable levels of HCV RNA at post-treatment weeks 2 and 4. At post-treatment weeks 8 and 12, a single subject had detectable HCV RNA (breakthrough), and the remaining 10 subjects did not have any detectable level of HCV RNA. These remaining ten subjects were further tested at post-treatment weeks 16 and 24, and all of them had undetectable levels of HCV RNA at both timepoints. One of the remaining ten subjects unexpectedly showed detectable HCV RNA at post-treatment week 36.

Example 2A

Use of 2-DAA Combination with Ribavirin to Treat Treatment-Naïve or Non-Responder Subjects Infected with HCV Genotype 1

Group 1. Previously untreated subjects having HCV infection were treated with a protease inhibitor (in combination with ritonavir), a polymerase inhibitor, and ribavirin. The treatment was without interferon.

Subjects included 19 treatment naïve subjects between the ages of 18 and 65. One subject discontinued the study at week 3. All of the remaining 18 subjects completed 12 weeks of therapy with Compound 1/r dosed in combination with Compound 2 and RBV. Compound 1 (250 mg QD) was dosed with 100 mg QD ritonavir, 400 mg BID Compound 2, and RBV in treatment naïve subjects infected with GT1 HCV.

Group 2. Previously untreated subjects having HCV infection were treated with a protease inhibitor (in combination with ritonavir), a polymerase inhibitor, and ribavirin. The treatment was without interferon.

Subjects included 14 treatment naïve subjects between the ages of 18 and 65. One subject discontinued the study at week 1. Therefore, a total of 13 subjects were under study. All of the thirteen subjects completed 12 weeks of therapy with Compound 1/r dosed in combination with Compound 2 and RBV. Compound 1 (150 mg QD) was dosed with 100 mg QD ritonavir, 400 mg BID Compound 2, and RBV in treatment naïve subjects infected with GT1 HCV.

Group 3. Peginterferon+ribavirin (P/RBV) non-responders were treated with a protease inhibitor (in combination with ritonavir), a polymerase inhibitor, and ribavirin. The treatment was without interferon.

Subjects included 17 P/RBV non-responders between the ages of 18 and 65. Subjects were treated with Compound 1/r dosed in combination with Compound 2 and RBV for 12 weeks. Compound 1 (150 mg QD) was dosed with 100 mg QD ritonavir, 400 mg BID Compound 2, and RBV in P/RBV non-responders infected with GT1 HCV. During the treatment, four patients had breakthroughs and discontinued the study before week 7.

The baseline characteristics of the patients are shown in the table below.

TABLE 2

	Group 1	Group 2	Group 3
Genotype (1a/1b)	17/2	11/3	16/1
IL28B:			
CC	10	5	0
CT	7	7	11
TT	2	2	5
Undetermined	0	0	1
Median baseline HCV RNA (log IU/mL)	6.4 [4.1-7.2]	6.9 [3.1-7.5]	6.9 [6.0-7.8]

Results from Group 1. Ten of the nineteen subjects had HCV RNA<25 IU/mL at 2 weeks. Another eight had undetectable levels of HCV RNA at 2 weeks. At week 3, one subject discontinued, four of the remaining 18 subjects had HCV RNA levels of less than 25 IU/mL, and fourteen of the remaining 18 subjects had undetectable levels of HCV RNA. At week 4, seventeen of the remaining 18 subjects had undetectable levels of HCV RNA; one subject had HCV RNA<25 IU/mL. At week 5, all of the remaining 18 subjects had undetectable levels of HCV RNA. At week 6, seventeen of the remaining 18 subjects had undetectable levels of HCV RNA, and one subject had HCV RNA<25 IU/mL. At weeks 7, 8, 9, 10, 11 and 12, all of the remaining 18 subjects had undetectable levels of HCV RNA (one subject was not tested at week 12). At post-treatment weeks 2, 4, 8, and 12 all of the remaining 18 subjects (including the one who was not tested at week 12 during treatment) had undetectable levels of HCV RNA. At post-treatment week 24, seventeen of the remaining 18 subjects were tested, and all of the seventeen subjects tested had undetectable levels of HCV RNA. At post-treatment week 24, all of the remaining 18 subjects were tested and found no detectable levels of HCV RNA.

Results from Group 2. Of the thirteen subjects tested, six had HCV RNA<25 IU/mL at 2 weeks. Another six subjects had undetectable levels of HCV RNA at 2 weeks. At week 3, two subjects had HCV RNA levels of less than 25 IU/mL, and ten subjects had undetectable levels of HCV RNA. Eleven of the thirteen subjects had undetectable levels of HCV RNA at 4 weeks and two had HCV RNA<25 IU/mL. At weeks 5, 6, 7, 8, 9 and 10, all thirteen subjects that were tested had undetectable levels of HCV RNA. One subject had detectable levels of HCV RNA at week 11 (the remaining 12 subjects had undetectable levels of HCV RNA at week 11), but HCV RNA levels in that subject, as well as all other subjects, were undetectable at week 12. At post-treatment weeks 2, 4, 8 and 12, all thirteen subjects tested (including the one who had detectable levels of HCV RNA at week 11 during treatment) had undetectable levels of HCV RNA. At post-treatment weeks 24, twelve of the thirteen subjects were tested and found no detectable levels of HCV RNA.

Results from Group 3. Seven of the seventeen subjects tested had HCV RNA<25 IU/mL at 2 weeks. Another seven subjects had undetectable levels of HCV RNA at 2 weeks. Three subjects had detectable levels of HCV RNA at 2 weeks. At week 3, three subjects had HCV RNA levels of less than 25 IU/mL, twelve subjects had undetectable levels of HCV

RNA, and two subjects had detectable levels of HCV RNA. At week 4, two subjects had HCV RNA levels of less than 25 IU/mL, thirteen subjects had undetectable levels of HCV RNA, and two subjects had detectable levels of HCV RNA. Sixteen subjects were tested at 5 weeks; thirteen subjects had undetectable levels of HCV RNA and three subjects had detectable levels of HCV RNA. Fifteen subjects were tested at 6 weeks; twelve subjects had undetectable levels of HCV RNA and three subjects had detectable levels of HCV RNA. All thirteen subjects that were tested at 7 weeks had undetectable levels of HCV RNA. Twelve of the thirteen subjects that were tested at 8 weeks had undetectable levels of HCV RNA; one subject had HCV RNA levels of less than 25 IU/mL. All ten subjects that were tested at 9 weeks had undetectable levels of HCV RNA. Twelve of the thirteen subjects that were tested at 9 weeks had undetectable levels of HCV RNA; one subject had detectable levels of HCV RNA. Twelve of the thirteen subjects that were tested at 10 weeks had undetectable levels of HCV RNA; one subject had detectable levels of HCV RNA. Eleven of the twelve subjects that were tested at 11 weeks had undetectable levels of HCV RNA; one subject had HCV RNA levels of less than 25 IU/mL. Ten of the twelve subjects that were tested at week-12 of the treatment had undetectable levels of HCV RNA; one subject had HCV RNA levels of less than 25 IU/mL, and another subject had detectable levels of HCV RNA. The one subject that had HCV RNA levels of less than 25 IU/mL at week-12 of the treatment had breakthrough at post-treatment week 2. At post-treatment weeks 2 and 4, ten subjects that had undetectable HCV RNA at week-12 of the treatment were tested: eight of the ten subjects had undetectable levels of HCV RNA; and the remaining two subjects had detectable HCV RNA (breakthrough). The eight subjects that had undetectable HCV RNA at post-treatment weeks 2 and 4 were further test at post-treatment weeks 8 and 12 and found no detectable HCV RNA.

The seventeen non-responder subjects in Group 3 included 6 null responders and 11 partial responders. Three out of the six null responders, and five out of the eleven partial responders, achieved SVR12.

The study also showed that IL28B host genotype appeared not to have significantly impact on SVR12 in this study (including Groups 1, 2 and 3).

Example 2B

Use of 2-DAA Combination with Ribavirin to Treat Treatment-Naïve Subjects Infected with Genotype 1, 2 or 3

Genotype 1

Ten previously untreated subjects infected with HCV genotype 1 were treated with a 2-DAA combination with ribavirin. The treatment was interferon-free and was designed to last 12 weeks. The 2-DAA combination included Compound 1/r (200/100 mg QD) and Compound 4 (25 mg QD). The weight based dosing of ribavirin ranged from 1000 to 1200 mg divided twice daily. At weeks 5, 6 and 7 of the treatment, nine of the ten subjects showed no detectable HCV RNA; and the remaining one subject had HCV RNA levels of less than 25 IU/mL. At week 8 of the treatment, five of the nine subjects were tested and showed no detectable HCV RNA. At weeks 9 and 10 of the treatment, four of the five subjects were further tested and found no detectable HCV RNA. At week 11, two of the four subjects were tested and found no detectable HCV RNA.

Additional testing showed that all of the initial ten subjects at weeks 8, 9, 10 and 11 of the treatment had no detectable HCV RNA. At week 12, nine of the initial ten subjects showed undetectable HCV RNA, and one had HCV RNA levels of less than 25 IU/mL. At post-treatment week 2, all of the ten subjects were tested (including the one with HCV RNA levels of less than 25 IU/mL at week 12 of the treatment), and all ten subjects showed no detectable HCV RNA. At post-treatment weeks 4 and 8, all of the ten subjects were tested and found no detectable HCV RNA. Two of the ten subjects were further tested at post-treatment week 12 and found no detectable HCV RNA.

Genotype 2

Ten previously untreated subjects infected with HCV genotype 2 were treated with the same regimen of this Example. At week 4 of the treatment, all of the ten subjects were tested and showed no detectable HCV RNA. At weeks 5 and 6 of the treatment, all of the ten subjects were tested and found no detectable HCV RNA. At weeks 9-11 of the treatment, all of the ten subjects were further tested, and nine of them showed no detectable HCV RNA, and one subject showed HCV RNA levels of less than 25 IU/mL. At week 12 of the treatment, nine of the initial ten subjects were tested, eight of the nine subjects found no detectable HCV RNA and one showed detectable HCV RNA.

The subject showing detectable HCV RNA at week 12 of the treatment was confirmed breakthrough at post-treatment week 2. Eight of the initial ten subjects were also tested at post-treatment week 2 and found no detectable HCV RNA; seven of the initial ten subjects were further tested at post-treatment week 4 and found no detectable HCV RNA; three of the initial ten subjects were further tested at post-treatment week 8 and found no detectable HCV RNA; and one of the initial ten subject was further tested at post-treatment week 12 and found no detectable HCV RNA.

Genotype 3

Similarly, ten previously untreated subjects infected with HCV genotype 3 were treated with the same regimen of this Example. At week 5 of the treatment, two subjects had viral rebound; seven of the remaining eight subjects had no detectable HCV RNA; and one of the remaining eight subjects had HCV RNA levels of less than 25 IU/mL. At week 12 of the treatment, and among the eight non-breakthrough subjects, one subject was lost from the study, another showed detectable HCV RNA, and the remaining six found no detectable HCV RNA.

At post-treatment weeks 2, 4 and 8, two more subjects had breakthrough, and five subjects had no detectable HCV RNA.

One of the two subjects that had viral rebound at week 5 of the treatment was treated with a combination of peginterferon and ribavirin (P/RBV) starting at week 12. After four weeks of the P/RBV treatment, the subject was tested and found no detectable HCV RNA.

Example 2C

Use of 2-DAA Combination with Ribavirin to Treat Treatment-Experienced Subjects Infected with Genotype 1

Six treatment-experienced subjects with HCV genotype 1 infection were treated with a 2-DAA combination with ribavirin for 12 weeks. The treatment was interferon-free. The 2-DAA combination included Compound 1/r (200/100 mg QD) and Compound 4 (25 mg QD). The weight based dosing of ribavirin ranged from 1000 to 1200 mg divided twice daily. These patients had previously undergone a standard interferon/ribavirin therapy but were not responsive (interferon null responders).

At week 6 of the treatment, all six subjects showed no detectable HCV RNA. At week 8 of the treatment, all six subjects were tested and, among them, five showed no detectable HCV RNA and one had HCV RNA levels of less than 25 IU/mL. At weeks 10 and 12 of the treatment, all six subjects were tested and found no detectable HCV RNA.

At post-treatment weeks 2 and 4, all six subjects were tested, one had breakthrough and the remaining five subjects found no detectable HCV RNA. At post-treatment week 8, the five non-breakthrough subjects were further tested and found no detectable HCV RNA.

Example 2D

Use of 3-DAA Combination with Ribavirin to Treat Treatment-Naïve or Treatment-Experienced Subjects Infected with Genotype 1

Treatment-Naïve Patients

Six previously untreated subjects having HCV genotype 1 infection were treated with a 3-DAA combination with ribavirin for 8 weeks. The treatment was interferon-free. The 3-DAA combination included Compound 1/r (150/100 mg QD), Compound 2 (400 mg BID), and Compound 4 (25 mg QD). The weight based dosing of ribavirin ranged from 1000 to 1200 mg divided twice daily. At week 8 of the treatment, all six subjects had no detectable HCV RNA. At post-treatment weeks 2, 4, 8 and 12, all six subjects had no detectable HCV RNA.

Nine previously untreated subjects having HCV genotype 1 infection were treated with a 3-DAA combination with ribavirin for 12 weeks. The treatment was interferon-free. The 3-DAA combination included Compound 1/r (150/100 mg QD or 100/100 mg QD), Compound 2 (400 mg BID), and Compound 4 (25 mg QD). The weight based dosing of ribavirin ranged from 1000 to 1200 mg divided twice daily. At week 8 of the treatment, all nine subjects had no detectable HCV RNA. At week 12 of the treatment, all nine subjects were tested and found no detectable HCV RNA. At post-treatment weeks 2, 4, 8 and 12, all of the nine subjects were further tested and showed no detectable HCV RNA.

Treatment-Experienced Patients

Ten treatment-experienced subjects with HCV genotype 1 infection were treated with a 3-DAA combination with ribavirin: four subjects were treated for 12-week, one subject was treated for 16-week treatment, and the remaining five subjects were treated for 24-week treatment. The treatment was interferon-free. The 3-DAA combination included Compound 1/r (150/100 mg QD or 100/100 mg QD), Compound 2 (400 mg BID), and Compound 4 (25 mg QD). The weight based dosing of ribavirin ranged from 1000 to 1200 mg divided twice daily. These patients had previously undergone a standard interferon/ribavirin therapy but were not responsive (interferon null responders).

At weeks 6, 8, 10 and 12 of the treatment, all ten subjects showed no detectable HCV RNA.

At post-treatment weeks 2, 4 and 8, all of the four subjects in the 12-week treatment regimen found no detectable HCV RNA; and two of the four subjects were further tested at post-treatment week 12 and found no detectable HCV RNA. At post-treatment weeks 2, 4 and 8, the one subject in the 16-week treatment regimen found no detectable HCV RNA. One of the five subjects in the 24-week treatment regimen were tested at post-treatment weeks 2 and 4 and found no detectable HCV RNA.

Example 3

Synergistic concentrations of Compound 1 and Compound 2 in Genotype 1b HCV Replicon Assay

Examples 3-5 are for illustration and do not limit the scope of this disclosure in any way. Not to be bound by any theory, the unexpected synergistic effects from combining different classes of HCV inhibitors (e.g., a combination of a protease inhibitor (such as Compound 1) and a polymerase inhibitor (such as Compound 2), or a combination of a protease inhibitor (such as Compound 1) and a NS5A inhibitor (such as compound 4)) may contribute to the effectiveness of the short-duration, interferon-free therapies of the present technology.

Materials:

A replicon cell line was derived from the human hepatoma cell line Huh7. It was derived from HCV genotype 1b (Con1), and is a bicistronic subgenomic replicon, essentially similar to those described in Science 285(5424):110-3 (1999). The first cistron of the construct contains a firefly luciferase reporter and a neomycin phosphotransferase selectable marker. Replicon cells were maintained in Dulbecco's Modified Eagle Media (DMEM) containing 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen), 200 mg/ml G418, an aminoglycoside antibiotic (Invitrogen) and 10% fetal bovine serum (FBS) at 37° C. and 5% CO2.

Replicon Cell Culture:

Replicon cells were seeded at a density of 5000 cells per well of a 96-well plate in 100 μl DMEM containing 5% FBS. The following day, Compounds 1 and 2 were diluted in dimethyl sulfoxide (DMSO) to generate a 200× stock in a series of 6 two-fold dilutions. The dilution series was then further diluted 100-fold in the medium containing 5% FBS.

Combination Studies:

Combination studies were performed to evaluate the interaction effects of therapeutic agent 1 and therapeutic agent 2 in the replicon assay described above. The purpose of these studies was to determine whether there are doses or concentrations of each compound where synergy or antagonism is demonstrated with the other compound. Three experiments with three plates in each experiment were performed on three separate days. Six concentrations of Compound 1 alone and six concentrations of Compound 2 alone were assayed in each plate. In addition, 36 combinations of concentrations of the two compounds were assayed for each plate. The variable analyzed was the fraction of inhibition of the luciferase signal.

The dilutions of each compound were combined with the dilutions of the other compound in a checkerboard fashion. The concentrations tested were chosen to ensure that the EC_{50} for each compound alone is in the middle of the serial dilution range. Medium with inhibitor(s) was added to the cell culture plates already containing 100 μl of DMEM with 5% FBS. The cells were incubated in a tissue culture incubator at 37° C. and 5% CO_2 for three days. The inhibitor effects of compounds on HCV replication were determined by measuring activity of a luciferase reporter gene using a Luciferase Assay System kit (Promega) following the manufacturer's instructions. Passive Lysis buffer (30 μl, Promega) was added to each well, and the plates were incubated for 15 minutes with rocking to lyse the cells. Luciferin solution (100 μl, Promega) was added to each well and the luciferase activity was measured using a Victor II luminometer (Perkin-Elmer). To determine the EC_{50}, the luciferase inhibition data were analyzed using GraphPad Prism 4 software. Three experiments were performed with three replicates per experiment. The percent inhibition results

were analyzed for synergy, additivity and antagonism according to the Pritchard and Shipman model (Antiviral Research 14:181-206 (1990)).

Combination Analysis:

Prichard and Shipman proposed a direct approach to solve this drug-drug interaction problem. The method was able to calculate theoretical additive effects directly from the individual dose-response curves determined in the assay. The calculated theoretical additivity was then compared to the experimental dose-response surface, and subsequently subtracted to reveal any areas of aberrant interaction. The following equation was used to calculate the theoretical additive effects:

$$Z=X+Y(1-X)=X+Y-XY,$$

where Z is the total inhibition produced by the combination of drugs X and Y, with X and Y representing the inhibition produced by drugs X and Y alone respectively.

A difference between the actual observed fraction of inhibition and the predicted value was calculated for each concentration combination for each plate in each experiment to determine whether the observed combined effect was greater than the theoretical additive effect Z calculated from the equation above. For each concentration combination, the replicates (across all plates and experiments) were used to calculate a mean difference between observed and predicted fraction of inhibition, its standard error and its two-sided 95% confidence interval.

Synergy or antagonism for a concentration combination was determined based on the following 2 rules: First, the 95% CI of the mean difference between observed and predicted fraction of inhibition at each concentration combination is calculated. If the lower bound of 95% CI is larger than zero, then the drug combination would be considered having a synergistic effect; if the upper bound of 95% CI is less than zero, then the drug combination would be considered having an antagonistic effect; otherwise, no significant antagonism or synergy at this concentration combination.

Second, the synergistic or antagonistic effect must have its relative mean difference, the absolute mean difference divided by its corresponding observed mean inhibition, greater than 1%. By doing this, small differences of statistical significance caused by very small variance could be excluded.

Combination of Therapeutic Agent 1 and Therapeutic Agent 2:

The inhibitory effects on replicons produced by each drug alone or in combination with the other at concentrations up to ten-fold above the EC_{50} were examined in the genotype 1b (Con1) replicon using a checkerboard titration pattern (two-fold serial dilutions) in a standard three-day antiviral assay. The concentrations tested were chosen to ensure that the EC_{50} values of the compounds were in the middle of the serial dilution range. For Compound 1, concentrations ranged from 0.031 nM to 1.0 nM. For Compound 2, concentrations ranged from 0.125 nM to 4.0 nM. Synergy, additivity, and antagonism were evaluated using the Pritchard and Shipman model.

Results:

The results of the assay analysis are illustrated in FIGS. **1** and **2** and Table 3. In the 3-D surface plot of FIG. **1**, deviations from expected interactions between Compound 1 and Compound 2 are purely additive at concentrations associated with a horizontal plane at 0%. Synergistic interactions between Compound 1 and Compound 2 appear as a peak above the horizontal plane with a height corresponding to the percent above calculated additivity. Antagonistic interactions between Compound 1 and Compound 2 appear as a pit or trough below the horizontal plane with a negative value signifying the percent below the calculated additivity. Synergistic interactions appear as dark grey, additive interactions appear white, and antagonistic interactions appear as speckled.

As illustrated in the 3-D surface plot of FIG. **1** and the contour plot of FIG. **2**, an additive or synergistic effect exists at most of the concentrations for Compound 1 and Compound 2. In particular, there is a concentration region showing synergy at most concentrations of Compound 1 and at the lower to mid-range dose concentrations of Compound 2.

Table 3 below lists combinations of concentrations of Compound 1 and Compound 2 with statistically significant synergistic or antagonistic effects based on the Prichard and Shipman model analysis. For each combination of concentrations, Table 3 includes the mean difference in the observed and predicted fraction of inhibition, the standard deviation or error of the mean difference, and the upper and lower limits of the 95% confidence interval.

According to Table 3, all of the combinations of Compound 1 and Compound 2 listed in the table have statistically significant synergistic effects.

The results presented in FIGS. **1** and **2** and Table 3 demonstrate that the combination of therapeutic agent 1 and therapeutic agent 2 achieves additivity or synergy at most of the concentration combinations of the two agents. Taken together, these in vitro replicon results suggest that therapeutic agent 2 should produce a significant antiviral effect in patients when administered in combination with therapeutic agent 1 in patients infected with HCV.

TABLE 3

Compound 2, nM	Compound 1, nM	Mean difference in fraction of inhibition: Observed – Predicted	Standard error of mean difference	Lower 95% confidence limit	Upper 95% confidence limit
.125	.12500	0.06176	0.023352	0.007912	0.11561
.125	.25000	0.05321	0.022199	0.002024	0.10440
.125	.50000	0.01176	0.002680	0.005583	0.01794
.250	.25000c	0.06626	0.020630	0.018692	0.11384
.250	.50000	0.01061	0.002677	0.004438	0.01679
.500	.06250	0.04373	0.014897	0.009375	0.07808
.500	.12500	0.10416	0.026757	0.042454	0.16586
.500	.25000	0.09327	0.019859	0.047471	0.13906
.500	.50000	0.01422	0.003333	0.006535	0.02191
1.00	.06250	0.06696	0.020488	0.019715	0.11421
1.00	.12500	0.14103	0.021289	0.091939	0.19013
1.00	.25000	0.11027	0.016762	0.071617	0.14892
1.00	.50000	0.01365	0.002312	0.008315	0.01898
2.00	.06250	0.05974	0.007690	0.042004	0.07747

TABLE 3-continued

Compound 2, nM	Compound 1, nM	Mean difference in fraction of inhibition: Observed – Predicted	Standard error of mean difference	Lower 95% confidence limit	Upper 95% confidence limit
2.00	.12500	0.10032	0.011820	0.073066	0.12758
2.00	.25000	0.07117	0.009428	0.049428	0.09291
4.00	.03125	0.03235	0.003950	0.023236	0.04145
4.00	.06250	0.05141	0.004313	0.041470	0.06136
4.00	.12500	0.06572	0.004692	0.054901	0.07654
4.00	.25000	0.03452	0.004775	0.023509	0.04553

Example 4

Synergistic Concentrations of Compound 1 and Compound 4 in Genotype 1b HCV Replicon Assay

Materials:

The replicon cell line was derived from the human hepatoma cell line Huh7. It was derived from HCV genotype 1b (Con1), and is a bicistronic subgenomic replicon, essentially similar to those described in Science 285(5424):110-3 (1999). The first cistron of the construct contains a firefly luciferase reporter and a neomycin phosphotransferase selectable marker. Replicon cells were maintained in Dulbecco's Modified Eagle Media (DMEM) containing 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen), 200 mg/ml G418 (Invitrogen) and 10% fetal bovine serum (FBS) at 37° C. and 5% CO_2.

Replicon Cell Culture:

Replicon cells were seeded at a density of 5000 cells per well of a 96-well plate in 100 μl DMEM containing 5% FBS. The following day, compounds were diluted in dimethyl sulfoxide (DMSO) to generate a 200× stock in a series of 6 two-fold dilutions. The dilution series was then further diluted 100-fold in the medium containing 5% FBS.

Combination Studies:

Combination studies were performed to evaluate the interaction effects of therapeutic agent 1 and therapeutic agent 4 in the replicon assay described above. The purpose of these studies was to determine doses or concentrations of each compound where synergy or antagonism is demonstrated with the other compound. Three experiments with three plates in each experiment were performed on three separate days. Six concentrations of Compound 1 alone and six concentrations of Compound 2 alone were assayed in each plate. In addition, 36 combinations of concentrations of the two compounds were assayed for each plate. The variable analyzed was the fraction of inhibition of the luciferase signal.

The dilutions of each compound were combined with the dilutions of the other compound in a checkerboard fashion. The concentrations tested were chosen to ensure that the EC_{50} for each compound alone is in the middle of the serial dilution range. Medium with inhibitor(s) was added to the cell culture plates already containing 100 μl of DMEM with 5% FBS. The cells were incubated in a tissue culture incubator at 37° C. and 5% CO_2 for three days. The inhibitor effects of compounds on HCV replication were determined by measuring activity of a luciferase reporter gene using a Luciferase Assay System kit (Promega) following the manufacturer's instructions. Passive Lysis buffer (30 μl, Promega) was added to each well, and the plates were incubated for 15 minutes with rocking to lyse the cells. Luciferin solution (100 μl, Promega) was added to each well and the luciferase activity was measured using a Victor II luminometer (Perkin-Elmer). To determine the EC_{50}, the luciferase inhibition data were analyzed using GraphPad Prism 4 software. Three experiments were performed with three replicates per experiment. The percent inhibition results were analyzed for synergy, additivity and antagonism according to the Pritchard and Shipman model (Antiviral Research 14:181-206 (1990)).

Combination Analysis:

The Prichard and Shipman approach to calculating theoretical additive effects (described in Example 3) was used for the present example.

The difference between the actual observed fraction of inhibition and the predicted value was calculated for each concentration combination for each plate in each experiment to determine whether the observed combined effect was greater than the theoretical additive effect Z calculated from the Prichard and Shipman equation. For each concentration combination, the replicates (across all plates and experiments) were used to calculate a mean difference between observed and predicted fraction of inhibition, its standard error and its two-sided 95% confidence interval.

Synergy or antagonism for a concentration combination was determined based on the same rules set forth in Example 3.

Combination of Therapeutic Agent 1 and Therapeutic Agent 4:

The inhibitory effects in replicon produced by each drug alone or in combination with the other at concentrations up to ten-fold above the EC_{50} were examined in the genotype 1b (Con1) replicon using a checkerboard titration pattern (two-fold serial dilutions) in the standard three-day antiviral assay. The concentrations tested were chosen to ensure that the EC_{50} values of the compounds were in the middle of the serial dilution range. For compound 4, concentrations ranged from 0.0002 nM to 0.0063 nM, and for Compound 1, concentrations ranged from 0.023 nM to 0.75 nM. Synergy, additivity, and antagonism were evaluated using the Pritchard and Shipman model.

Results:

The results of the assay analysis are illustrated in FIGS. **3** and **4** and Table 4. In the 3-D surface plot of FIG. **3**, deviations from expected interactions between Compound 1 and compound 4 are purely additive at concentrations associated with a horizontal plane at 0%. Synergistic interactions between Compound 1 and compound 4 appear as a peak above the horizontal plane with a height corresponding to the percent above calculated additivity. Antagonistic interactions between Compound 1 and compound 4 appear as a pit or trough below the horizontal plane with a negative value signifying the percent below the calculated additivity. Synergistic interactions appear as shades of dark grey, additive interactions appear white, and antagonistic interactions appear as speckled.

As illustrated in the 3-D surface plot of FIG. **3** and the contour plot of FIG. **4**, an additive or synergistic effect exists at most of the concentrations for Compound 1 and compound

4. In particular, there is a concentration region showing synergy at the lower dose concentrations of compound 4 and mid-range dose concentrations of Compound 1.

Table 4 below lists combinations of concentrations of Compound 1 and compound 4 with statistically significant synergistic or antagonistic effects based on the Prichard and Shipman Model analysis. For each combination of concentrations, Table 4 includes the mean difference in the observed and predicted fraction of inhibition, the standard deviation or error of the mean difference, and the upper and lower limits of the 95% confidence interval.

According to Table 4, most of the combinations of Compound 1 and compound 4 listed in the table have statistically significant synergistic effects. A small amount of antagonism was observed at the lowest concentrations of Compound 1.

The results presented in FIGS. **3** and **4** and Table 4 demonstrate that the combination of therapeutic agent 4 and therapeutic agent 1 achieves additivity at most of the concentration combinations of the two agents and achieves synergy at certain concentration combinations, in particular, at low concentrations of therapeutic agent 4 and mid-range concentrations of therapeutic agent 1. Taken together, these in vitro replicon results suggest that therapeutic agent 4 should produce a significant antiviral effect in patients when administered in combination with therapeutic agent 1 in patients infected with HCV.

TABLE 4

Compound 4, nM	Compound 1, nM	Mean difference in fraction of inhibition: Observed – Predicted	Standard error of mean difference	Lower 95% confidence limit	Upper 95% confidence limit
0.000197	0.375000	0.09895	0.033975	0.02060	0.17729
0.000394	0.187500	0.16900	0.038934	0.07922	0.25878
0.000394	0.375000	0.11401	0.027710	0.05011	0.17791
0.000788	0.187500	0.15349	0.038860	0.06388	0.24310
0.000788	0.375000	0.09992	0.027266	0.03704	0.16279
0.001575	0.023438	−0.08326	0.027126	−0.14582	−0.02071
0.001575	0.046875	−0.11894	0.026099	−0.17913	−0.05876
0.001575	0.187500	0.07958	0.020080	0.03328	0.12588
0.003150	0.023438	−0.10156	0.018406	−0.14401	−0.05912
0.003150	0.046875	−0.08091	0.014615	−0.11462	−0.04721

Example 5

Reduction of HCV-Infected Cells with Combinations of Therapeutic Agents 1, 2 and 4

In order to quantify the frequency of resistant replicon colonies selected by therapeutic agent 1, therapeutic agent 2, therapeutic agent 4, or various combinations of these agents, the stable subgenomic replicon cell line derived from HCV genotype 1a (H77; Genbank accession number AF011751) was utilized. The replicon construct was bicistronic and the cell line was generated by introducing the constructs into cell lines derived from the human hepatoma cell line Huh-7. The replicon also has a firefly luciferase reporter and a neomycin phosphotransferase (Neo) selectable marker. The two coding regions, separated by the FMDV 2a protease, comprise the first cistron of the bicistronic replicon construct, with the second cistron containing the HCV NS3-NS5B coding region with addition of adaptive mutations E1202G, K1691R, K2040R and S2204I. This HCV replicon cell line was maintained in Dulbecco's modified Eagles medium (DMEM; Invitrogen) containing 10% (v/v) fetal bovine serum, 100 IU/ml penicillin, 100 μg/ml streptomycin, and 200 μg/ml G418 (all from Invitrogen). 1a-H77 replicon cells (105-106) were plated in 150 mm cell culture plates and grown in the presence of G418 (400 μg/ml) and Compound 1, Compound 2, and/or compound 4 at concentrations that were either 10-fold (10×) or 100-fold (100×) above the EC50 value for the HCV genotype 1a replicon cell line. The EC50 values for Compound 1, Compound 2, and compound 4 used for this experiment were 0.9, 7.7, and 0.01 nM, respectively. After three weeks of treatment, the majority of replicon cells were cleared of replicon RNA and, therefore, were unable to survive in the G418-containing medium since the replicon RNA included the neo marker conferring G418 resistance. The cells containing resistant replicon variants survived and formed colonies, and these colonies were stained with 1% crystal violet in 10% Protocol SafeFix II reagent (Fisher Scientific), and counted. As shown in FIG. **5**A, the combination of compound 4 plus either Compound 1 or Compound 2 at either 10-fold or 100-fold above their respective EC50 value resulted in significantly fewer colonies than either Compound 1, Compound 2, or compound 4 alone at 10-fold or 100-fold above their respective EC50 value.

FIG. **5**B illustrates the percentage of colonies surviving two vs. three DAA combinations. In colony survival assays, 1a-H77 replicon cells were grown in the presence of a DAA combination and G418 for approximately three weeks, after which time the cells containing resistant replicon variants had formed colonies. The cells were stained with crystal violet and counted. "Triple Combination" is either a combination of Compounds 1, 2 and 4 at concentrations of 5-fold (5×) over their respective EC50 values, or a combination of Compounds 1, 2 and 4 at concentrations of 10-fold (10×) over their respective EC50 values.

FIGS. **5**C and **5**D show the effect of a combination of Compounds 1 and 4 in long-term HCV RNA reduction assays in genotype 1 replicon cell lines. In long-term replicon RNA reduction assays, 106 replicon cells were plated in the absence of G418. The inhibitors at concentrations of either 10-fold (10×) or 100-fold (100×) over their respective EC_{50} values were added, and the cells were grown to approximately 95% confluence (4 days). At each passage, 106 cells were removed and frozen, and an additional 106 cells were passed into another flask with fresh media and inhibitors. RNA was extracted from 106 cells and HCV RNA was measured in a Real-Time RT-PCR assay. FIGS. **5**C and **5**D show that in both 1a and 1b replicon cells, the combination of Compounds 1 and 4, each at 10-fold over EC_{50}, is more effective at clearing cells of replicon than 100-fold over EC_{50} of either inhibitor alone.

Predominant resistant variants selected by Compound 1, 2, or 4 in genotype 1 replicons were also determined. For Compound 1, the predominant resistance variants in 1a-H77 replicons include R155K, D168A and D168V with fold resistance of 26, 48 and 128, respectively; and the predominant

resistance variants in 1b-Con1 replicons include R155K, A156T and D168V with fold resistance of 48, 9 and 190, respectively. For Compound 2, the predominant resistance variants in 1a-H77 replicons include C316Y, M414T, Y448C and S556G with fold resistance of 1600, 36, 980 and 15, respectively; and the predominant resistance variants in 1b-Con1 replicons include C316Y, M414T and D559G with fold resistance of 1400, 26 and 100, respectively. For Compound 4, the predominant resistance variants in 1a-H77 replicons include M28T, M28V, Q30R, Y93C and Y93H with fold resistance of 9000, 60, 800, 1700 and 41000, respectively; and the predominant resistance variants in 1b-Con1 replicons include Y93H with fold resistance of 55. These experiments also showed that in genotype 1a, a number of variants selected by Compounds 2 or 4 conferred higher levels of resistance than those selected by Compound 1, and that in genotype 1b, one variant (C316Y) selected by Compound 2 conferred a higher level of resistance than those selected by either Compound 1 or Compound 4.

The above examples show that the combination of two different classes of DAAs (e.g., a combination of a HCV protease inhibitor and a HCV polymerase inhibitor, or a combination of a HCV protease inhibitor and a HCV NS5A inhibitor, or a combination of a HCV polymerase inhibitor and a HCV NS5A inhibitor) can lead to an improved resistance barrier in patients relative to a single DAA alone, while the combination of three different classes of DAAs (e.g., a combination of a HCV protease inhibitor, a HCV polymerase inhibitor, and a HCV NS5A inhibitor) can lead to even more significant barrier to resistance. Improvement in the barrier to resistance achieved through co-administration of multiple DAAs of different classes or with different mechanism of action is expected to correlate with enhanced efficacy in patients.

Example 6

Clinical Modeling for Interferon-Free DAA Combination Therapies

This example describes a novel clinical model for evaluating optimal doses and durations of interferon-free HCV therapies using combinations of different DAAs. This model reasonably predicted the effectiveness of numerous DAA combinations in interferon-free, short-duration therapies.

A mechanistic model was used to model the relationship between DAA exposures and antiviral efficacy in HCV-infected subjects. This model was used to conduct clinical trial simulations of clinical outcomes following administration of various DAA combination regimens (e.g., specific DAA combinations and different doses of DAAs) and durations of therapy.

Numerous DAAs have been extensively documented to select mutants following short duration of monotherapy (e.g., less than 1 week). The viral dynamic model of this Example included single and double mutants. Specifically, the model included 2 single mutants and one double mutant for each of the 2-DAA combination regimens. Thus, a 2-DAA combination regimen (e.g., a combination of a protease inhibitor and a NS5A inhibitor) included 2 single mutants and one double mutant. A 3-DAA combination (e.g., a combination of a protease inhibitor, a polymerase inhibitor and a NS5A inhibitor, such as a combination of a protease inhibitor, a non-nucleoside polymerase inhibitor (NNPI) and a NS5A inhibitor) included 3 single and 2 double mutants.

The model has 3 components: hepatocytes (uninfected or target cell), infected cell and viral dynamics. The differential equations describing the dynamics of the 3 components are as follows:

(1) Hepatocytes (Uninfected or Target Cell) Dynamics

$$dT/dt=s-de*T-(1-\eta)*\beta*T*(VLWT+VLPoly+VLProt+VLNS5A+VLNS5AProt+VLPoly/Prot)$$

(2) Infected Cell Dynamics

(a) Infected with Wild type Virus

$$d\,IWT/dt=(1-\eta)*\beta*T*VLWT-\delta*IWT$$

(b) Infected with Polymerase Mutant Virus

$$d\,IPoly/dt=(1-\eta)*\beta*T*VLPoly-\delta*IPoly$$

(c) Infected with Protease Mutant Virus

$$d\,IProt/dt=(1-\eta)*\beta*T*VLProt-\delta*IProt$$

(d) Infected with NS5A Mutant Virus

$$d\,INS5A/dt=(1-\eta)*\beta*T*VLNS5A-\delta*INS5A$$

(e) Infected with Protease-NS5A Double Mutant Virus

$$ti\ d\,INS5AProt/dt=(1-\eta)*\beta*T*VLNS5AProt-\delta*INS5AProt$$

(f) Infected with Protease-Polymerase Double Mutant Virus

$$d\,IPolyProt/dt=(1-\eta)*\beta*T*VLPolyProt-\delta*IPolyProt$$

(3) Viral Dynamics

(a) Wild Type Virus

$$ti\ \ d\ \ VLWT/dt=(1-3*\mu)*\rho*(1-Eff1)*IWT+\mu*(\rho*(1-Eff2)*Fit1*IPoly+\rho*(1-Eff3)*Fit2*IProt+\rho*(1-Eff4)*Fit3*INS5A)-c*VLWT$$

(b) Polymerase Mutant Virus

$$d\,VLProt/dt=(1-\mu-\phi)*\rho*(1-Eff2)*Fit1*IPoly+\mu*\rho*(1-Eff1)*IWT+\phi*\rho*(1-Eff5)*Fit4*IPoly-Prot-c*VLPoly$$

(c) Protease Mutant Virus

$$d\,VLProt/dt=(1-\mu-2*\phi)*\rho*(1-Eff3)*Fit2*IProt+\mu*\rho*(1-Eff3)*IWT+\phi*(\rho*(1-Eff5)*Fit4*IPolyProt+\rho*(1-Eff6)*Fit5*INS5AProt)-c*VLProt$$

(d) NS5A Mutant Virus

$$d\,VLNS5A/dt=(1-\mu-\phi)*\rho*(1-Eff4)*Fit3*INS5A+\mu*\rho*(1-Eff1)*IWT+\phi*\rho*(1-Eff6)*Fit5*INS5AProt-c*VLNS5A$$

(e) NS5A and Protease Double Mutant Virus

$$d\,VLNS5AProt/dt=(1-2*\phi)*\rho*(1-Eff6)*Fit5*INS5AProt+\phi*(\rho*(1-Eff4)*Fit3*INS5A+\rho*(1-Eff3)*Fit2*IProt)-c*VLNS5AProt$$

(f) Poly and Protease Mutant Double Mutant Virus

$$d\,VLPolyProt/dt=(1-2*\phi)*\rho*(1-Eff5)*Fit4*IPolyProt+\phi*(\rho*(1-Eff2)*Fit1*IPoly+\rho*(1-Eff3)*Fit2*IProt)-c*VLPolyProt$$

The parameters used in the above equations are described in Table 5.

TABLE 5

Viral Dynamic Parameters

Parameter	Description
s	zero-order production of hepatocytes
T	number of Target or uninfected hepatocytes
de	first-order rate constant for the death of hepatocytes
β	rate-constant for the infection of hepatocytes by virus

TABLE 5-continued

Viral Dynamic Parameters

Parameter	Description
δ	first-order rate constant for the death of infected hepatocytes
η	fractional reduction of the rate-constant for the infection of hepatocytes by virus
μ	probability of the formation of single mutants and mutation back to Wild-Type
ϕ	probability of the formation of double mutants and mutation back to single mutant
ρ	production rate of the Wild-Type virus
c	clearance rate of the virus
Eff1, Eff2, Eff3, Eff4	inhibition of production of Wild Type, polymerase, protease, and NS5A mutant, respectively
Eff5, Eff6	inhibition of production of polymerase-protease and NS5A-protease double mutant, respectively
Fit1, Fit2, Fit3	fitness of polymerase, protease and NS5A mutant relative to wild type virus, respectively
Fit4, Fit5	fitness of polymerase-protease and NS5A-protease double mutant relative to wild type virus, respectively
IWT, IPoly, Iprot, INS5A	number of cells infected with wild type, polymerase, protease and NS5A mutants, respectively
IPoly-Prot, INS5A-Prot	number of cells infected with polymerase-protease and NS5A-protease double mutant, respectively
VLWT, VLPoly, VLProt, VLNS5A	viral load for wild type virus, polymerase, protease and NS5A mutant virus, respectively
VLPoly-Prot, VLNS5A-Prot	viral load for polymerase-protease and NS5A-protease double mutant, respectively

As shown in the differential equations for viral dynamics, the effect of DAA is included as an inhibition of viral load production. For example, the effect of DAA(s) on production of wild type virus is given as $(1-Eff1)*\rho$ where Eff1 is the fraction of viral production that is inhibited. In the absence of drug Eff1=0 and in the presence of drug Eff1 takes a value between 0 and 1. Eff1 is described using an Emax model:

$$Eff1=Emax*Conc/(EC_{50}+Conc)$$

where Emax represents maximum inhibition, Conc is the plasma DAA concentration and EC_{50} is the concentration that inhibits viral load production by 50%. As the fold-change in EC_{50} for the mutants compared to wild type virus was based on values obtained from in vitro replicon studies, EC_{50} was estimated only for wild type virus.

For DAA combinations, the effect was assumed to be multiplicative and incorporated as follows:

$$(1-Eff1)=(1-Eff_{DAA1})*(1-Eff_{DAA2})*(1-Eff_{DAA3})$$

The effect of ribavirin (RBV) was added on infection rate β as an Emax model. In presence of ribavirin, the infection rate decreases by a factor $(1-\eta)$ where

$$\eta=Conc_{RBV}/(EC_{50\text{-}RBV}+Conc_{RBV})$$

The model does not include a double mutant to the polymerase+NS5A inhibitors. In a 3-DAA regimens, a polymerase+NS5A double mutant is often wild type for the protease inhibitor. Hence, this double mutant is not expected to significantly affect clinical outcomes for a 3-DAA regimen simulation. On the other hand, the model can be readily adapted to simulate a 2-DAA regimen containing a polymerase inhibitor and a NS5A inhibitor by treating the polymerase inhibitor (e.g., PSI-7977) as a protease inhibitor in the model.

The lowest available limit of detection (LOD) of viral load assays is 10 IU/mL. Assuming 3 virion particles per IU, this constitutes about 0.5 million viruses in the body at LOD. Hence, subjects have to be treated for significant period of time after their viral load falls below the LOD to achieve cure. This duration depends on the potency of the compounds and the individual response to therapy.

In order to predict the duration required for cure, a "threshold" concept was used. For simulations, an HCV-infected subject was assumed to achieve SVR when viral load reaches less than 1 virion in the total plasma and extracellular fluid volume (about 15000 mL), i.e., viral load measurement of <1 copy/15000 mL or <0.33 IU/15000 mL. This translates to about 5 log IU/mL. Cf. Snoeck E et al., Clin Pharmacol Ther. 87(6):706-13 (2010), wherein based on data from patients treated with peg-IFN and ribavirin, subjects were estimated to achieve SVR when the predicted number of infected cells fell below 1. While such low viral loads cannot be measured experimentally, they can be simulated using the viral dynamic model.

The model can be used to predict SVR for any combination of DAAs, with or without interferon, and with or without ribavirin.

As non-limiting examples, various interferon-free treatment regimens using different combinations of Compound 1, Compound 2 and/or Compound 4, with or without ribavirin, were evaluated using the model of this Example. The following approach was used to include mutants in the model:

a. One single mutant per DAA

b. One double mutant per DAA combination

For a combination of two DAAs, e.g., a combination of Compound 1 and Compound 2, the model included one mutant resistant to Compound 1, one mutant resistant to Compound 2, and one double mutant resistant to both Compound 1 and Compound 2. Compound 1 is coadministered or co-formulated with ritonavir (or another pharmacokinetics enhancer) to improve its drug exposure.

A double mutant to Compound 2 and Compound 4 was not included in the modeling. In the 3-DAA regimens, a Compound 2/Compound 4 double mutant is likely wild type for Compound 1 due to the high potency and resistant profile of Compound 1. Hence, the Compound 2/Compound 4 double mutant is not expected to affect clinical outcomes for treatments containing Compound 1.

Single mutants included in the model were based on mutants observed for the individual DAAs in the Phase 1b and 2a studies (e.g., clinical studies M10-351, M12-116, and M11-602). For double mutants with resistance to 2 DAA classes, the sensitivity (EC_{50}) of double mutants to drug was assumed to be a combination of the 2 single mutants. Thus, for Compound 1 and Compound 2, the single mutants were D168V and M414T, respectively, and the double mutant was D168V-M414T. In this scenario, the D168V mutant would be less sensitive to Compound 1 but would be as sensitive to Compound 2 as wild type virus. Similarly, the M414T mutant would be less sensitive to Compound 2 but would be as sensitive to Compound 1 as wild type virus. The double mutant D168V-M414T would be less sensitive to both Compound 1 and Compound 2.

The fold change in EC_{50} for the mutants compared to wild type virus was based on values obtained from in vitro replicon studies. Since monotherapy data for Compound 4 indicated a variety of mutants with different EC_{50}s, a value of 1000× fold change in EC_{50} was used for Compound 4 for modeling and simulations.

Baseline prevalence of the mutants was estimated during model fitting, while the mutation rate was based on the literature values. Both baseline prevalence and mutation rate determined mutant fitness.

Pharmacokinetic data and viral load data from 140 treatment-naïve HCV-infected subjects were used to construct the model. For modeling, number of target cells at baseline, num-

ber of infected cells at baseline, death rate of target cells and mutation rates were based on literature values. See, e.g., Snoeck et al. supra; Rong et al. Sci Transl Med. 2(30):30ra32 (2000); Neal and Pravin, ACOP 2009 (http://2009.go-acop.org/sites/all/assets/webform/Lauren-Neal_ACoP_2009.pdf); Neumann et al. Science 282(5386):103-7 (1998); Shudo et al. Antivir Ther. 13(7):919-26 (2008); and Dahari et al. J Theor Biol. 247(2):371-81 (2007). The production rate of virus and infection rate of virus were derived from other parameters in the model. All other parameters were estimated. Exposure-antiviral response modeling was performed using NONMEM 7.2.

Clinical trial simulations were performed using Trial Simulator version 2.2.1. Fifty subjects and 50 replicates were simulated for each treatment. A subject drop out rate from the study due to any reason was assumed to be 8% over 24 weeks based on available literature on trials in subjects with HCV. All simulations were conducted assuming 100% compliance. Covariates included in the simulations were genotype 1a/1b status. Clinical outcomes simulated included: (1) percentage of subjects below limit of detection (LOD) of 10 IU/mL and (2) percentage of subjects achieving SVR.

Clinical trial simulations were conducted to determine optimal dose and duration for SVR. Over 80 scenarios were simulated to predict the percentage of subjects with SVR following administration of various 2- and 3-DAA combinations (e.g., Compound 1+Compound 2, or Compound 1+Compound 4, or Compound 1+Compound 2+Compound 4), without RBV, at a range of doses for each DAA (e.g., Compound 1/ritonavir at 250/100, 150/100 or 100/100 mg QD, Compound 4 at 5, 25 or 100 mg QD, and Compound 2 at 400 or 800 mg BID) and across a range of treatment durations (e.g., 2. 4, 6, 8, 10, 12, 16, and 24 weeks).

Optimal dose and duration were predicted based on percentage of subjects with viral load of less than −5 log IU/mL threshold for SVR. Selected and relevant results of simulation for the 2- and 3-DAA combinations of Compounds 1, 2 and/or 4 are shown in FIGS. **6**A, **6**B and **6**C for two different doses of Compound 1. FIG. **6**A shows the predicted median SVR percentage ("% SVR") and 90% confidence interval (the vertical bar at the top of each SVR percentage column) for different treatment durations using a combination of Compound 1 and Compound 2; FIG. **6**B shows the predicted median and 90% confidence interval for different treatment durations using a combination of Compound 1 and Compound 4; and FIG. **6**C shows the predicted median and 90% confidence interval for different treatment durations using a combination of Compound 1, Compound 2 and Compound 4. In each simulation, RBV was included, and Compound 1 was used with 100 mg ritonavir, and the subjects are HCV genotype 1, treatment-naïve patients. SVR24 is lower than SVR12 in some cases due to drop out; longer durations are not necessarily predicted to improve SVR but could result in more dropouts resulting in lower SVR.

The model predicted that with 8-12 weeks of dosing at least 80 to 90% subjects can achieve SVR with 2 and 3 DAA combinations. The model also predicted that durations shorter than 8 weeks can cure a significant number of subjects. A 2-DAA regimen was predicted to cure over 40% of the subjects and a 3-DAA regimen was predicted to cure about 60% of the subjects with only 6 weeks of dosing. Dosing for durations of over 12 weeks was not expected to increase the percentage of subjects with SVR significantly. Addition of the 3rd DAA was predicted to shorten treatment duration by 2 to 4 weeks as optimal durations for the 3-DAA combination of Compound 1, Compound 2 and Compound 4 were predicted to be 8-10 weeks.

FIGS. **6**A, **6**B and **6**C illustrate the predictions for DAA combinations without ribavirin. The model also predicts similar or comparable SVR percentages for these DAA combinations when used with ribavirin. In addition, the effect of interferon (e.g., pegylated interferon) can also be added by incorporating interferon similar to a DAA but without any resistant mutants.

One of the advantages that the model provides is that it allows examination of various viral parameters and its effect on dose, duration and SVR. For example while experimentally determining the effect of mutants parameters is very difficult if not impossible, they can be examined using the model. Thus SVR in patient population that have different mutants can be predicted with the model.

The model was used to simulate the treatment described in Example 1 which included 150/100 mg Compound 1/ritonavir QD+400 mg Compound 3 QD+weight-based amounts of RBV BID for 12 weeks, and the percentage of subjects with HCV RNA less than LOD at 2, 4, 8, 10, and 12 weeks was summarized in FIG. **7**. The mean predicted versus observed percentage of subjects with below LOD ("% LOD") at respective weeks are shown FIG. **7**. 95% confidence intervals for the predicted data (the vertical bar at the top of each respective predicted LOD percentage column) were also indicated. As shown in FIG. **7**, the model reasonably predicted the clinical outcome of % LOD.

The model was also used to simulate the treatment described in Example 2A. The mean predicted versus observed percentage SVR ("% SVR") after 12-week treatment are shown FIG. **8**. 95% confidence intervals for the predicted data (the vertical bar at the top of each respective predicted SVR percentage column) were also indicated. As shown in FIG. **8**, the predicted SVR percentages aligned well with the observed SVR percentages. Simulations also predict that the same treatment regimen as described in Example 2A but without ribavirin has similar or comparable LOD percentages for different treatment durations.

The exposure response viral dynamic model of this Example provided a quantitative method to reasonably predict SVR for various combination of antiviral compounds. Based on the exposure-antiviral response modeling and clinical trial simulations, it demonstrated that (1) addition of a 3rd DAA to a 2-DAA combination can reduce optimal duration of treatment and/or increase SVR; (2) 8-12 weeks of dosing is the optimal duration of therapy for 2 and 3 DAA combinations of Compound 1/r, Compound 2 and Compound 4; and (3) durations shorter than 8 weeks of interferon-free treatment have been predicted to cure a significant percent of the subjects.

Example 7

Clinical Modeling for Interferon-Free DAA Combination Therapies Containing BMS-790052 and BMS-650032

The model described above was also used to predict the SVR percentage of interferon-free treatment regimens containing BMS-790052 and BMS-650032 without ribavirin, based on existing published clinical data including two Phase 1 and one Phase 2 study of BMS-790052 and one Phase 1 and one Phase 2a study of BMS-650032. FIG. **9** shows the predicted median SVR percentage and 90% SVR confidence interval for different treatment durations of a 2-DAA regimen containing BMS-790052 (60 mg QD) and BMS-650032 (600 BID) in genotype 1 naïve subjects. The combination of BMS-790052 (60 mg QD) plus BMS-650032 (600 mg BID) in

genotype 1 subjects was predicted to achieve improved SVR for durations of 12 weeks or greater with predicted SVR rates of about 70% for 10 weeks of dosing. Similar regimens but containing ribavirin, or regimens with similar dosings of BMS-790052 and BMS-650032 with or without ribavirin, are expected to achieve similar SVR rates.

Example 8

Clinical Modeling for Interferon-Free Therapies Containing PSI-7977

Likewise, a 3-DAA regimen without interferon and ribavirin was modeled for genotype 1 patients based on existing clinical data. The 3-DAA regimen contains 200/100 mg QD Compound 1/r, 50 mg QD Compound 4, and 400 mg QD PSI-7977. FIG. **10** depicts the predicted median SVR rates for different treatment durations of this 3-DAA combination. This 3-DAA combination was predicted to have over 60% SVR in 6 weeks and over 80% SVR at duration of 8-week, 10-week, 12-week or longer treatment. Similar regimens but containing ribavirin, or regimens with similar dosings of Compound 1/r, Compound 4 and PSI-7977 with or without ribavirin, are expected to achieve similar SVR rates.

The model can also be used to predict SVR for regimens containing single DAA or single DAA with ribavirin. For example, the model predictions for PSI-7977+ribavirin for various durations for treating HCV genotype 1 treatment-naïve patients were obtained. FIG. **11** depicts the predicted median and 90% confidence interval of SVR percentage for different treatment durations of such a regimen containing PSI-7977 (as the sole DAA; 400 mg QD) and ribavirin (600 mg BID). The 90% confidence interval for the predicted SVR (the vertical bar at the top of each respective predicted SVR percentage column) is also indicated in FIG. **11**. The prediction was based on the already published clinical data for PSI-7977. SVR rate for PSI-7977+ribavirin was predicted to be around 75-90% following 12 weeks of dosing, and about 55-75% following 8 weeks dosing, in genotype 1 subjects. Similar SVR percentages for genotype 1 treatment-naïve patients are expected for similar regimens containing similar PSI-7977 QD dosing (e.g., 200-600 mg QD) and weight-based amounts of ribavirin (e.g., 1000 to 1200 mg divided twice daily).

Data from two Phase 1 and one Phase 2 study of Daclatasvir (BMS-790052) and one Phase 1 and one Phase 2 study of PSI-7977 were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for a 2-DAA combination with Daclatasvir (BMS-790052) and PSI-7977 in genotype 1 naïve patients are shown in FIG. **12**. The model predicted that following 10-12 weeks of dosing with the combination of Daclatasvir and PSI-7977 without ribavirin, at least 90% of HCV genotype 1 naïve patients can achieve SVR. Similar or better SVR rates are predicted if ribavirin is included in the regimens.

Similarly, data from one Phase 1a study of TMC-435 and one Phase 1 and one Phase 2 study of PSI-7977 were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for a 2-DAA combination with the TMC-435 and PSI-7977 in genotype 1 naïve patients are shown in FIG. **13**. The model predicts that following 10-12 weeks of dosing with the combination of TMC-435 and PSI-7977 without ribavirin, at least 90% of HCV patients can achieve SVR. Similar or better SVR rates are predicted if ribavirin is included in the regimens.

Example 9

Clinical Modeling for Interferon-Free DAA Combination Therapies Containing Danoprevir and Mercitabine

In addition, data from one Phase 1 and one Phase 2 study of Danoprevir and Mercitabine were used for estimating the pharmacokinetic and viral dynamic model parameters. Ritonavir was co-administered with danoprevir to improve the pharmacokinetics of Danoprevir. Predictions for a 2-DAA combination with Danoprevir and Mercitabine in genotype 1 naïve patients are shown in FIG. **14**. The model predicts that following 16 weeks of dosing with the combination of Danoprevir and Mercitabine without ribavirin, at least 90% of HCV patients can achieve SVR. Similar or better SVR rates are predicted if ribavirin is included in the regimens

Example 10

Clinical Modeling for Interferon-Free DAA Combination Therapies Containing Tegobuvir (GS-9190), GS-9451 and GS-5885

Data from Phase 1 and Phase 2 studies of GS-9190 (tegobuvir), GS-9451 and GS-5885 were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for the combination with GS-9190 (tegobuvir), GS-9451 and GS-5885 in genotype 1 naive patients are shown in FIG. **15**. The model predicts that following 12 weeks of dosing with the combination of GS-9190 (tegobuvir)+GS-9451+GS-5885+RBV, about 70% of genotype 1 naïve patients can achieve SVR and following 24 weeks of treatment >80% of genotype 1 naïve patients can achieve SVR. Similar or better SVR rates are expected when ribavirin is included in the regimen.

Example 11

Clinical Modeling for Interferon-Free DAA Combination Therapies Containing PSI-7977 (GS-7977)

Data from Phase 1 and Phase 2 studies of GS-9451 and GS-7977 (PSI-7977) were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for the combination with GS-9451 and GS-7977 (PSI-7977) in genotype 1 naive patients are shown in FIG. **16**.

Data from Phase 1 and Phase 2 studies of GS-5885 and GS-7977 (PSI-7977) were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for the combination with GS-5885 and GS-7977 (PSI-7977) in genotype 1 naive patients are shown in FIG. **16**.

Data from Phase 1 and Phase 2 studies of GS-9451, GS-5885 and GS-7977 (PSI-7977) were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for the combination with GS-9451, GS-5885 and GS-7977 (PSI-7977) in genotype 1 naive patients are shown in FIG. **16**.

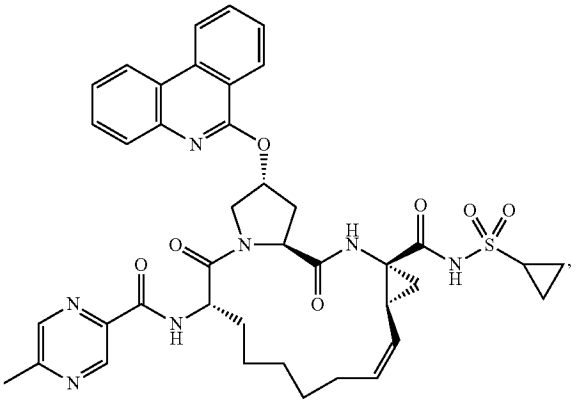
The model predicts that following 12 weeks of dosing with the combination of GS-9451 and GS-7977 (PSI-7977), or the combination of GS-5885 and GS-7977 (PSI-7977), or the combination of GS-9451, GS-5885 and GS-7977 (PSI-7977), at least 90% of genotype 1 naïve patients can achieve SVR. Similar or better SVR rates are expected when ribavirin is included in these regimens.

The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

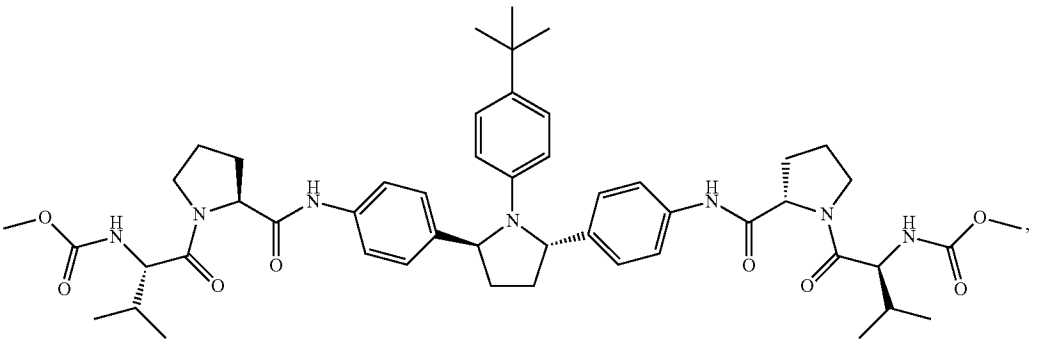
1. A method of treatment for HCV, comprising administering at least two direct acting antiviral agents (DAAs) to an HCV patient infected with HCV genotype 1, wherein said treatment does not include administration of interferon to said patient, and said treatment lasts for 12 weeks, and wherein said at least two DAAs comprise:

Compound 1 having formula of



or a pharmaceutically acceptable salt thereof, and

Compound 4 having formula of

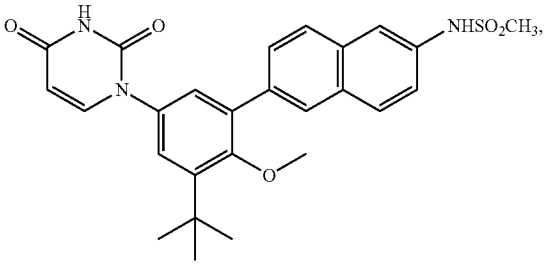


or a pharmaceutically acceptable salt thereof,

wherein Compound 1 or the salt thereof is co-administered with ritonavir.

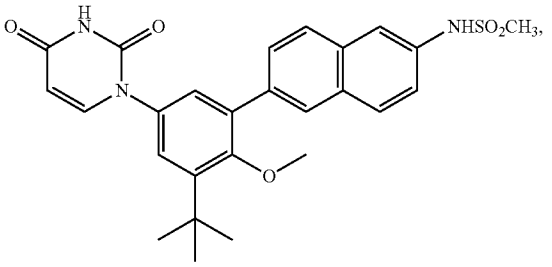
2. The method of claim **1**, wherein said patient is a treatment-naïve patient.

3. The method of claim **1**, wherein said at least two DAAs further comprise compound 2 having formula of



or a pharmaceutically acceptable salt thereof.

4. The method of claim **2**, wherein said at least two DAAs further comprise compound 2 having formula of



or a pharmaceutically acceptable salt thereof.

5. The method of claim **1**, wherein said patient is infected with HCV genotype 1a.

6. The method of claim **2**, wherein said patient is infected with HCV genotype 1a.

7. The method of claim **3**, wherein said patient is infected with HCV genotype 1a.

8. The method of claim **4**, wherein said patient is infected with HCV genotype 1a.

9. A method of treatment for HCV, comprising administering at least two direct acting antiviral agents (DAAs) and ribavirin to an HCV patient infected with HCV genotype 1, wherein said treatment does not include administration of interferon to said patient, wherein said at least two DAAs comprise PSI-7977 and TMC-435, and wherein said treatment lasts for 12 weeks.

10. The method of claim **9**, wherein said patient is a treatment-naïve patient.

11. The method of claim **9**, wherein said patient is infected with HCV genotype 1a.

12. The method of claim **10**, wherein said patient is infected with HCV genotype 1a.

13. A method of treatment for HCV, comprising administering at least two direct acting antiviral agents (DAAs) and ribavirin to an HCV patient infected with HCV genotype 1, wherein said treatment does not include administration of interferon to said patient, wherein said at least two DAAs comprise PSI-7977 and GS-5885, and wherein said treatment lasts for 12 weeks.

14. The method of claim **13**, wherein said patient is a treatment-naïve patient.

15. The method of claim **13**, wherein said patient is infected with HCV genotype 1a.

16. The method of claim **14**, wherein said patient is infected with HCV genotype 1a.

* * * * *

Exhibit B

US008492386B2

(12) **United States Patent**
Bernstein et al.

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(45) **Date of Patent: *Jul. 23, 2013**

(54) **METHODS FOR TREATING HCV**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

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(51) **Int. Cl.**

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A61K 31/33	(2006.01)
A61K 31/505	(2006.01)
A61K 31/47	(2006.01)
A61K 31/415	(2006.01)
A61K 31/40	(2006.01)
A61K 31/675	(2006.01)

(52) **U.S. Cl.**
USPC **514/255.05**; 514/183; 514/269; 514/314; 514/397; 514/309; 514/394; 514/422; 514/81

(58) **Field of Classification Search**
USPC 514/183, 269, 314, 397, 309, 394, 514/81, 274, 255.05, 422
See application file for complete search history.

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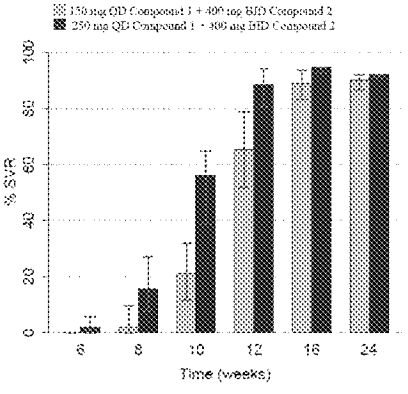
(74) *Attorney, Agent, or Firm* — Xu Zhang

(57) **ABSTRACT**

The present invention features interferon- and ribavirin-free therapies for the treatment of HCV. Preferably, the treatment is over a shorter duration of treatment, such as no more than 12 weeks. In one aspect, the therapies comprise administering at least two direct acting antiviral agents without interferon and ribavirin to a subject with HCV infection. For example, the therapies comprise administering to a subject an effective amounts of therapeutic agent 1, therapeutic agent 2 (or therapeutic agent 3), and an inhibitor of cytochrome P450 (e.g., ritonavir).

16 Claims, 21 Drawing Sheets



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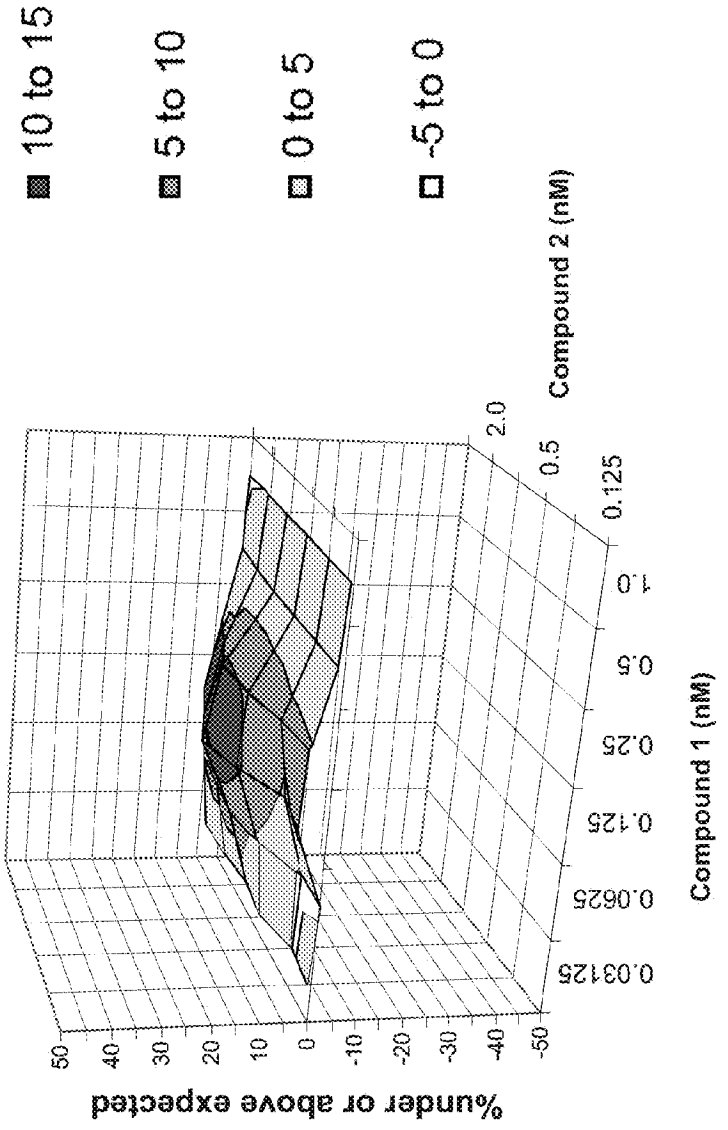

10 to 15
5 to 10
0 to 5
-5 to 0
%under or above expected
50
40
30
20
10
0
-10
-20
-30
-40
-50
Compound 1 (nM)
0.03125
0.0625
0.125
0.25
0.5
1.0
Compound 2 (nM)
0.125
0.5
2.0

Figure 1

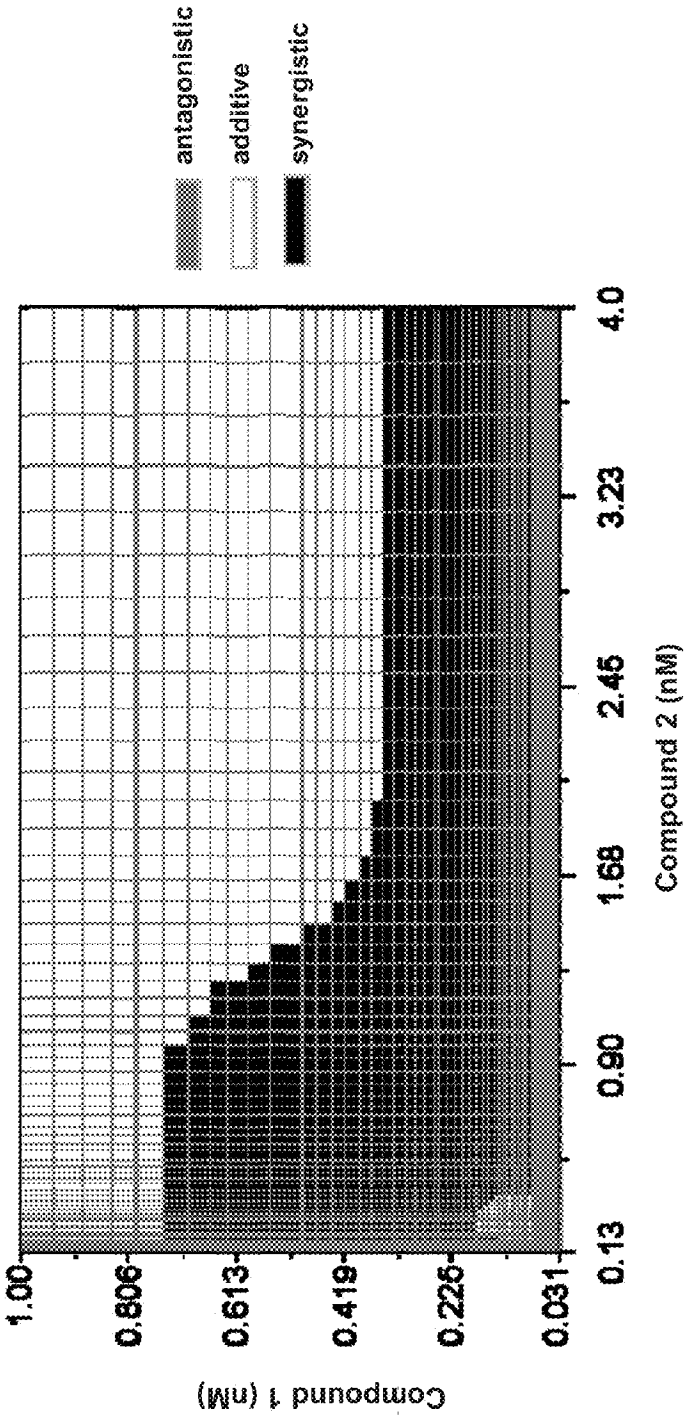

antagonistic
additive
synergistic
1.00
0.806
0.613
0.419
0.226
0.031
Compound 1 (nM)
0.13
0.90
1.68
2.45
3.23
4.0
Compound 2 (nM)

Figure 2

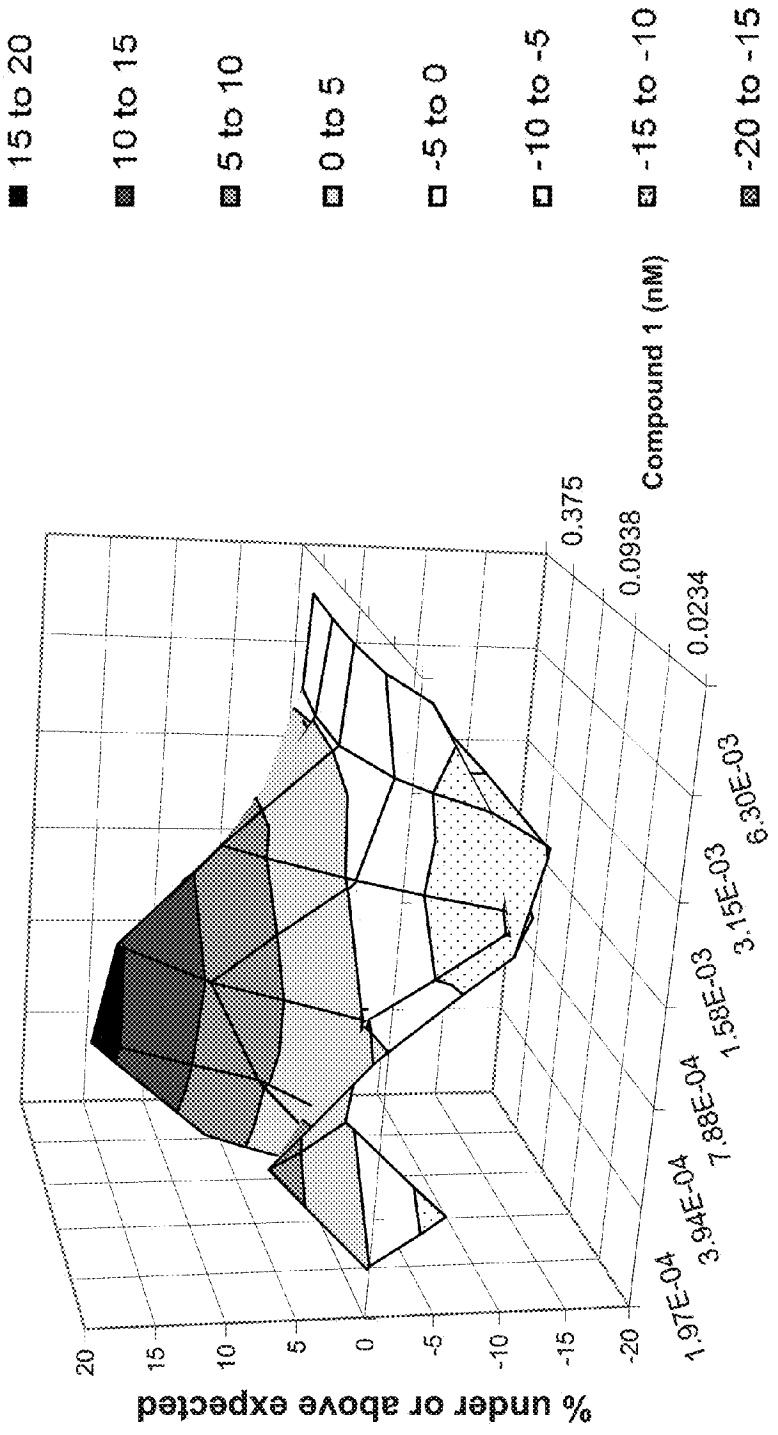

15 to 20
10 to 15
5 to 10
0 to 5
-5 to 0
-10 to -5
-15 to -10
-20 to -15
% under or above expected
20
15
10
5
0
-5
-10
-15
-20
Compound 4 (nM)
1.97E-04
3.94E-04
7.88E-04
1.58E-03
3.15E-03
6.30E-03
Compound 1 (nM)
0.375
0.0938
0.0234

Figure 3

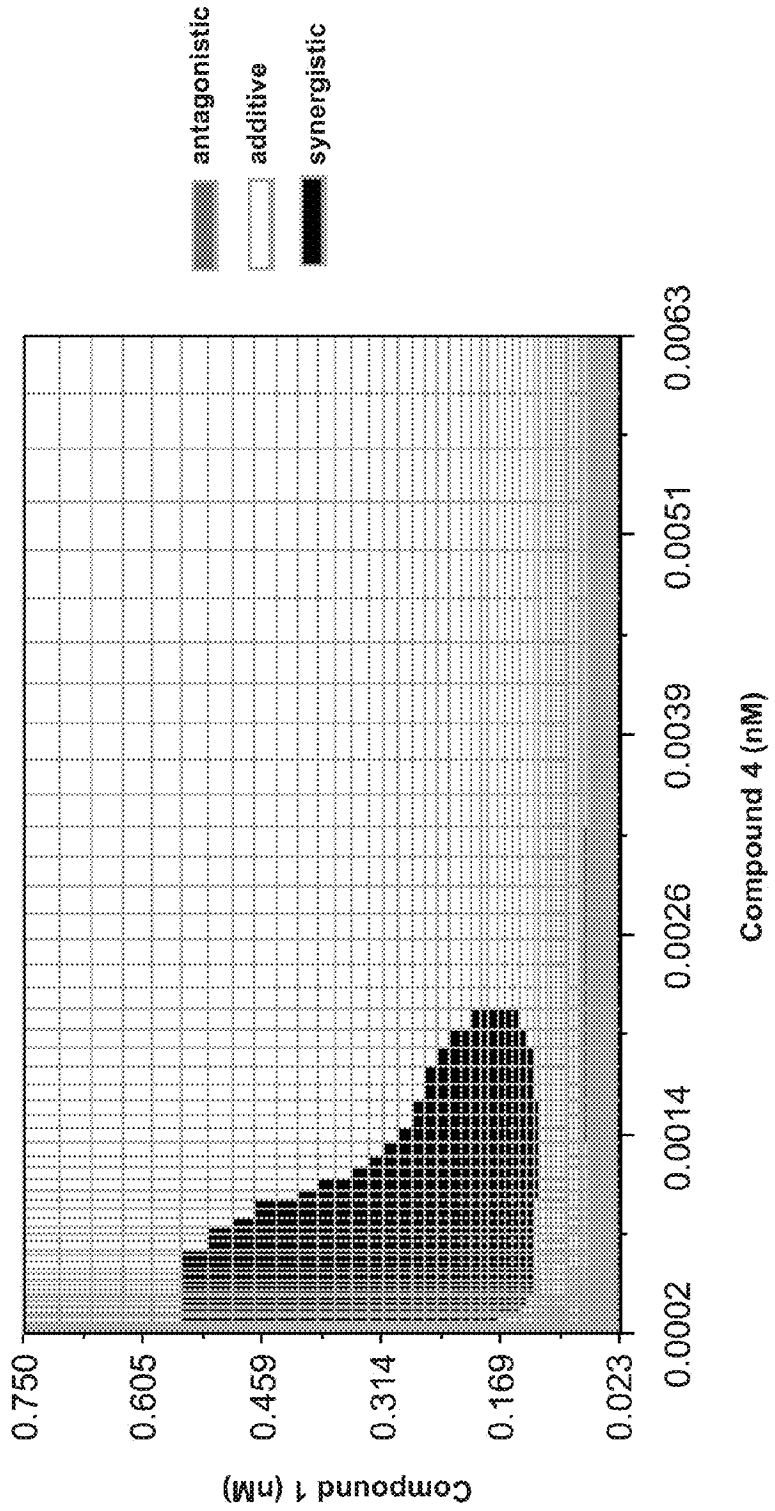

antagonistic
additive
synergistic
0.750
0.605
0.459
0.314
0.169
0.023
Compound 1 (nM)
0.0002
0.0014
0.0026
0.0039
0.0051
0.0063
Compound 4 (nM)

Figure 4

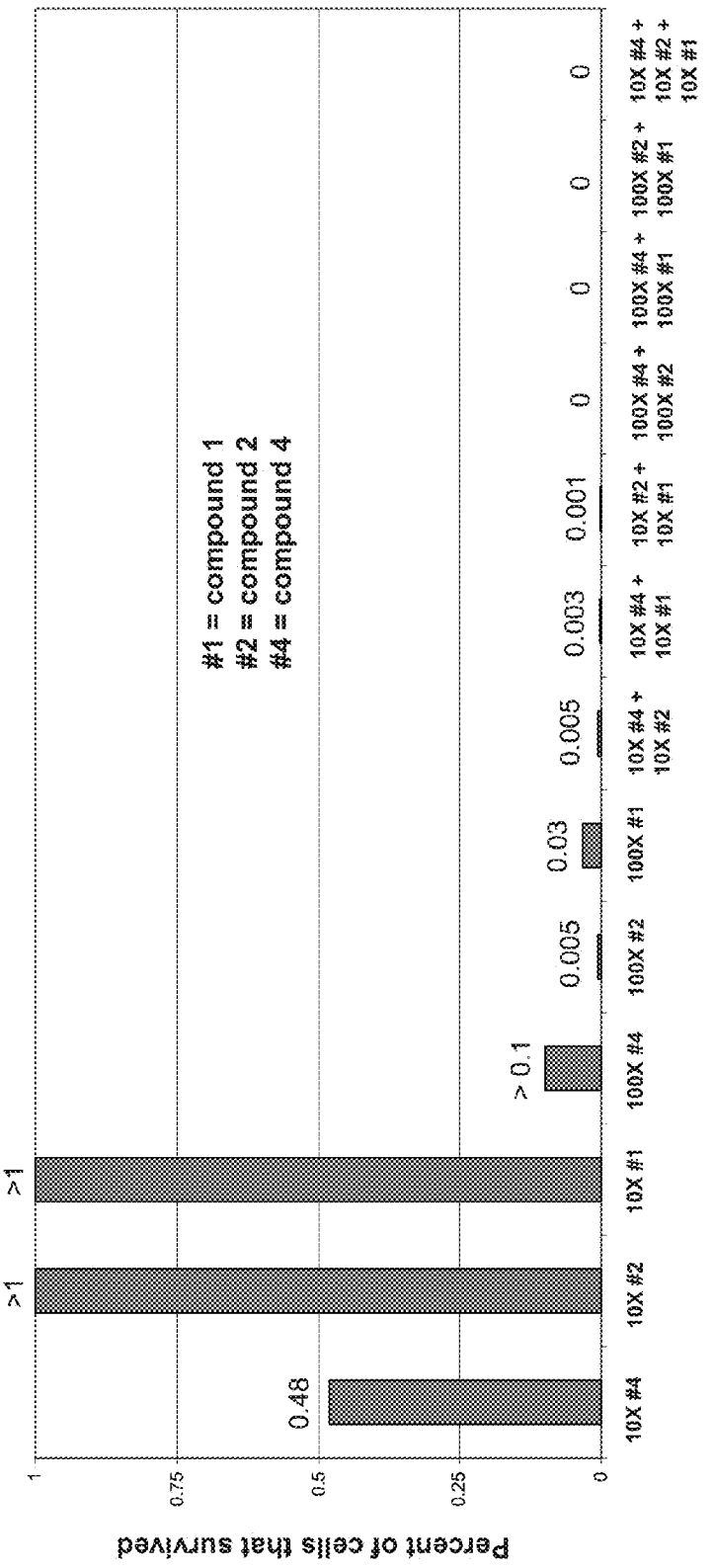

Percent of cells that survived
1
0.75
0.5
0.25
0
#1 = compound 1
#2 = compound 2
#4 = compound 4
0.48
>1
>1
> 0.1
0.005
0.03
0.005
0.003
0.001
0
0
0
0
10X #4
10X #2
10X #1
100X #4
100X #2
100X #1
10X #4 + 10X #2
10X #4 + 10X #1
10X #2 + 10X #1
100X #4 + 100X #2
100X #4 + 100X #1
100X #2 + 100X #1
10X #4 + 10X #2 + 10X #1

Figure 5A

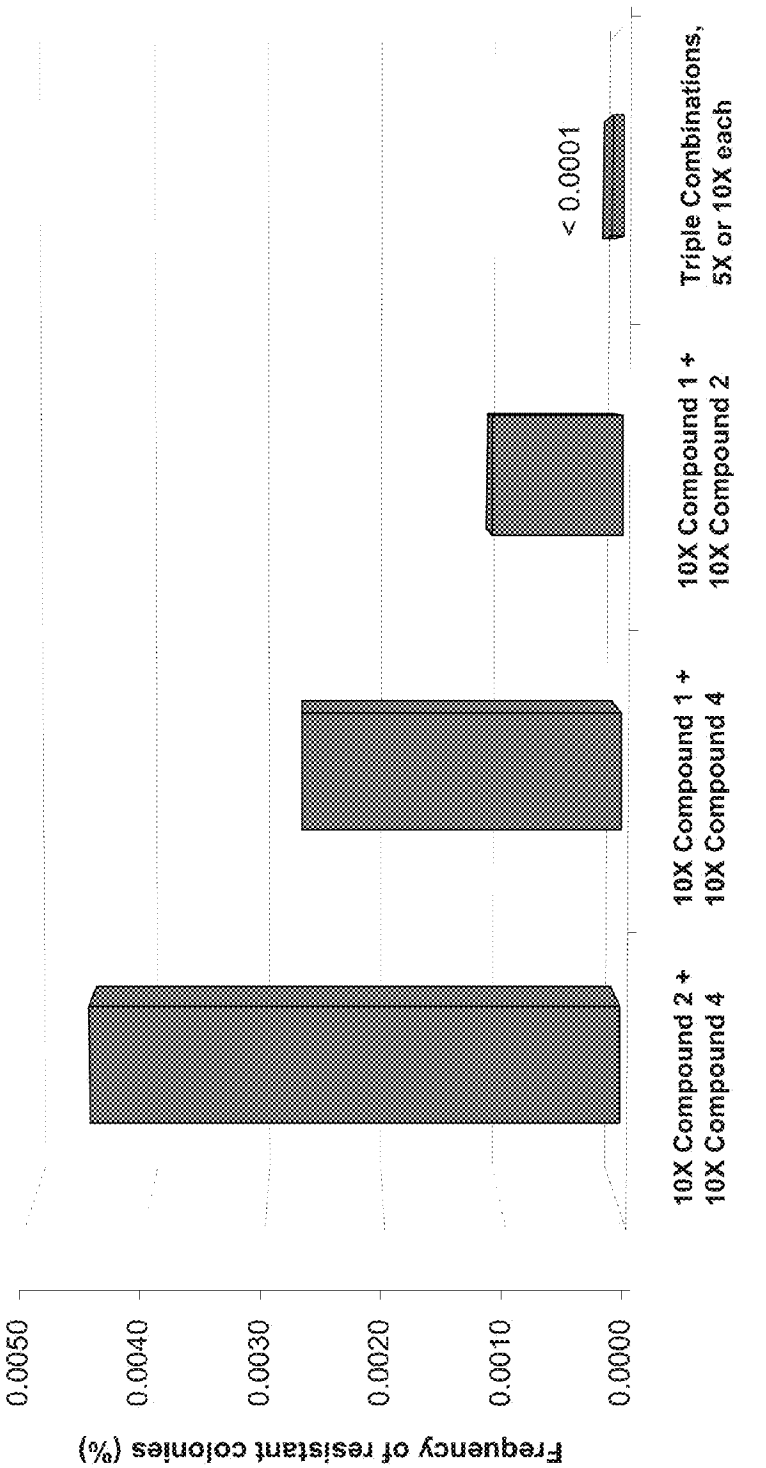

Frequency of resistant colonies (%)
0.0050
0.0040
0.0030
0.0020
0.0010
0.0000
< 0.0001
10X Compound 2 + 10X Compound 4
10X Compound 1 + 10X Compound 4
10X Compound 1 + 10X Compound 2
Triple Combinations, 5X or 10X each

Figure 5B

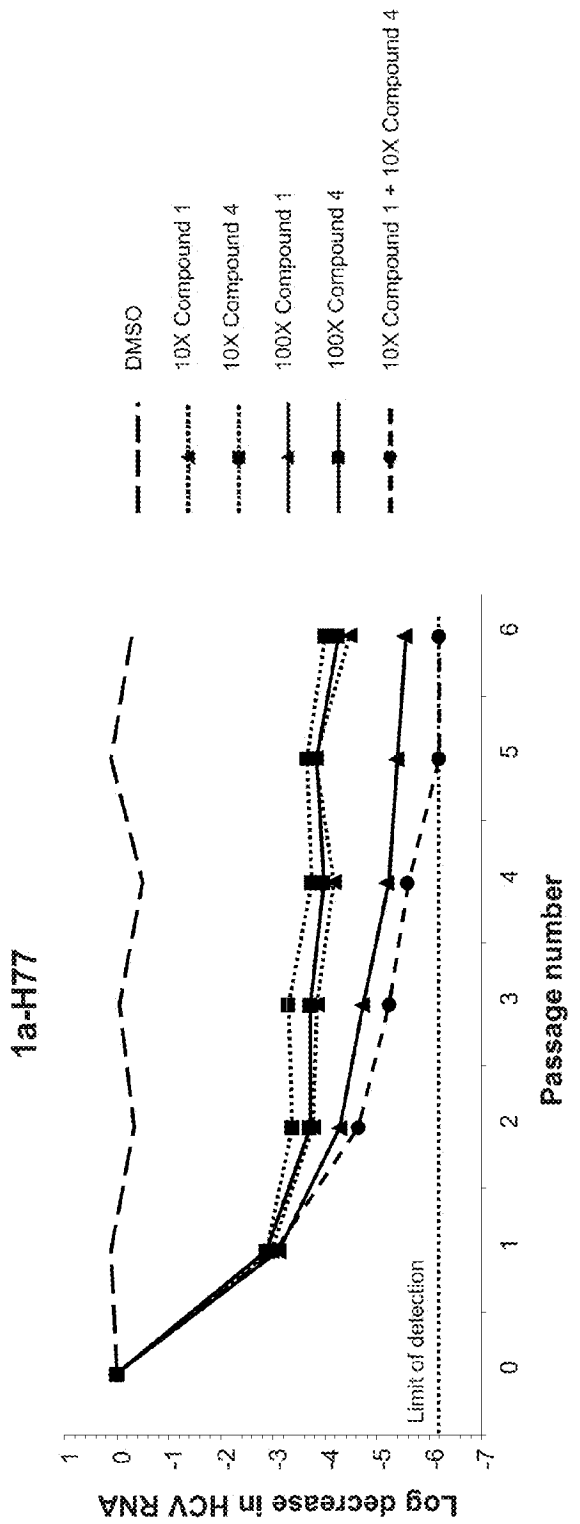

DMSO
10X Compound 1
10X Compound 4
100X Compound 1
100X Compound 4
10X Compound 1 + 10X Compound 4
1a-H77
Log decrease in HCV RNA
Passage number
Limit of detection
1
0
-1
-2
-3
-4
-5
-6
-7
0
1
2
3
4
5
6

Figure 5C

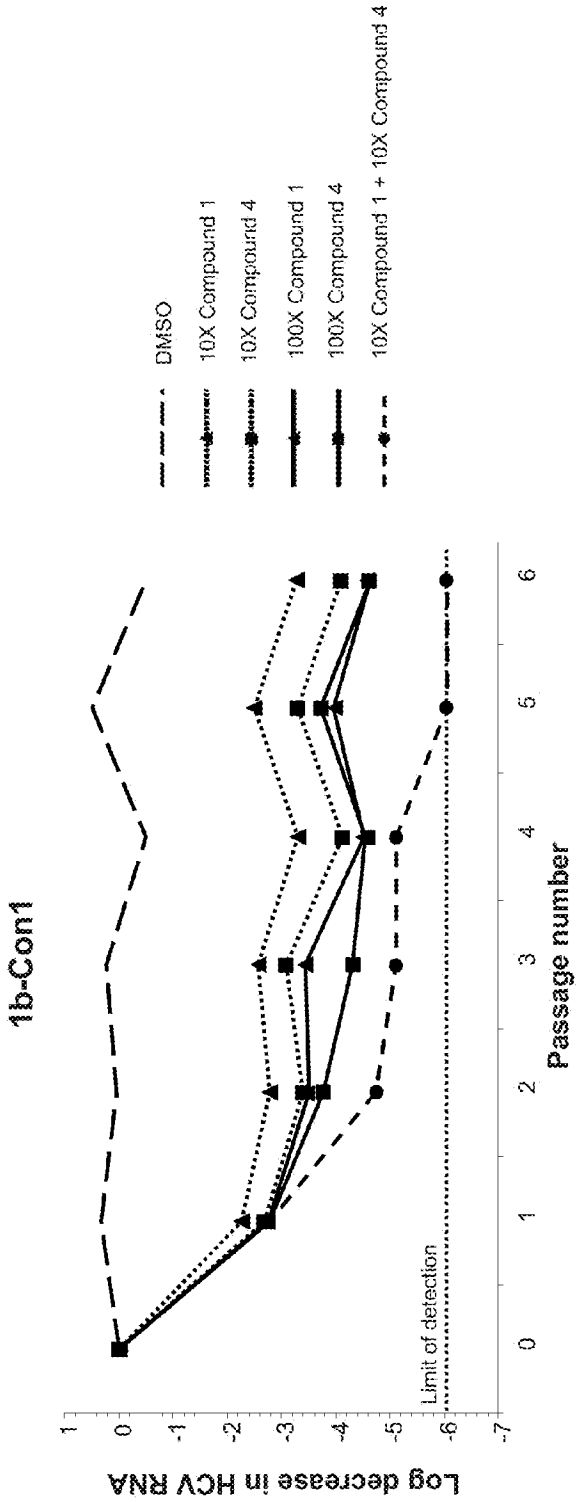

1b-Con1
DMSO
10X Compound 1
10X Compound 4
100X Compound 1
100X Compound 4
10X Compound 1 + 10X Compound 4
Log decrease in HCV RNA
Passage number
Limit of detection
1
0
-1
-2
-3
-4
-5
-6
-7
0
1
2
3
4
5
6

Figure 5D

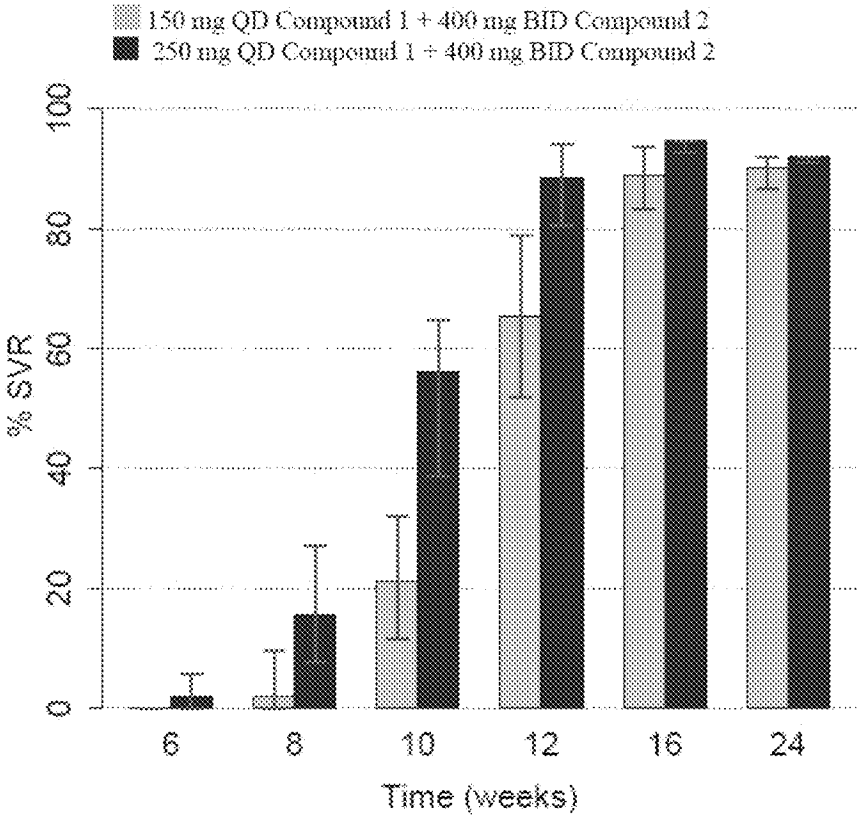

150 mg QD Compound 1 + 400 mg BID Compound 2
250 mg QD Compound 1 + 400 mg BID Compound 2
% SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 6A

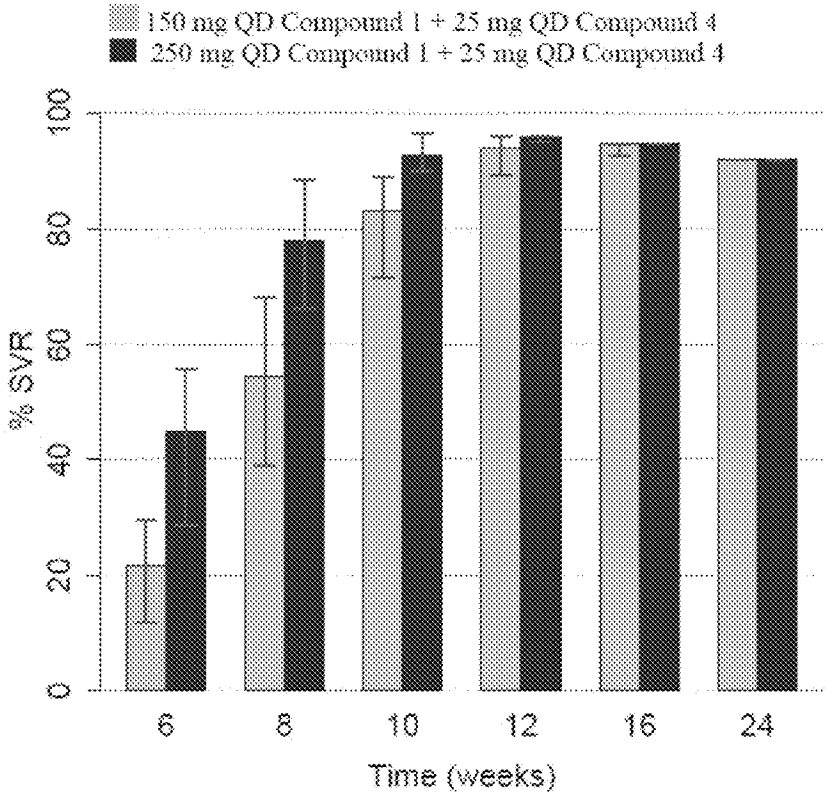

150 mg QD Compound 1 + 25 mg QD Compound 4
250 mg QD Compound 1 + 25 mg QD Compound 4
% SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 6B

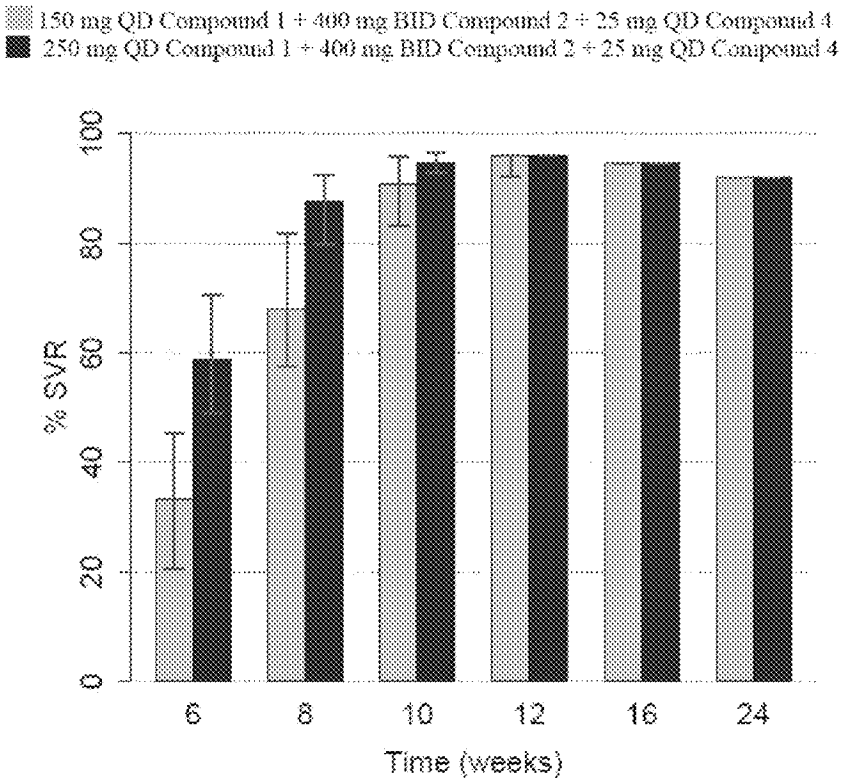

150 mg QD Compound 1 + 400 mg BID Compound 2 + 25 mg QD Compound 4
250 mg QD Compound 1 + 400 mg BID Compound 2 + 25 mg QD Compound 4
% SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 6C

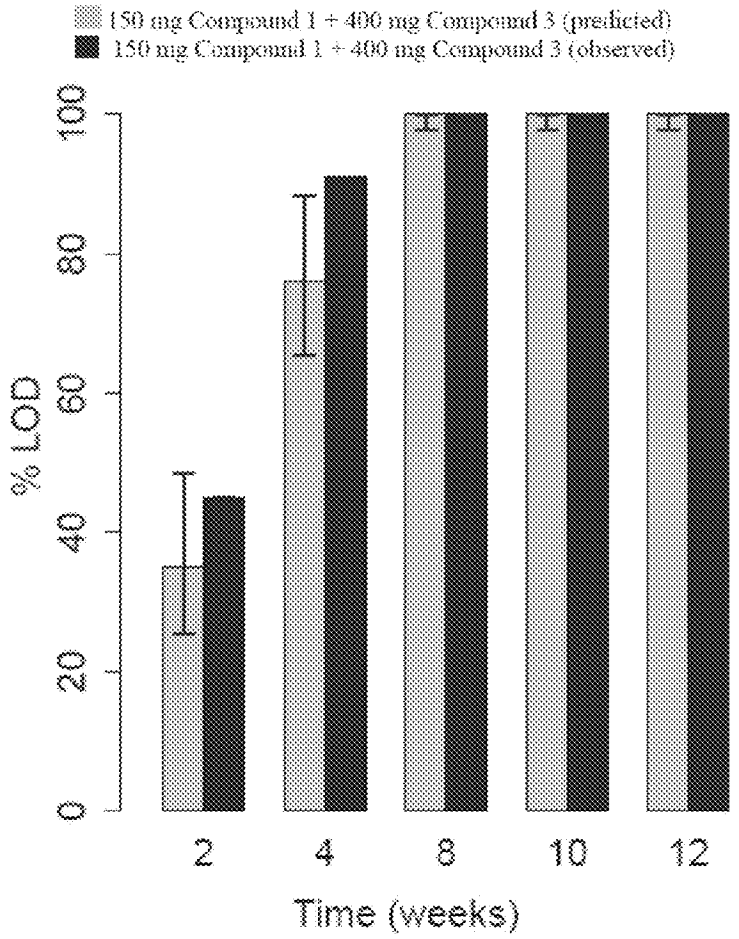

150 mg Compound 1 + 400 mg Compound 3 (predicted)
150 mg Compound 1 + 400 mg Compound 3 (observed)
% LOD
0
20
40
60
80
100
2
4
8
10
12
Time (weeks)

Figure 7

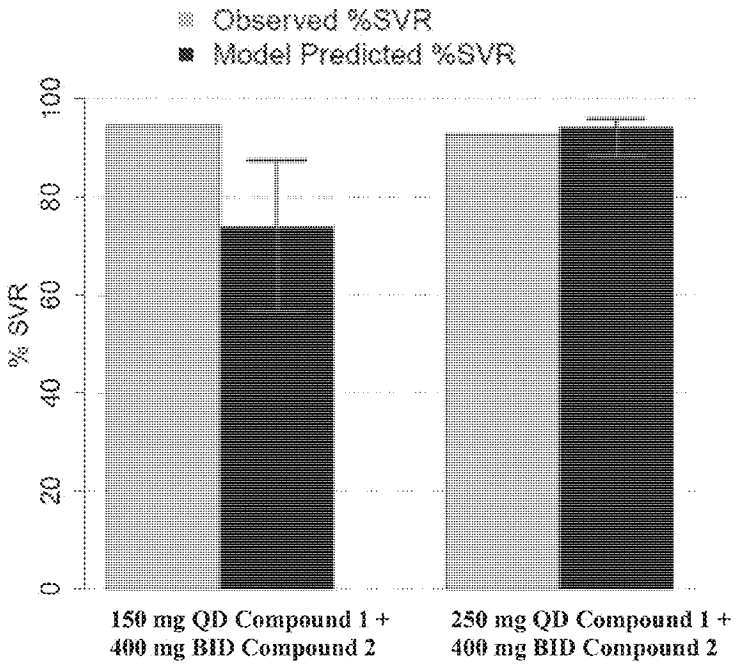

Observed %SVR
Model Predicted %SVR
% SVR
0
20
40
60
80
100
150 mg QD Compound 1 +
400 mg BID Compound 2
250 mg QD Compound 1 +
400 mg BID Compound 2

Figure 8

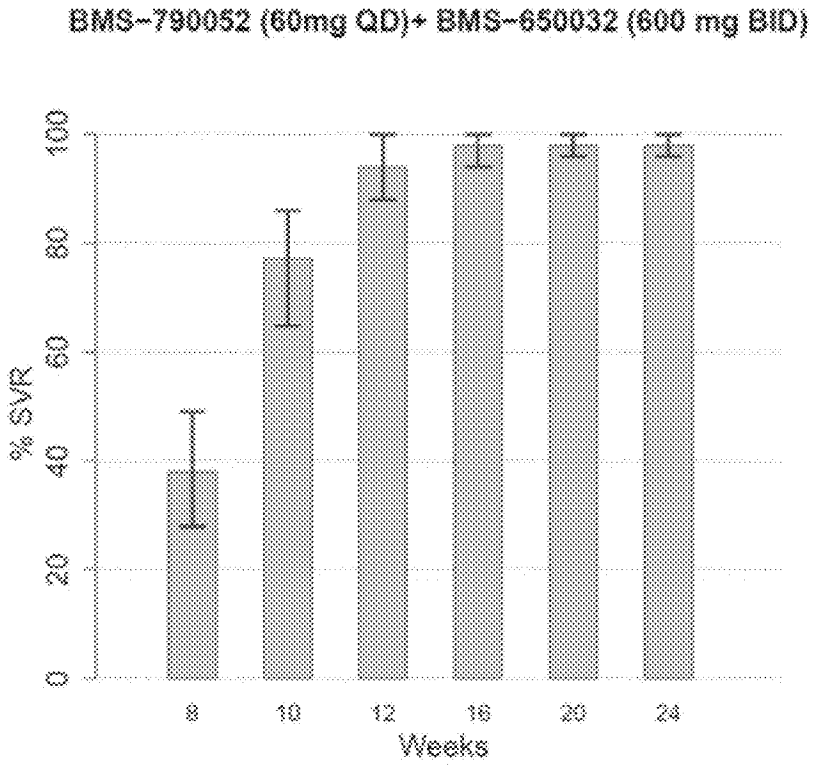

BMS-790052 (60mg QD)+ BMS-650032 (600 mg BID)
% SVR
0
20
40
60
80
100
8
10
12
16
20
24
Weeks

Figure 9

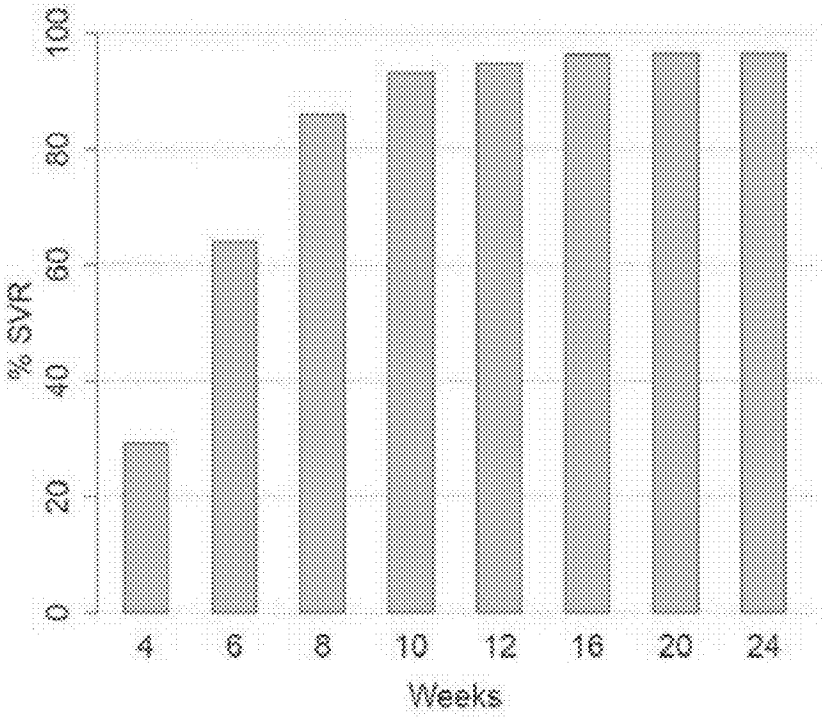


Figure 10

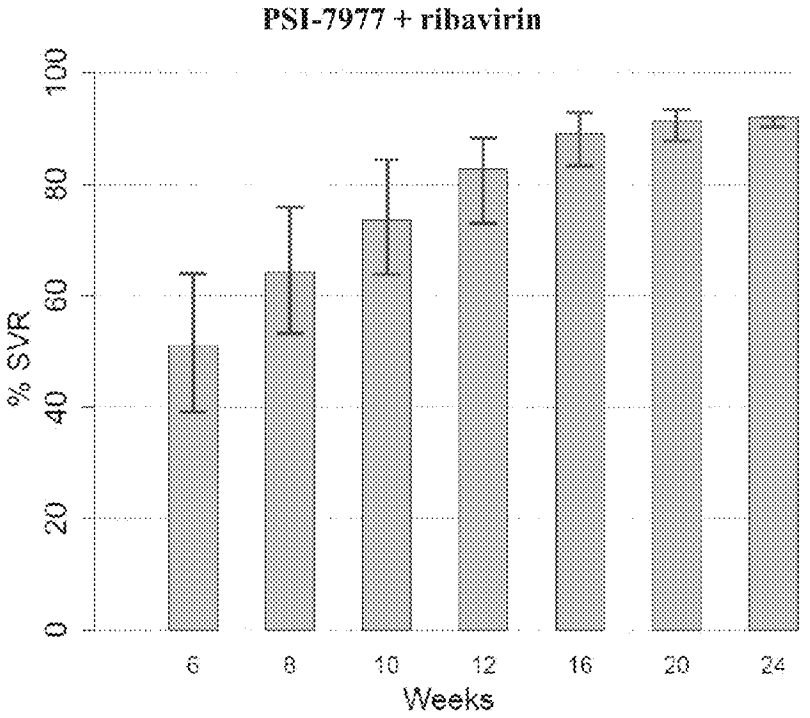


Figure 11

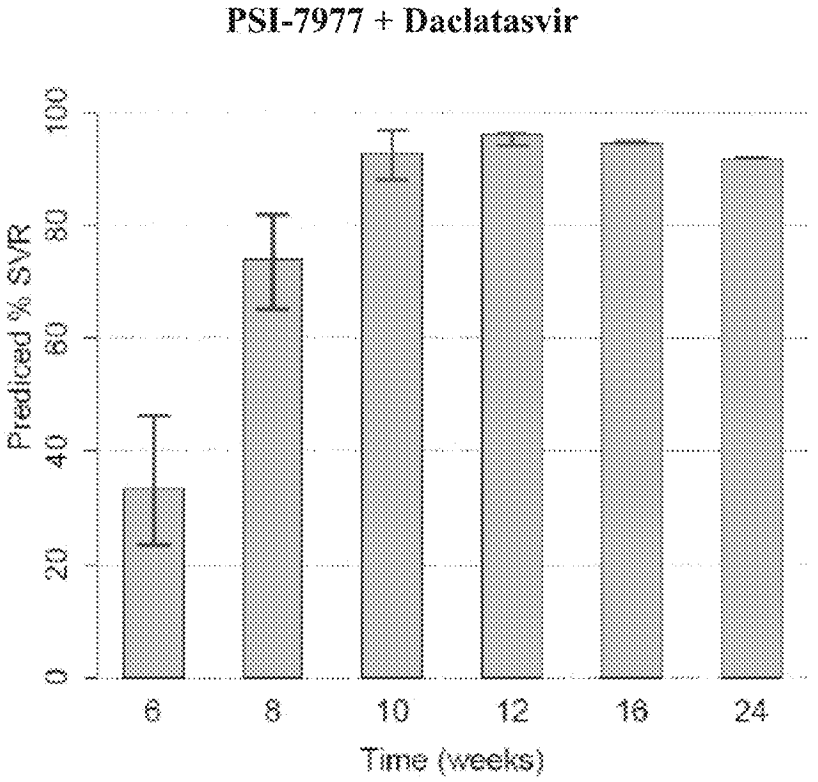

PSI-7977 + Daclatasvir
Predicted % SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 12

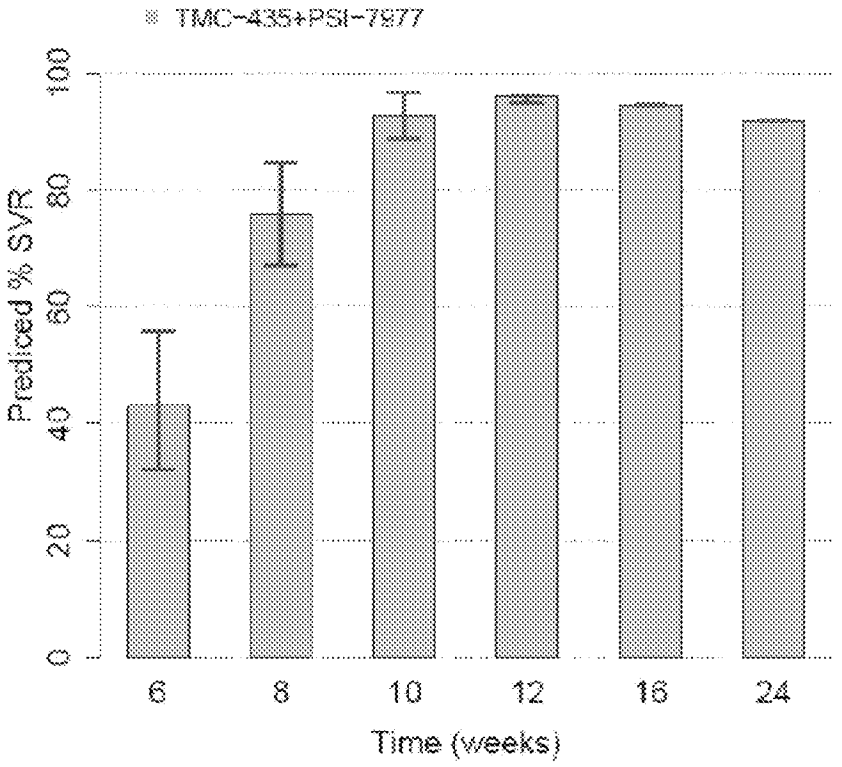

TMC-435+PSI-7977
Predicted % SVR
0
20
40
60
80
100
6
8
10
12
16
24
Time (weeks)

Figure 13

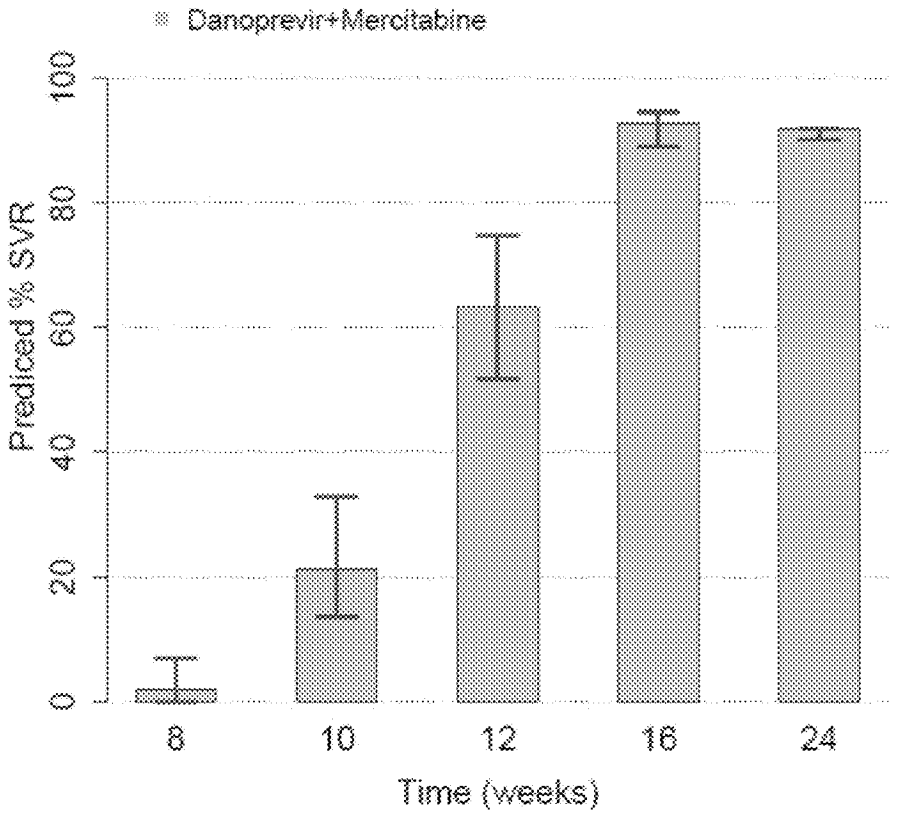

Danoprevir+Mercitabine
Prediced % SVR
0
20
40
60
80
100
8
10
12
16
24
Time (weeks)

Figure 14

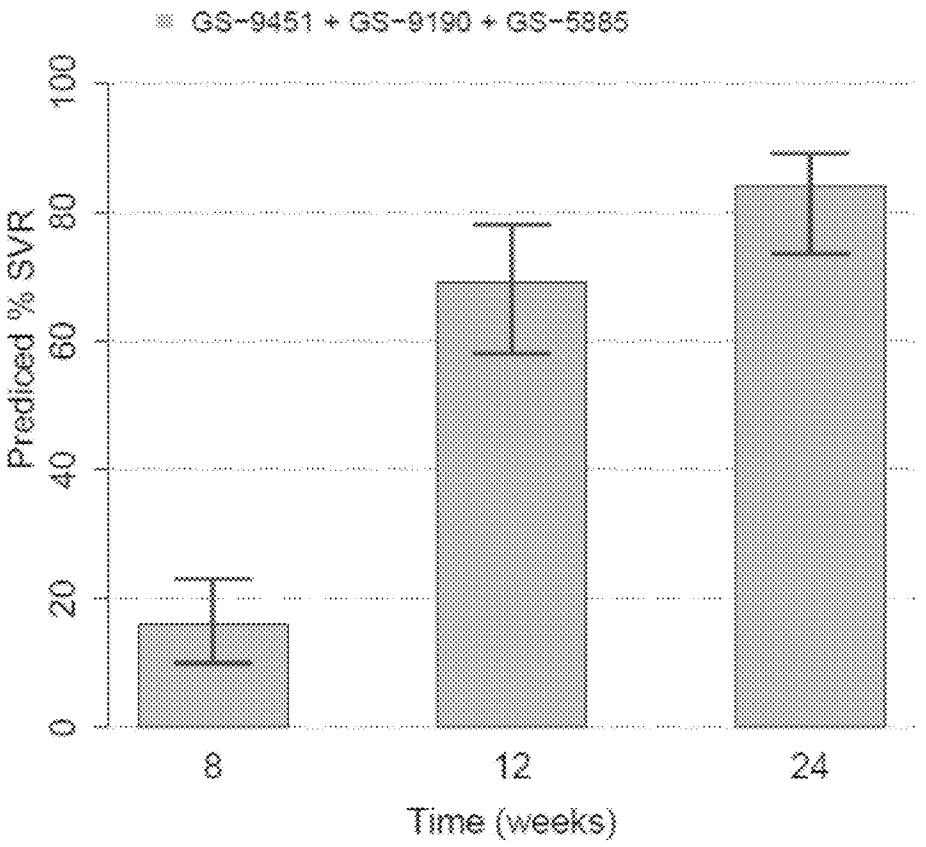

GS-9451 + GS-9190 + GS-5885
Predicted % SVR
0
20
40
60
80
100
8
12
24
Time (weeks)

Figure 15

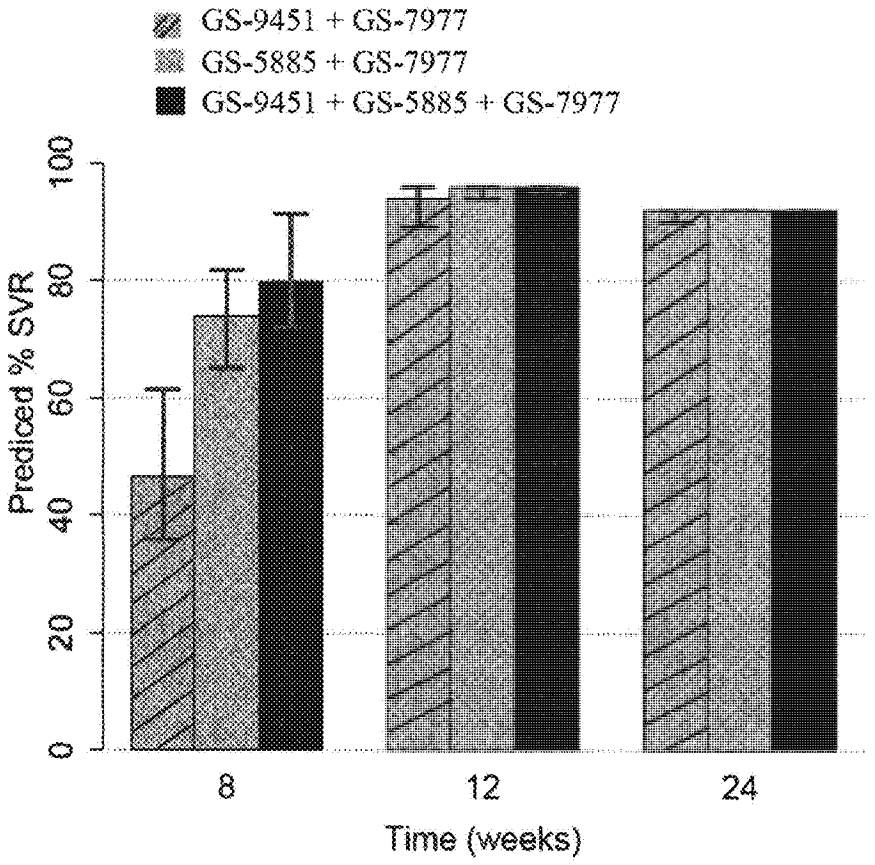

GS-9451 + GS-7977
GS-5885 + GS-7977
GS-9451 + GS-5885 + GS-7977
Predicted % SVR
0
20
40
60
80
100
8
12
24
Time (weeks)

Figure 16

METHODS FOR TREATING HCV

The application claims the benefit of U.S. Provisional Application No. 61/550,360 filed Oct. 21, 2011, U.S. Provisional Application No. 61/562,176 filed Nov. 21, 2011, U.S. Provisional Application No. 61/587,197 filed Jan. 17, 2012, U.S. Provisional Application No. 61/600,468 filed Feb. 17, 2012, U.S. Provisional Application No. 61/619,883 filed Apr. 3, 2012, and U.S. Provisional Application No. 61/656,253 filed Jun. 6, 2012.

FIELD OF THE INVENTION

The present invention relates to interferon-free and ribavirin-free treatment for hepatitis C virus (HCV).

BACKGROUND OF THE INVENTION

The HCV is an RNA virus belonging to the *Hepacivirus* genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

Chronic HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often incomplete. Therefore, there is a need for new therapies to treat HCV infection.

BRIEF SUMMARY OF THE INVENTION

As one aspect of the present invention, methods for treating HCV infection in a subject are provided. The methods comprise administering at least two direct acting antiviral agents (DAAs) for a duration of no more than twelve weeks, or for another duration as set forth herein. Preferably, the duration of the treatment is twelve weeks. The duration of the treatment can also be no more than eight weeks. Preferably, the two or more direct acting antiviral agents (DAAs) are administered in amounts effective to provide a sustained virological response (SVR) or achieve another desired measure of effectiveness in a subject. The subject is not administered ribavirin during the duration of administering the at least two DAAs. Put another way, the methods exclude the administration of ribavirin to the subject during the treatment regimen. The subject is also not administered interferon during the treatment regimen. Put another way, the methods exclude the administration of interferon to the subject, thereby avoiding the side effects associated with interferon. In some embodiments, the methods further comprise administering an inhibitor of cytochrome P-450 (such as ritonavir) to the subject to improve the pharmacokinetics or bioavailability of one or more of the DAAs.

As another aspect, methods for treating HCV infection in a subject are provided. The methods comprise administering (a) therapeutic agent 1, (b) at least one polymerase inhibitor selected from the group consisting of therapeutic agent 2, therapeutic agent 3, and combinations thereof, and (c) an inhibitor of cytochrome P-450 to the subject for a duration of

no more than twelve weeks, or for another duration as set forth herein (e.g., the treatment regimen can last for a duration of no more than 8 weeks). Preferably, therapeutic agent 1, the polymerase inhibitor(s), and the inhibitor of cytochrome P-450 are administered in amounts effective to provide high rates of SVR or another measure of effectiveness in the subject. As non-limiting examples, therapeutic agent 1 and the inhibitor of cytochrome P-450 can be co-formulated and administered once daily, and the polymerase inhibitor(s) can be administered once daily or twice daily, and the treatment regimen preferably lasts for twelve weeks (the treatment regimen can also last, for example, for eight weeks).

As still another aspect, methods for treating a population of subjects having HCV infection are provided. The methods comprise administering at least two DAAs to the subjects for a duration of no more than 12 weeks. Preferably, the at least two DAAs are administered to the subjects in amounts effective to result in SVR or another measure of effectiveness in at least about 50% of the population, preferably at least about 70% of the population.

In the foregoing methods as well as methods described hereinbelow, the DAAs can be selected from the group consisting of protease inhibitors, nucleoside or nucleotide polymerase inhibitors, non-nucleoside polymerase inhibitors, NS3B inhibitors, NS4A inhibitors, NS5A inhibitors, NS5B inhibitors, cyclophilin inhibitors, and combinations of any of the foregoing. For example, in some embodiments, the DAAs used in the present methods comprise or consist of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor. The HCV polymerase inhibitor can be a nucleotide or nucleoside polymerase inhibitor or a non-nucleoside polymerase inhibitor. The HCV polymerase inhibitor can also be a non-nucleotide polymerase inhibitor.

In some embodiments, the HCV protease inhibitor is therapeutic agent 1 (described below) and the HCV polymerase inhibitor is therapeutic agent 2 and/or therapeutic agent 3 (also described below). By way of example, therapeutic agent 1 is administered a total daily dose of from about 100 mg to about 250 mg, or administered at least once daily at a dose of from about 150 mg to about 250 mg, and therapeutic agent 2 is administered in a total daily dose of from about 300 mg to about 1800 mg or administered at least twice daily at doses from about 200 mg to about 400 mg. For some embodiments, the HCV protease inhibitor is therapeutic agent 1 and the non-nucleoside HCV polymerase inhibitor is therapeutic agent 3. By way of example, therapeutic agent 1 can be administered at a total daily dose of about 100 mg, alternatively about 200 mg, or alternatively about 250 mg; and therapeutic agent 3 is administered at a total daily dose of about 400 mg. Ritonavir (or another cytochrome P-450 3A4 inhibitor) can be co-administered with therapeutic agent 1 to improve the pharmacokinetics and bioavailability of therapeutic agent 1.

In some embodiments, the at least two DAAs comprise at least one HCV protease inhibitor and at least one NS5A inhibitor. Preferably, the HCV protease inhibitor is therapeutic agent 1 and the NS5A inhibitor is therapeutic agent 4. By way of example, therapeutic agent 1 can be administered at a total daily dosage from about 100 mg to about 250 mg, and therapeutic agent 4 can be administered in a total daily dose from about 25 mg to about 200 mg. Ritonavir (or another cytochrome P-450 3A4 inhibitor) can be co-administered with therapeutic agent 1 to improve the pharmacokinetics and bioavailability of therapeutic agent 1.

In the foregoing methods as well as methods described herein, the DAAs can be administered in any effective dosing schemes and/or frequencies, for example, they can each be

administered daily. Each DAA can be administered either separately or in combination, and each DAA can be administered at least once a day, at least twice a day, or at least three times a day. In some preferred embodiments, therapeutic agent 3 is administered once daily (QD) or twice daily (BID), and therapeutic agent 1 is administered once daily.

In some aspects, the present technology provides a method for treating HCV infection comprising administering to a subject in need thereof at least two DAAs for a duration of no more than twelve weeks, wherein the subject is not administered with either interferon or ribavirin during said duration. In some aspects, the at least two DAAs are administered in an amount effective to result in SVR. Some methods further comprise administering an inhibitor of cytochrome P450 to the subject. In some aspects, the duration is no more than eight weeks.

In some aspects of the present technology, the at least two direct acting antiviral agents comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, which is co-administered or co-formulated with ritonavir, and (ii) Compound 2 or a pharmaceutically acceptable salt thereof.

In other aspects, the at least two direct acting antiviral agents comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, which is co-administered or co-formulated with ritonavir, and (ii) Compound 3 or a pharmaceutically acceptable salt thereof.

In yet another aspect, the at least two direct acting antiviral agents comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, which is co-administered or co-formulated with ritonavir, and (ii) Compound 4 or a pharmaceutically acceptable salt thereof.

In yet a further aspect, the at least two direct acting antiviral agents comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, which is co-administered or co-formulated with ritonavir, (ii) Compound 2 or a pharmaceutically acceptable salt thereof, and (iii) Compound 4 or a pharmaceutically acceptable salt thereof.

In yet another aspect, the at least two direct acting antiviral agents comprises a drug combination selected from the group consisting of: a combination of PSI-7977 and PSI-938, a combination of BMS-790052 and BMS-650032, a combination of GS-5885 and GS-9451, a combination of GS-5885, GS-9190 and GS-9451, a combination of BI-201335 and BI-27127, a combination of telaprevir and VX-222, a combination of PSI-7977 and TMC-435, and a combination of danoprevir and R7128. In yet another aspect, the at least two direct acting antiviral agents comprises a combination of PSI-7977 and BMS-790052 (daclatasvir). In yet another aspect, the at least two direct acting antiviral agents comprises a combination of PSI-7977 and BMS-650032 (asunaprevir). In still another aspect, the at least two direct acting antiviral agents comprises a combination of PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir).

In other aspects, the present technology provides a method for treating HCV infection in a subject comprising administering (a) therapeutic agent 1, (b) at least one polymerase inhibitor selected from the group consisting of therapeutic agent 2, therapeutic agent 3 and combinations thereof, and (c) an inhibitor of cytochrome P450 to the subject and for a duration of no more than twelve weeks, wherein the therapeutic agent 1, the at least one polymerase inhibitor, and the inhibitor of cytochrome P450 are administered in amounts effective to result in SVR in the subject.

In yet another aspect, the present technology provides a method for treating a population of subjects having HCV infection, the method comprising administering at least two DAAs to the subjects for a duration of no more than 12 weeks, wherein the at least two DAAs are administered to the subjects in amounts and for a duration effective to provide a SVR in at least about 70% of the population.

In another aspect, the present technology features a combination of at least two DAAs for use in treating HCV infection, wherein the duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment comprises administering the at least two DAAs to a subject infected with HCV. The treatment does not include administering interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder, a partial responder, or a relapser), or not a candidate for interferon treatment.

In another aspect, the present technology features a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof) for use in treating HCV infection. The treatment comprises administering the DAAs to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering interferon or ribavirin. Ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) is administered with Compound 1 (or the salt thereof) to improve the pharmacokinetics of the latter. Compound 1 (or the salt thereof) and Compound 2 (or the salt thereof) can be administered concurrently or sequentially. For example, Compound 1 (or the salt thereof) can be administered once daily, together with ritonavir or another CYP3A4 inhibitor (e.g., cobicistat), and Compound 2 (or the salt thereof) can be administered twice daily. For yet another example, Compound 1 (or the salt thereof) and ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat) are co-formulated in a single composition and administered concurrently (e.g., once daily). For yet another example, Compound 1 (or the salt thereof), co-formulated with ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat), is administered once daily; and Compound 2 (or the salt thereof) is administered twice daily. As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-re-

sponder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In another aspect, the present technology features a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 3 (or a pharmaceutically acceptable salt thereof) for use in treating HCV infection. The treatment comprises administering the DAAs to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering interferon or ribavirin. Ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) is administered with Compound 1 (or the salt thereof) to improve the pharmacokinetics of the latter. Compound 1 (or the salt thereof) and Compound 3 (or the salt thereof) can be administered concurrently or sequentially. For example, Compound 1 (or the salt thereof) can be administered once daily, together with ritonavir or another CYP3A4 inhibitor (e.g., cobicistat), and Compound 3 (or the salt thereof) can be administered twice daily. For another example, Compound 1 (or the salt thereof) and Compound 3 (or the salt thereof) are administered once daily. For yet another example, Compound 1 (or the salt thereof) and ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat) are co-formulated in a single composition and administered concurrently (e.g., once daily). For yet another example, Compound 1 (or the salt thereof), ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat), and Compound 3 (or the salt thereof) are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In another aspect, the present technology features a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 4 (or a pharmaceutically acceptable salt thereof) for use in treating HCV infection. The treatment comprises administering the DAAs to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering interferon or ribavirin. Ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) is administered with Compound 1 (or the salt thereof) to improve the pharmacokinetics of the latter. Compound 1 (or the salt thereof) and Compound 4 (or the salt thereof) can be administered concurrently or sequentially. For example, Compound 1 (or the salt thereof) can be administered once daily, together with ritonavir or another CYP3A4 inhibitor (e.g., cobicistat), and Compound 4 (or the salt thereof) can be administered twice daily. For another example, Compound 1 (or the salt thereof) and Compound 4 (or the salt thereof) are administered once daily. For yet another example, Compound 1 (or the salt thereof) and ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat) are co-formulated in a single composition and administered concurrently (e.g., once daily). For yet another example, Compound 1 (or the salt thereof), ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat), and Compound 4 (or the salt thereof) are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In another aspect, the present technology features a combination of Compound 1 (or a pharmaceutically acceptable salt thereof), Compound 2 (or a pharmaceutically acceptable salt thereof), and Compound 4 (or a pharmaceutically acceptable salt thereof) for use in treating HCV infection. The treatment comprises administering the DAAs to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering interferon or ribavirin. Ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) is administered with Compound 1 (or the salt thereof) to improve the pharmacokinetic of the latter. Compound 1 (or the salt thereof), Compound 2 (or the salt thereof), and Compound 4 (or the salt thereof) can be administered concurrently or sequentially. For example, Compound 1 (or the salt thereof) can be administered once daily, together with ritonavir or another CYP3A4 inhibitor (e.g., cobicistat), and Compound 4 (or the salt thereof) can be administered once daily, and Compound 2 (or the salt thereof) can be administered twice daily. For another example, Compound 1 (or the salt thereof), Compound 4 (or the salt thereof), and ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat) are co-formulated in a single composition and administered concurrently (e.g., once daily). For yet another example, Compound 1 (or the salt thereof), ritonavir (or another CYP3A4 inhibitor, e.g., cobicistat), and Compound 4 (or the salt thereof) are co-formulated in a single composition and administered concurrently (e.g., once daily); and Compound 2 (the salt thereof) are administered twice daily. As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve

patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In another aspect, the present technology features a combination of at least two DAAs for use in treating HCV infection, wherein said combination comprises a combination selected from:

- a combination of PSI-7977 and PSI-938,
- a combination of BMS-790052 and BMS-650032,
- a combination of GS-5885 and GS-9451,
- a combination of GS-5885, GS-9190 and GS-9451,
- a combination of BI-201335 and BI-27127,
- a combination of telaprevir and VX-222,
- a combination of PSI-7977 and TMC-435, and
- a combination of danoprevir and R7128.

The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In yet another aspect, the present technology features a combination of at least two DAAs for use in treating HCV infection, wherein said combination comprises a combination selected from:

- a combination of PSI-7977 and BMS-790052
- a combination of PSI-7977 and BMS-650032,
- a combination of PSI-7977, BMS-790052 and BMS-650032,
- a combination of INX-189 and BMS-790052
- a combination of INX-189 and BMS-650032, or
- a combination of INX-189, BMS-790052 and BMS-650032.

The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In still another aspect, the present technology features PSI-7977, or a combination of at least two DAAs, for use in treating HCV infection, wherein said combination comprises a combination selected from:

- a combination of mericitabine and danoprevir,
- a combination of INX-189, daclatasvir and BMS-791325, and
- a combination of PSI-7977 and GS-5885.

The treatment comprises administering PSI-7977 or the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). For example, the duration of the treatment regimen is no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering either interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting

example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In still another aspect, the present technology features PSI-7977, or a combination of at least two DAAs, for use in treating HCV infection, wherein said combination comprises a combination selected from:

- a combination of mericitabine and danoprevir,
- a combination of INX-189, daclatasvir and BMS-791325, and
- a combination of PSI-7977 and GS-5885.

The treatment comprises administering PSI-7977 or the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering either interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In still another aspect, the present technology features a combination of at least two DAAs, for use in treating HCV infection, wherein said combination comprises a combination selected from:

- a combination of tegobuvir and GS-9256,
- a combination of BMS-791325, asunaprevir and daclatasvir, and
- a combination of TMC-435 and daclatasvir.

The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering either interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment.

In yet another aspect, the present technology features a combination of PSI-7977 and BMS-790052 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering either interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12

weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In yet another aspect, the present technology features a combination of PSI-7977 and TMC-435 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering either interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In yet another aspect, the present technology features a combination of danoprevir and mercitabine for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than sixteen weeks (e.g., the duration being 16 weeks; or the duration being 14, 12 or 10 weeks). The duration of the treatment regimen may also be less than 10 weeks. The treatment does not include administering either interferon or ribavirin. The treatment also includes co-administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) with danoprevir to improve the pharmacokinetics of danoprevir. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and

the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In yet another aspect, the present technology features a combination of INX-189, daclatasvir and BMS-791325 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than sixteen weeks (e.g., the duration being 16 weeks; or the duration being 14, 12 or 10 weeks). The duration of the treatment regimen may also be less than 10 weeks. The treatment does not include administering either interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In yet another aspect, the present technology features a combination of PSI-7977 and GS-5885 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV. The duration of the treatment regimen is no more than sixteen weeks (e.g., the duration being 16 weeks; or the duration being 14, 12 or 10 weeks). The duration of the treatment regimen may also be less than 10 weeks. The treatment does not include administering either interferon or ribavirin. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. In one example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1.

In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 2. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 15 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 16 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 15 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 14 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 13 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1.

In another aspect, the present invention features methods for treatment of HCV infection, wherein the methods comprise administering to a subject in need thereof at least two direct acting antiviral agents (DAAs), and the treatment does not include administration of either interferon or ribavirin to the subject. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In one embodiment of this aspect of the invention, the at least two DAAs comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, and (ii) Compound 2 or a pharmaceutically acceptable salt thereof, and said method further comprises administering ritonavir to the subject. Ritonavir improves the pharmacokinetics or drug exposure of Compound 1. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In another embodiment of this aspect of the invention, the at least two DAAs comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, and (ii) Compound 4 or a pharmaceutically acceptable salt thereof, and the method further comprises administering ritonavir to the subject to improve the pharmacokinetics or drug exposure of Compound 1. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In another embodiment of this aspect of the invention, the at least two DAAs comprise (i) Compound 1 or a pharmaceutically acceptable salt thereof, (ii) Compound 2 or a pharmaceutically acceptable salt thereof, and (iii) Compound 4 or a pharmaceutically acceptable salt thereof, and the method further comprises administering ritonavir to the subject to improve the pharmacokinetics or drug exposure of Compound 1. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV protease inhibitor and a HCV polymerase inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV protease inhibitor and a non-nucleoside or non-nucleotide HCV polymerase inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV protease inhibitor and a nucleoside or nucleotide HCV polymerase inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a

treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV protease inhibitor and a HCV NS5A inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV polymerase inhibitor and a HCV NS5A inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV non-nucleoside or non-nucleotide polymerase inhibitor and a HCV NS5A inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise a HCV nucleoside or nucleotide polymerase inhibitor and a HCV NS5A inhibitor. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise PSI-7977 and TMC-435. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise PSI-7977 and daclatasvir. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise PSI-7977 and GS-5885. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise mericitabine and danoprevir. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise BMS-790052 and BMS-650032. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1b. As a non-limiting example, the subject being treatment is infected with HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the invention, the at least two DAAs comprise INX-189, daclatasvir and BMS-791325. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another aspect, the present invention features methods for treatment of a treatment-naïve subject with HCV genotype 1 infection, wherein the method comprises admin-

istering an effective amount of PSI-7977 to said patient, and the treatment does not include administration of either interferon or ribavirin to the subject. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. Preferably, the subject being treated is infected with genotype 1a. More preferably, the subject being treated is a naïve patient infected with genotype 1. The subject being treated can also be a treatment-experienced patient or an interferon non-responder (e.g., a null responder), and/or is infected with HCV genotype 3. In one example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with genotype 1. The present invention also features PSI-7977 or a pharmaceutical acceptable salt thereof for use in any treatment described in this aspect of the invention.

A treatment regimen of the present technology generally constitutes a complete treatment regimen, i.e., no subsequent interferon-containing regimen is intended. Thus, a treatment or use described herein generally does not include any subsequent interferon-containing treatment. Preferably, a treatment or use described herein does not include any subsequent ribavirin-containing treatment.

Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a 3-D surface plot illustrating deviations from expected inhibitory effects from varying concentrations of Compound 1 and Compound 2 in a genotype 1b HCV replicon assay.

FIG. **2** is a contour plot showing concentrations at which Compound 1 and Compound 2 exhibited syngeristic, additive, or antagonistic interactions in the genotype 1b HCV replicon assay.

FIG. **3** is a 3-D surface plot illustrating deviations from expected inhibitory effects from varying concentrations of Compound 1 and Compound 4 in a genotype 1b HCV replicon assay.

FIG. **4** is a contour plot showing concentrations at which Compound 1 and Compound 4 exhibited syngeristic, additive, or antagonistic interactions in the genotype 1b HCV replicon assay.

FIG. **5**A is a bar graph showing the percentage of cells containing HCV genotype 1a replicon constructs surviving after three weeks of exposure to therapeutic agent 1, therapeutic agent 2, therapeutic agent 4, or a combination of some or all of those therapeutic agents in the presence of G418.

FIG. **5**B is another bar graph showing the percentage of surviving 1a-H77 replicon cells grown in the presence of G418, and two or containing HCV genotype 1a replicon constructs surviving two vs. three DAA combinations, for approximately three weeks.

FIG. **5**C depicts the effect of Compound 1, Compound 2 and a combination thereof in long-term HCV RNA reduction assays in 1a-H77 replicon cell lines.

FIG. **5**D demonstrates the effect of Compound 1, Compound 2 and a combination thereof in long-term HCV RNA reduction assays in 1b-Con1 replicon cell lines.

FIG. **6**A shows the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen without ribavirin; the 2 DAAs include (i) Compound 1 with ritonavir (Compound 1/r) and (ii) Compound 2.

FIG. **6**B illustrates the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen without ribavirin; the 2 DAAs include (i) Compound 1 with ritonavir (Compound 1/r) and (ii) Compound 4.

FIG. **6**C depicts the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 3-DAA regimen without ribavirin; the 3 DAAs include (i) Compound 1 with ritonavir (Compound 14), (ii) Compound 2 and (iii) Compound 4.

FIG. **7** shows the exposure-response model predicted versus observed percentage of subjects with HCV RNA less than LOD over time in a clinical study.

FIG. **8** demonstrates the exposure-response model predicted versus observed percentage of subjects with SVR12 in another clinical study.

FIG. **9** shows the predicted median and 90% confidence interval of SVR rates for different treatment durations of a 2-DAA regimen containing BMS-790052 and BMS-650032.

FIG. **10** shows the predicted median of SVR rates for different treatment durations of a 3-DAA regimen containing Compound 1/r, Compound 4 and PSI-7977.

FIG. **11** shows the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 1-DAA regimen containing PSI-7977 and ribavirin.

FIG. **12** depicts the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen containing daclatasvir (BMS-790052) 60 mg QD and PSI-7977 400 mg QD.

FIG. **13** shows the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen containing TMC-435 150 mg QD and PSI-7977 400 mg QD.

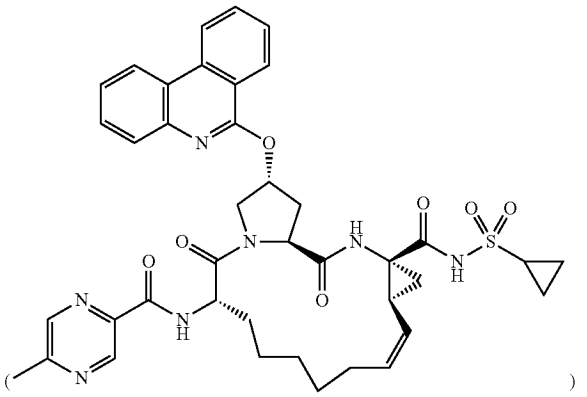
FIG. **14** illustrates the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen containing danoprevir 100 mg BID and mercitabine 750 mg BID.

FIG. **15** depicts the predicted median and 90% confidence interval of SVR percentage for different treatment durations of a 2-DAA regimen containing GS-9190 (tegobuvir) 30 mg BID+GS-9451 200 mg QD+GS-5885 90 mg QD.

FIG. **16** shows the predicted median and 90% confidence interval of SVR percentage for different treatment durations of the following DAA combo regimens: (1) GS-9451 200 mg QD+GS-7977 (PSI-7977) 400 mg QD; (2) GS-5885 90 mg QD+GS-7977 (PSI-7977) 400 mg QD; and (3) GS-9451 200 mg QD+GS-5885 90 mg QD+GS-7977 (PSI-7977) 400 mg QD.

DETAILED DESCRIPTION OF THE INVENTION

The present methods can include administering therapeutic agent 1 to a subject. Therapeutic agent 1 is Compound 1

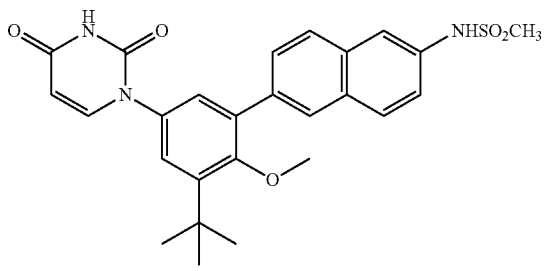


or a pharmaceutically acceptable salt thereof. Compound 1 is also known as (2R,6S,13aS,14aR,16aS,Z)—N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. Compound 1 is a potent HCV protease inhibitor. The synthesis and formulation of Compound 1 are described in U.S. Patent Application Publication No. 2010/0144608, U.S. Provisional Application Ser. No. 61/339,964 filed on Mar. 10, 2010, and U.S. Patent Application Publication No. 2011/0312973 filed on Mar. 8, 2011. All of these applications are incorporated herein by reference in their entireties. Therapeutic agent 1 includes various salts of Compound 1. Therapeutic agent 1 may be administered in any suitable amount such as, for example, in doses of from about 0.01 to about 50 mg/kg body weight, alternatively from about 0.1 to about 25 mg/kg body weight. As non-limiting examples, therapeutic agent 1 may be administered in a total daily dose amount of from about 50 mg to about 250 mg, preferably from about 100 mg to about 250 mg, and includes, but is not limited to, for example, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg and suitable amounts there between.

In preferred embodiments, ritonavir or another inhibitor of cytochrome P-450 is co-administered with therapeutic agent 1 to improve the pharmacokinetics of Compound 1.

The present methods can include administering therapeutic agent 2 to a subject. Therapeutic agent 2 is Compound 2 or a salt thereof.

Compound 2

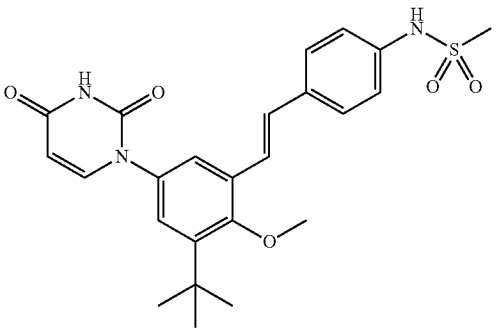


Compound 2 is also known N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide. As described in, for example, International Publication No. WO2009/039127, therapeutic agent 2 includes various salts of Compound 2, such as sodium salts, potassium salts, and choline salts. Therapeutic agent 2 also includes crystalline forms of Compound 2 and its salts such as solvate, hydrate, and solvent-free crystalline forms of Compound 2 and its salts. Compositions comprising therapeutic agent 2 can be prepared as described in, for example, International Publication No. WO2009/039127 which is incorporated by reference herein.

Therapeutic agent 2 may be administered as a free acid, salt or particular crystalline form of Compound 2. In some embodiments, therapeutic agent 2 is administered as a sodium salt. Therapeutic agent 2 may be administered in any suitable amount such as, for example, in doses of from about 5 mg/kg to about 30 mg/kg. As non-limiting examples, therapeutic agent 2 may be administered in a total daily dose amount of from about 300 mg to about 1800 mg, or from about 400 mg to about 1600 mg, or from about 600 mg to about 1800 mg, or from about 800 mg to about 1600 mg or any amounts there between. In some embodiments, the total daily dosage amount for therapeutic agent 2 is about 600 mg. In some embodiments, the total daily dosage amount for therapeutic agent 2 is about 800 mg. In some embodiments, the total daily dosage amount for therapeutic agent 2 is about 1200 mg. In some embodiments, the total daily dosage amount for therapeutic agent 2 is about 1600 mg.

The present methods can include administering therapeutic agent 3 or a salt thereof to a subject. Therapeutic agent 3 is Compound 3 or a salt thereof.

Compound 3



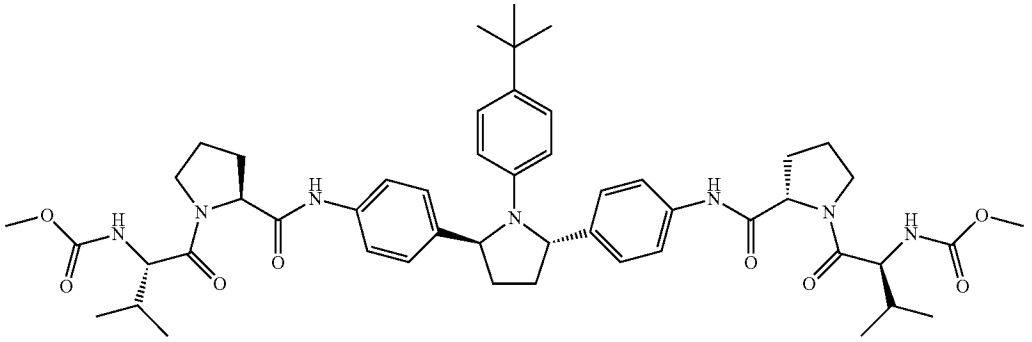
Compound 3 is also known as (E)-N-(4-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxystyryl)phenyl)methanesulfonamide. As described in, for example, International Publication No. WO2009/039127, therapeutic agent 3 includes various salts of Compound 3, such as sodium salts, potassium salts, and choline salts. Therapeutic agent 3 also includes crystalline forms of Compound 3 and its salts such as solvate, hydrate, and solvent-free crystalline forms of Compound 3 and its salts. Compositions comprising therapeutic agent 3 can be prepared as described in, for example, International Publication No. WO2009/039127 which is incorporated by reference herein.

Therapeutic agent 3 may be administered as a free acid, salt or particular crystalline form of Compound 3. In some embodiments, Compound 3 is administered as a potassium salt. Therapeutic agent 3 may be administered in any suitable amount such as, for example, in doses of from about 0.5 mg/kg to about 15 mg/kg or from about 1 mg/kg to about 10 mg/kg. As non-limiting examples, therapeutic agent 3 may be administered in a total daily dose amount of from about 100

mg to about 600 mg. In some embodiments, the total daily dosage amount for therapeutic agent 3 is about 300 mg. In some embodiments, the total daily dosage amount for therapeutic agent 3 is about 320 mg. In some embodiments, the total daily dosage amount for therapeutic agent 3 is about 400 mg. In some embodiments, the total daily dosage amount for therapeutic agent 3 is about 600 mg.

The present methods can include administering therapeutic agent 4 or a salt thereof to a subject. Therapeutic agent 4 is Compound 4 or a salt thereof.

Compound 4



Compound 4 is also known as dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5,diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene) bis(pyrrolidine-2,1-diyl)bis(3-methyl-1-oxobutane-2,1-diyl) dicarbamate. Compound 4 can be prepared as described in, for example, U.S. Publication No. 2010/0317568, which is incorporated herein by reference.

Therapeutic agent 4 may be administered as a free acid, or a salt form. Therapeutic agent 4 may be administered in any suitable amount such as, for example, in doses of from about 0.1 mg/kg to about 200 mg/kg body weight, or from about 0.25 mg/kg to about 100 mg/kg, or from about 0.3 mg/kg to about 30 mg/kg. As non-limiting examples, therapeutic agent 4 may be administered in a total daily dose amount of from about 5 mg to about 300 mg, or from about 25 mg to about 200 mg, or from about 25 mg to about 50 mg or any amounts there between. In some embodiments, the total daily dosage amount for therapeutic agent 4 is about 25 mg.

The current standard of care (SOC) for the treatment of HCV includes a course of treatment of interferon, e.g. pegylated interferon (e.g., pegylated interferon-alpha-2a or pegylated interferon-alpha-2b, such as PEGASYS by Roche, or PEG-INTRON by Schering-Plough) and the antiviral drug ribavirin (e.g., COPEGUS by Roche, REBETOL by Schering-Plough, or RIBASPHERE by Three Rivers Pharmaceuticals). The treatment often lasts for 24-48 weeks, depending on hepatitis C virus genotype. Other interferons include, but are not limited to, interferon-alpha-2a (e.g., Roferon-A by Roche), interferon-alpha-2b (e.g., Intron-A by Schering-Plough), and interferon alfacon-1 (consensus interferon) (e.g., Infergen by Valeant). Less than 50% of patients with chronic HCV infection with genotype 1 virus respond to this therapy. Further, interferon therapy has many side effects that hinder patient compliance and results in premature discontinuation of the treatment.

The interferon/ribavirin-based treatment may be physically demanding, and can lead to temporary disability in some cases. A substantial proportion of patients will experience a panoply of side effects ranging from a "flu-like" syndrome (the most common, experienced for a few days after the weekly injection of interferon) to severe adverse events including anemia, cardiovascular events and psychiatric problems such as suicide or suicidal ideation. The latter are exacerbated by the general physiological stress experienced by the patients. Ribavirin also has a number of side effects, including, anemia, high pill burden (e.g. 5-6 pills a day split BID) and teratogenicity restricting use in women of childbearing age.

The present methods provide effective treatment of HCV infection without the use of interferon or ribavirin and for a shorter period of time, such as a treatment duration of no more than twelve weeks, alternatively no more than eleven weeks, alternatively no more than ten weeks, alternatively no more than nine weeks, alternatively no more than eight weeks, alternatively no more than seven weeks, alternatively no more than six weeks, alternatively no more than five weeks, alternatively no more than four weeks, or alternatively, no more than three weeks.

In some embodiments, the present technology provides methods for treating HCV infection in a subject comprising administering at least two DAAs in the absence of interferon and ribavirin for a duration of no more than twelve weeks, alternatively no more than eight weeks. Put another way, the present methods exclude interferon and ribavirin, or the subject does not receive interferon or ribavirin for the duration of the treatment. The at least two DAAs can be co-administered or can be administered independently (with the same or different dosing frequencies) and can be administered once a day, alternatively twice a day, alternatively three times a day.

In some embodiments, the methods of treatment comprise daily administration of two or more DAAs, wherein a first DAA may be administered once a day, twice a day, or three times a day, and a second DAA may be administered once a day, twice a day, or three times a day. In some embodiments, a third DAA may be administered once a day, twice a day, or three times a day. The DAAs may be co-administered or administered at different times or frequencies. Preferably, in the methods, at least two DAAs are administered in effective amounts to provide a desired measure of effectiveness in the subject. Preferably, the treatment has reduced side effects as compared with interferon-containing treatments.

Various measures may be used to express the effectiveness of the present methods of HCV treatment. One such measure is rapid virological response (RVR), meaning that HCV is undetectable in the subject after 4 weeks of treatment, for example, after 4 weeks of administration of two or more of DAAs. Another measure is early virological response (EVR),

meaning that the subject has >2 $\log_{10}$ reduction in viral load after 12 weeks of treatment. Another measure is complete EVR (cEVR), meaning the HCV is undetectable in the serum of the subject after 12 weeks of treatment. Another measure is extended RVR (eRVR), meaning achievement of RVR and cEVR, that is, HCV is undetectable at week 4 and 12. Another measure is the presence or absence of detectable virus at the end of therapy (EOT). Another measure is SVR, which, as used herein, means that the virus is undetectable at the end of therapy and for at least 8 weeks after the end of therapy (SVR8); preferably, the virus is undetectable at the end of therapy and for at least 12 weeks after the end of therapy (SVR12); more preferably, the virus is undetectable at the end of therapy and for at least 16 weeks after the end of therapy (SVR16); and highly preferably, the virus is undetectable at the end of therapy and for at least 24 weeks after the end of therapy (SVR24). SVR24 is often considered as a functional definition of cure; and a high rate of SVR at less than 24 week post-treatment (e.g., SVR8 or SVR12) can be predictive of a high rate of SVR24. Likewise, a high rate of SVR at less than 12 week post-treatment (e.g., SVR4 or SVR8) can be predictive of a high rate of SVR12. A high rate of EOT (e.g., at week 8 or week 12) can also be indicative of a significant rate of SVR12 or SVR24.

In some embodiments, the amounts of the two or more DAAs, and/or the duration of the treatment regimen of the two or more DAAs, are effective to provide an RVR in a subject, or an EVR in a subject, or a cEVR in a subject, or an eRVR in a subject, or an absence of detectable virus at EOT in a subject. In some embodiments, the present methods comprise treating a population of subjects having HCV infection (e.g. treatment naïve subjects), and the methods comprise administering at least two DAAs to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein the at least two DAAs are administered to the subjects in amounts effective to provide an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment) in at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, alternatively about 100% of the population. In some embodiments, the present methods comprise treating a population of IFN experienced subjects (e.g., interferon non-responders) having HCV infection, and the methods comprise administering at least two DAAs to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein the at least two DAAs are administered to the subjects in amounts effective to provide an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment) in at least about 50% of the population, alternatively at least about 55% of the population, alternatively at least about 60% of the population, alternatively at least about 65% of the population. In other embodiments, the amount of DAAs and the duration of the treatment are effective to provide one or more of an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment), an RVR, an EVR, a cEVR, an eRVR, or an absence of detectable virus at EOT, in at least about 50% of the population, alternatively at least about 55%, in at least about 60% of the population, alternatively at least about 65% of the population, alternatively at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, alternatively about 100% of the population. For example, the present methods comprise administering at least two DAAs in amounts and for durations effective to provide an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment) in a subject. In some embodiments, the present technology provides for an SVR (e.g., SVR after 8 weeks post-treatment, or SVR after 24 weeks post-treatment) in at least about 50% of the population, alternatively at least about 55% of the population, in at least about 60% of the population, preferably in at least about 65% of the population, preferably in at least about 70% of the population, preferably at least about 75% of the patients treated by such methods herein described, more preferably in at least 80% of the population, and highly preferably in at least about 90% of the patients being treated. In some embodiments, a treatment of the present technology provides an RVR or undetectable level of HCV RNA in the bloodstream at four (4) weeks of treatment (preferably in addition to a SVR).

A DAA of the present technology includes, but is not limited to, a protease inhibitor, a HCV polymerase inhibitor, an HCV NS5A inhibitor, an HCV NS3B inhibitor, an HCV NS4A inhibitor, an HCV NS5B inhibitor, an HCV entry inhibitor, a cyclophilin inhibitor, a CD81 inhibitor, or an internal ribosome entry site inhibitor. The HCV polymerase inhibitor may be a nucleoside or nucleotide polymerase inhibitor or a non-nucleoside polymerase inhibitor. The HCV polymerase inhibitor may be a nucleotide polymerase inhibitor or a non-nucleotide polymerase inhibitor.

In yet another example of this aspect of the technology, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir).

It was unexpected that an interferon-free and ribavirin-free treatment using a combination of two or more DAAs, and for a duration of no more than 12 weeks, can achieve significant SVR. In some cases, such a treatment can achieve an SVR in at least about 75% of patients, and in some cases, such a treatment can achieve an SVR in at least about 85% of patients, and in certain cases, such a treatment can achieve an SVR in at least about 90% of patients. It was also unexpected that an interferon-free and ribavirin-free treatment using a combination of two or more DAAs, and for a duration of no more than 12 weeks, may achieve significant SVR in inter-

feron non-responders (e.g., null responders), for example, such a treatment may achieve an SVR in at least about 50% of patients in the interferon non-responder population, preferably at least about 60% of patients in the interferon non-responder population, more preferably at least about 65% of patients in the interferon non-responder population.

Accordingly, in one aspect, the present technology features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 8 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, or an interferon non-responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 can be co-formulated with ritonavir. In yet another example of this aspect of the technology, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir with ritonavir and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400

mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 7 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated or co-administered with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily.

In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 6 weeks and does not include administration of any interferon or any ribavirin. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with

100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 5 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, or an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Com-

pound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 4 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, or an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg

Compound 1 together with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 3 weeks (or even less, depending on the patient's condition) and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, or an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir with ritonavir and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises

administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 24 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another

example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts from 13 to 23 weeks (e.g., the duration of the treatment is selected from 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 weeks) and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir (with ritonavir) and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the

method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 12 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, or an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir with ritonavir and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises

administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 11 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, or an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir with ritonavir and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together

with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 10 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, or an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir with ritonavir and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two

or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 9 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a treatment naïve patient, a treatment experienced patient, including, but not limited to, a relapser, or an interferon partial responder, or an interferon non-responder (e.g., a null responder), or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times, and can be co-formulated in a single formulation or formulated in different compositions. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. For another instance, the combination of two or more DAAs can be a combination of at least two HCV polymerase inhibitors (e.g., a combination of at least two nucleoside or nucleotide polymerase inhibitors, or a combination of at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least two non-nucleoside polymerase inhibitors). For another instance, the combination of two or more DAAs can be a combination of at least two HCV protease inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least two HCV NS5A inhibitors. For another instance, the combination of two or more DAAs can be a combination of at least one HCV polymerase inhibitor and at least one NS5A inhibitor (e.g., a combination of at least one HCV NS5A inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV NS5A inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor). In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222. In another example, the combination of two or more DAAs comprises GS-5885 and GS-9451. In yet another example, the combination of two or more DAAs includes danoprevir with ritonavir and R7128. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-790052. In yet another example, the combination of two or more DAAs includes PSI-7977 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes PSI-7977, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In yet another example, the combination of two or more DAAs includes INX-189 and BMS-650032 (asunaprevir). In still another example, the combination of two or more DAAs includes INX-189, BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir). In still another example, the combination of two or more DAAs includes mericitabine and danoprevir. In still another example, the combination of two or more DAAs includes INX-189, daclatasvir and BMS-791325. In still another example, the combination of two or more DAAs includes PSI-7977 and GS-5885. In still another example, the combination of two or more DAAs includes PSI-7977, Compound 1 (with ritonavir), and Compound 4. In still another example, the method comprises

administering to a patient in need thereof an effective amount of PSI-7977 as the sole DAA in lieu of a combination of two or more DAAs. In still another example, the method comprises administering 100 or 200 mg Compound 1 together with 100 mg ritonavir once daily, and 25 mg Compound 4 once daily. In yet another example, the method comprises administering 150 mg or 250 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 once daily. In another example, the method comprises administering 150 mg Compound 1 together with 100 mg ritonavir once daily, and 400 mg Compound 3 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 2 twice daily. In another example, the method comprises administering 100 or 150 mg Compound 1 together with 100 mg ritonavir once daily, 25 mg Compound 4 once daily, and 400 mg Compound 3 twice daily. Other DAA(s) can also be included in a treatment regimen according to this aspect of the technology.

In another embodiment, the present technology provides interferon- and ribavirin-free treatment comprising administering daily two DAAs, where the two DAAs include a HCV polymerase inhibitor, for example PSI-7977 and a NS5A inhibitor, for example BMS-790052 for a duration of no more than twelve weeks (e.g., no more than eleven weeks), preferably no more than eight weeks.

In some embodiments, the present technology provides a method of treating Hepatitis C virus infection in a subject comprising administering daily a HCV protease inhibitor and a HCV polymerase inhibitor to the subject in the absence of interferon and ribavirin for a duration of no more than twelve weeks, preferably no more than eight weeks. In some embodiments, ritonavir (or an equivalent thereof) is co-administered with one or more protease inhibitors to improve the pharmacokinetics of the protease inhibitor(s). The treatment excludes administering ribavirin to the patient. In some embodiments, the HCV polymerase inhibitor is at least one nucleoside or nucleotide polymerase inhibitor or at least one non-nucleoside polymerase inhibitor. In some embodiments, both a nucleoside or nucleotide polymerase inhibitor and a non-nucleoside polymerase inhibitor may be administered.

The methods of the present technology as described herein may be used to treat a naïve patient or a treatment experienced patient. Treatment experienced patients include interferon non-responders (e.g., null responders), partial responders (patients whose HCV RNA levels declined but never became undetectable), and relapsers (patients who achieved undetectable levels of HCV RNA during therapy but rebound). Methods of the present technology may also be used to treat patients who are not candidates for interferon treatment. Patients who are not candidates for interferon treatment include, but are not limited to, one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon.

In some embodiments, a cytochrome P-450 inhibitor, e.g. ritonavir, is administered either in the same or separate pharmaceutical composition with the protease inhibitor (e.g. Compound 1 (or a pharmaceutically acceptable salt thereof)) to improve the pharmacokinetics. A cytochrome P450 inhibitor reduces the metabolism of some protease inhibitors, such as Compound 1, thereby improving the pharmacokinetics and bioavailability of the protease inhibitor, for example Compound 1. More preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is co-formulated with ritonavir in the same dosage form. Other cytochrome P450 inhibitors, such as cobicistat, may also be administered in lieu of ritonavir, to enhance the pharmacokinetics of Compound 1 (or a pharmaceutically acceptable salt thereof).

Inhibitors of cytochrome P450, such as ritonavir, may be co-administered with the DAAs, either sequentially or simultaneously, in the same or different compositions. In some embodiments, the cytochrome P450 inhibitors are administered in order to improve the pharmacokinetics of at least one of the DAAs. Not to be bound by any theory, but a cytochrome P450 inhibitor may also reduce the development of resistant strains of HCV when co-administered with a DAA, thus providing the effectiveness in a shorter treatment. In some embodiments, ritonavir is co-administered with therapeutic agent 1. In some embodiments, ritonavir is co-administered with therapeutic agent 1 in the same compositions.

In some embodiments, the present technology provides a method of treating HCV infection comprising administering at least one protease inhibitor and at least one HCV polymerase inhibitor in a course of treatment of no more than, or less than, eight weeks in the absence of interferon and ribavirin. In some embodiments, the HCV polymerase inhibitor is Compound 1 (or a pharmaceutically acceptable salt thereof).

In some embodiments, the present technology provides a method of treating HCV infection without using interferon and ribavirin, the method comprising administering at least two DAAs to a patient in need of such treatment, wherein the at least two DAAs include at least one protease inhibitor and at least one HCV polymerase inhibitor. In some embodiments, the at least two DAAs includes therapeutic agent 1 with at least one HCV polymerase inhibitor. In some embodiments, the HCV polymerase inhibitor is at least one non-nucleoside polymerase inhibitor. In some embodiments, the non-nucleoside polymerase inhibitor is therapeutic agent 2 or therapeutic agent 3 or a combination thereof.

In some embodiments, the present technology provides a method of treating HCV infection without using interferon and ribavirin, the method comprising administering a HCV protease inhibitor, preferably therapeutic agent 1, with at least one HCV NSSA inhibitor to a patient in need of such treatment. In some embodiments, the NSSA inhibitor is therapeutic agent 4.

In some embodiments of the present technology, a method of treating HCV infection without using interferon and ribavirin, the method comprises administering at least three DAAs to a subject for no more than 8 weeks without administering interferon or ribavirin. The at least three DAAs can be at least one protease inhibitor, at least one HCV polymerase inhibitor, and at least one NSSA inhibitors. In a preferred embodiment, the at least one protease inhibitor is therapeutic agent 1, the at least one polymerase inhibitor is therapeutic agent 2 or therapeutic agent 3, and the at least one NSSA inhibitor is therapeutic agent 4.

Preferred HCV protease inhibitors include, but are not limited to, therapeutic agent 1, telaprevir (Vertex), boceprevir (Merck), BI-201335 (Boehringer Ingelheim), GS-9451 (Gilead), and BMS-650032 (BMS). Other suitable protease inhibitors include, but are not limited to, ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BMS-650032 (BMS), danoprevir (RG7227/ITMN-191, Roche), GS-9132 (Gilead), GS-9256 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir (Schering-Plough Corp), PHX-1766 (Phenomix), TMC-435 (Tibotec),

vaniprevir (MK-7009, Merck), VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof.

Preferred non-nucleoside HCV polymerase inhibitors for use in the present technology include, but are not limited to, therapeutic agent 2, therapeutic agent 3, GS-9190 (Gilead), BI-207127 (Boehringer Ingelheim), and VX-222 (VCH-222) (Vertex & ViraChem). Preferred nucleotide HCV polymerase inhibitors include, but are not limited to, PSI-7977 (Pharmasset), and PSI-938 (Pharmasset). Other suitable and non-limiting examples of suitable HCV polymerase inhibitors include ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination thereof. A polymerase inhibitor may be a nucleoside or nucleotide polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination therefore. A polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as PF-00868554 (Pfizer), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir (Gilead), TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof.

Preferred NS5A inhibitors include, but are not limited to, therapeutic agent 4, BMS-790052 (BMS) and GS-5885 (Gilead). Non-limiting examples of suitable NS5A inhibitors include GSK62336805 (GlaxoSmithKline), ACH-2928 (Achillion), AZD2836 (Astra-Zeneca), AZD7295 (Astra-Zeneca), BMS-790052 (BMS), BMS-824393 (BMS), GS-5885 (Gilead), PPI-1301 (Presidio), PPI-461 (Presidio) A-831 (Arrow Therapeutics), A-689 (Arrow Therapeutics) or a combination thereof.

Non-limiting examples of suitable cyclophilin inhibitors include alisporovir (Novartis & Debiopharm), NM-811 (Novartis), SCY-635 (Scynexis), or a combination thereof.

Non-limiting examples of suitable HCV entry inhibitors include ITX-4520 (iTherx), ITX-5061 (iTherx), or a combination thereof.

Specific examples of other DAA agents that are suitable for the present methods include, but are not limited to, AP-H005, A-831 (Arrow Therapeutics) (NS5A inhibitor), A-689 (Arrow Therapeutics) (NS5A inhibitor), INX08189 (Inhibitex) (polymerase inhibitor), ITMN-191 (Intermune/Roche) (NS3/4A Protease inhibitor), VBY-376 (Protease Inhibitor) (Virobay), ACH-1625 (Achillion, Protease inhibitor), IDX136 (Idenix, Protease Inhibitor), IDX316 (Idenix, Protease inhibitor), VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191 (Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), R7128 (Roche), PF-868554 (Pfizer) (non-nucleoside polymerase inhibitor), PF-4878691 (Pfizer), IDX-184 (Idenix), IDX-375 (Idenix, NS5B polymerase inhibitor), PPI-461 (Presidio), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), CTS-1027 (Conatus), GS-9620 (Gilead), PF-4878691 (Pfizer), RO5303253 (Roche), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), GSK62336805 (GlaxoSmithKline), or any combinations thereof.

In some embodiments, the present technology features methods for treating patients with genotype 1, such as 1a or 1b, HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. Patients with genotype 1, such as 1a or 1b, infection can be treated with a combination of at least 2 DAAs without interferon and without ribavirin where the at least two DAAs include therapeutic agent 1 and therapeutic agent 2. Therapeutic agent 1 and therapeutic agent 2 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) after a treatment duration of no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks). The patients may be treatment naïve patients or treatment experienced HCV patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 2 can be administered with therapeutic agent 1 in any of the dosages of therapeutic agent 1 described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, for example, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1500 mg, or 1800 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, but are not limited to, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of no more than 12 weeks, the patient may be treated with a ribavirin-containing regimen.

In some embodiments, the present technology features methods for treating patients with genotype 2 or 3 HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. Patients with genotype 2 or 3 HCV infection can be treated with a combination of at least 2 DAAs without interferon and without ribavirin where the at least two DAAs include therapeutic agent 1 and therapeutic agent 2. Therapeutic agent 1 and therapeutic agent 2 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) with a treatment duration of no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the

duration being 8 weeks). The patients may be treatment naïve HCV patients or treatment experienced HCV patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 300 mg. Therapeutic agent 2 can be administered in connection with therapeutic agent 1 in any of the dosages of therapeutic agent 1 described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, for example, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1500 mg, or 1800 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of no more than 12 weeks, the patient may be treated with a ribavirin-containing regimen.

In some embodiments, the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1 and therapeutic agent 2. Suitably, the patient may be a treatment naïve patient, a treatment experienced patient or an interferon nonresponder. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. In some embodiments, the patient is infected with HCV genotype 1b. In some embodiments, the patient is infected with HCV genotype 2 or 3, such as 2a or 2b. In some other embodiments, the patient is infected with HCV genotype 3a. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The treatment duration can be for no more than 12 weeks, preferably no more than 8 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). Therapeutic agent 1 and therapeutic agent 2 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) after treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 2 can be administered with therapeutic agent 1 in any of the dosages described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, for example, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after a treatment duration of no more than 12 weeks, the patient may be treated with a ribavirin-containing regimen.

In some embodiments, the present technology features methods for treating patients with HCV infection who are not candidates for interferon treatment. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. Patients who are not candidates for interferon treatment include, but are not limited to, one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon. A non-candidate for interferon treatment can be infected with HCV genotype 1 or 2, for example, genotype 1a or 1b. A non-candidate for interferon treatment can be infected with HCV genotype 2, for example, genotype 2a or 2b. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. In some embodiments, non-candidate for interferon treatment patients can be treated with a combination of at least 2 DAAs without interferon and without ribavirin for a treatment duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The at least two DAAs include at least one HCV protease inhibitor and at least one HCV polymerase inhibitor. Suitably, the at least one HCV protease inhibitor can be therapeutic agent 1 and the at least one HCV polymerase inhibitor can be therapeutic agent 2. Therapeutic agent 1 and therapeutic agent 2 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) after a treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 2 can be administered with therapeutic agent 1 with therapeutic agent 1 administered at any of the dosages described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, for example, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of no more than 12 weeks, the patient may be treated with a ribavirin-containing regimen.

In another aspect, the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the dura-

tion being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1, therapeutic agent 2 and therapeutic agent 4. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). Therapeutic agent 1, therapeutic agent 2, and therapeutic agent 3 can be provided in effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) after a treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 300 mg. Therapeutic agent 2 can be administered with therapeutic agent 1 with therapeutic agent 1 being administered in any of the dosages described above. The total daily dosage of therapeutic agent 2 can be, but is not limited to, for example, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg. Therapeutic agent 4 can be provided in combination with therapeutic agent 1 and therapeutic agent 2 in which therapeutic agent 1 and therapeutic agent 2 are administered in any combination of the dosages for therapeutic agent 1 and therapeutic agent 2 described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1 and therapeutic agent 2 in a total daily dose of therapeutic agent 4 of an amount from about 5 mg to about 350 mg, preferably about 5 mg to about 300 mg, more preferably about 25 mg to about 200 mg. The total daily dosage of therapeutic agent 4 can be, but are not limited to, for example, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, or about 100 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. Suitably, in some embodiments, the patient may be a treatment naïve patient, a treatment experienced patient, or an interferon nonresponder. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of 12 weeks, the patient may be treated with a ribavirin-containing regimen.

In some embodiments, the present technology features methods for treating patients with genotype 1, such as genotype 1a or 1b, HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1 and therapeutic agent 3. The treatment duration may be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 3 can be administered in connection with therapeutic agent 1 with therapeutic agent 1 being administered at any of the dosages of described above. Therapeutic agent 3 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 3 can be, but is not limited to, for example, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg. Therapeutic agent 1 and therapeutic agent 3 can be administered in any of the suitable dosages of therapeutic agent 1 or therapeutic agent 3 recited above. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of no more than 12 weeks, the patient may be treated with a ribavirin-containing regimen.

In some embodiments, the present technology features methods for treating patients with genotype 2 or 3, such as genotype 2a, 2b or 3a, HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1 and therapeutic agent 3. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). Therapeutic agent 1 and therapeutic agent 3 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) in a treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 3 can be administered with therapeutic agent 1 with therapeutic agent 1 being administered at any of the dosages described above. Therapeutic agent 3 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 3 can be, but is not limited to, for example, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about

490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg. Therapeutic agent 1 and therapeutic agent 3 can be administered in any combination of dosage of therapeutic agent 1 or therapeutic agent 3 recited above. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of no more than 12 weeks, the patient may be treated with a ribavirin-containing regime.

In some embodiments, the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1 and therapeutic agent 3. Suitably, the patient may be a treatment naïve patient, a treatment experienced patient or an interferon nonresponder. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. In some embodiments, the patient is infected with HCV genotype 1b. In some other embodiments, the patient is infected with HCV genotype 2 or 3, such as 2a or 2b. In some other embodiments, the patient is infected with HCV genotype 3a. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 3 can be administered in connection with therapeutic agent 1 with therapeutic agent 1 being administered at any of the dosages described above. Therapeutic agent 3 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 3 can be, but is not limited to, for example, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of no more than 12 weeks, the patient may be treated with a ribavirin-containing regimen.

In some embodiments, the present technology features methods for treating patients with HCV infection who are not candidates for interferon treatment. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1 and therapeutic agent 3. Patients who are not candidates for interferon treatment include, but are not limited to, one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. In some embodiments, the patient is infected with HCV genotype 1b. In some other embodiments, the patient is infected with HCV genotype 2 or 3, such as 2a or 2b. In some other embodiments, the patient is infected with HCV genotype 3a. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 3 can be administered with therapeutic agent 1 with therapeutic agent 1 being administered at any of the dosages described above. Therapeutic agent 3 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 3 can be, but is not limited to, for example, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day.

In some embodiments, the present technology features methods for treating patients with HCV genotype 1, such as 1a or 1b, infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1 and therapeutic agent 4. Patients with genotype 1a

or 1b infection can be treated with a combination of at least 2 DAAs without interferon and without ribavirin in which the at least two DAAs include therapeutic agent 1 and therapeutic agent 4. Therapeutic agent 1 and therapeutic agent 4 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) in a treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered in connection with therapeutic agent 1 where therapeutic agent 1 is administered in any of the dosages described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1 in a total daily dose of therapeutic agent 4 of from about 25 mg to about 200 mg. The total daily dosage of therapeutic agent 4 can be, but is not limited to, for example, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1 and therapeutic agent 4 are administered once a day.

In some embodiments, the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1 and therapeutic agent 4. The patients may be treatment naïve patients or treatment experienced patients. The treatment can be administered for a duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The patient can have HCV genotype 1, such as HCV genotype 1a or 1b. In other embodiments, the patient may have HCV genotype 1b. In some embodiments, it is contemplated to treat other HCV genotypes. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered in connection with therapeutic agent 1 in any of the dosages described above. Therapeutic agent 4 can be provided alone or in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 4 can be, but is not limited to, for example, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1 and therapeutic agent 4 are administered once a day.

In some embodiments, the present technology features methods for treating patients with HCV infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1 and therapeutic agent 4. The patients may be treatment naïve patients or treatment experienced patients. The treatment can be administered for a duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The patient can have HCV genotype 2 or 3, such as HCV genotype 2a. In some embodiments, the patient may have HCV genotype 2b. In other embodiments the patient may have HCV genotype 3a. The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered in connection with therapeutic agent 1 in which therapeutic agent 1 is administered in any of the dosages described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 4 can be, but is not limited to, for example, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1

and therapeutic agent 4 are administered once a day. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of no more than 12 weeks, the patient may be treated with a ribavirin-containing regimen.

In some embodiments, the present technology features methods for treating patients with HCV infection who are not candidates for interferon treatment. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. The combination comprises therapeutic agent 1 and therapeutic agent 4. Patients who are not candidates for interferon treatment include, but are not limited to, one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon. In some embodiments, the patient is infected with HCV genotype 1, such as genotype 1a. In some embodiments, the patient is infected with HCV genotype 1b. In some other embodiments, the patient is infected with HCV genotype 2 or 3, such as 2a or 2b. In some other embodiments, the patient is infected with HCV genotype 3a. The treatment according to this aspect of the technology can also be effective against other HCV genotypes. Therapeutic agent 1 and therapeutic agent 4 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) after treatment of no more than 12 weeks, preferably no more than 8 weeks. The interferon non-responder patients include partial interferon responders and interferon rebound patients. See Guidance for Industry—Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment (FDA, September 2010, draft guidance) for the definitions of naive, partial responder, responder relapser (i.e., rebound), and null responder patients. The interferon non-responder patients also include null responder patients. The treatment can be administered for a duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered with therapeutic agent 1 where therapeutic agent 1 is administered in any of the dosages described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 4 can be, but is not limited to, for example, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1 and therapeutic agent 4 are administered once a day. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of no more than 12 weeks, the patient may be treated with a ribavirin-containing regimen.

In some embodiments, the present technology features methods for treating patients with HCV infection who are interferon non-responders (e.g., null responders). The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), preferably no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon or ribavirin. Interferon nonresponder patients can be treated with a combination of at least 2 DAAs without interferon and without ribavirin wherein the two DAAs include therapeutic agent 1 and therapeutic agent 4. Therapeutic agent 1 and therapeutic agent 4 can be administered in therapeutically effective amounts to provide a SVR (for example, a SVR8, SVR12, SVR16, or SVR24) after treatment duration of no more than 12 weeks, preferably no more than 8 weeks. The interferon non-responder patients include partial interferon responders and interferon rebound patients. The interferon nonresponder patient may have HCV genotype 1, such as 1a. The interferon nonresponder patient may have HCV genotype 1b. The interferon nonresponder patient can have HCV genotype 2 or 3, such as HCV genotype 2a. In some embodiments, the patient may have HCV genotype 2b. In other embodiments the patient may have HCV genotype 3a. In some embodiments, it is contemplated to treat other HCV genotypes. The treatment can be administered for a duration of no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks (e.g., the duration being 12 weeks, or the duration being 8 weeks). The total daily dosage of therapeutic agent 1 can be, but is not limited to, for example, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. Therapeutic agent 4 can be administered with therapeutic agent 1 wherein therapeutic agent 1 is administered in any of the dosages described above. Therapeutic agent 4 can be provided in combination with therapeutic agent 1. The total daily dosage of therapeutic agent 4 can be, but is not limited to, for example, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, or about 350 mg. In some embodiments, ritonavir can be either co-administered or administered separately with therapeutic agent 1. Suitable dosages of ritonavir include, from about 50 mg to about 400 mg per day, preferably about 100 mg per day. In suitable embodiments, therapeutic agent 1 and therapeutic agent 4 are administered once a day. Therapeutic agent 1 and

therapeutic agent 4 can be administered in any combination of suitable dosages as described above. In some embodiments, if the treatment regimen of the present technology does not provide the desired SVR after treatments of no more than about 12 weeks, the patient may be treated with ribavirin-containing regimen.

Accordingly, in some embodiments, the present technology features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs without ribavirin. The treatment lasts no more than 12 weeks (e.g., the duration being 12 weeks), alternatively no more than 11 weeks, alternatively no more than 10 weeks, alternatively no more than 9 weeks, preferably no more than 8 weeks (e.g., the duration being 8 weeks), alternatively no more than 7 weeks, alternatively no more than 6 weeks, alternatively no more than 5 weeks, alternatively no more than 4 weeks, alternatively no more than 3 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be an HCV-treatment naïve patient or HCV-treatment experienced patient, including, interferon non-responders (e.g., null responders), interferon partial responders (patients whose HCV RNA levels declined but never became undetectable when treated with interferon), or relapsers (patients who achieved undetectable levels of HCV RNA during therapy but rebound) or a patient unable to take interferon. The patient can be infected with, for example and without limitation, HCV genotypes 1 or 2. In some embodiments are preferably genotypes 1a or 1b. In other embodiments, the HCV genotype is 2 or 3. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors.

For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside or nucleotide polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside or nucleotide polymerase inhibitor and at least one non-nucleoside polymerase inhibitor).

For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. In an example, the combination of two or more DAAs comprises GS-5885 (an NS5A inhibitor), and GS-9451 (a protease inhibitor or an NS3 protease inhibitor). In some examples, GS-5885 is provided in a daily dose from about 3 mg to about 200 mg, alternatively from about 3 mg to about 100 mg, alternatively from about 30 mg to about 90 mg, including, but not limited to, for example, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, or about 200 mg. GS-9451 can be administered in combination with any of the daily dosages of GS-5885 described above. GS-9451 can be administered in a total daily dose from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, for example, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, or about 500 mg. Suitably examples include total daily dosages of about 30 mg GS-5885 and about 200 mg GS-9451; alternatively about 60 mg GS-5885 and about 200 mg GS-9451; alternatively about 90 mg GS-5885 and about 200 mg GS-9451.

In another instance, the present technology provides the at least two DAAs comprise at least two HCV polymerase inhibitors. In some embodiments, the at least two HCV polymerase inhibitors comprise at least one nucleoside or nucleotide analog polymerase inhibitor. In some embodiments, the at least two HCV polymerase inhibitors comprise at least two nucleoside or nucleotide analog polymerase inhibitors. Suitable nucleotide analog polymerase inhibitors include PSI-7977 (Pharmasset) and PSI-938 (Pharmasset). Suitable daily dosages of the at least one nucleoside or nucleotide analog polymerase inhibitor include from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, for example, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, or about 500 mg. For example, a suitable combination includes a total daily dose of PSI-7977 of about 400 mg and a total daily of PSI-938 of about 300 mg, alternatively a total daily dose of about 200 mg PSI-7977 and a total daily dose of about 300 mg PSI-938. In yet another instance, the combination of two or more DAAs comprises at least one HCV protease inhibitor and at least one HCV polymerase inhibitor. In some embodiments, the at least one protease inhibitor is TMC-435 (Medivir) and the at least one polymerase inhibitor is a nucleotide/nucleoside analog polymerase inhibitor, for example PSI-7977. Suitably, the at least one protease inhibitor, e.g. TMC-435, is provided in a total daily dosage from about 25 mg to about 250 mg, alternatively from about 25 mg to about 200 mg, alternatively from about 50 mg to about 200 mg, alternatively from about 75 mg to about 150 mg, for example, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg; and the at least one polymerase inhibitor (e.g. PSI-7977) is provided in a total daily dose from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, for example, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, or about 500 mg. For example, a combination can be a total daily dosage of about 75 mg TMC-435 and about 400 mg PSI-7977, alternatively about 100 mg TMC-435 and about 400 mg PSI-7977, alternatively about 150 mg TMC-435 and about 400 mg PSI-7977, alternatively about 100 mg TMC-435 and about 400 mg PSI-7977, alternatively about 75 mg TMC-435 and about 200 mg PSI-7977, alternatively about 150 mg TMC-435 and about 200 mg PSI-7977, alternatively about 100 mg TMC-435 and about 200 mg PSI-7977, alternatively about 75 mg TMC-435 and about 100 mg PSI-7977, alternatively about 100 mg TMC-435 and about 100 mg PSI-7977, alternatively about 150 mg TMC-435 and about 100 mg PSI-7977, and can include other suitable combinations. Suitably, in some embodiments, ritonavir or a suitable equivalent can be added to the at least two DAAs comprising at least one protease inhibitor, suitably in an amount from about 100 mg to about 400 mg per day, preferably about 100 mg per day. In alternative embodiments, the at least one protease is BI-201335 (NS3/4A protease inhibitor) and the at least one HCV polymerase inhibitor is a non-nucleoside polymerase inhibitor, e.g. BI-207127. In some examples, the BI-201335 is provided in a total daily dose from about 100 mg to about 400 mg, alternatively from about 120 mg to about 240 mg, including about 100 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240

mg, about 250 mg, about 275 mg, about 300 mg, about 320 mg, about 330 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, or about 400 mg; and BI-207127 can be administered in a total daily dose from about 300 mg to about 3600 mg, preferably from about 1200 mg to about 2100 mg, including, but not limited to, for example, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 750 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, about 2100 mg, about 2200 mg, about 2400 mg, about 2500 mg, about 2600 mg, about 2700 mg, about 2800 mg, about 3000 mg, about 3200 mg, about 3400 mg, or about 3600 mg. Suitable examples, include, but are not limited to, a combination of a total daily dose of about 120 mg BI-201335 and about 1200 mg BI-207127, alternatively about 120 mg BI-201335 and about 1500 mg BI-207127, alternatively about 120 mg BI-201335 and about 1800 mg BI-207127, alternatively about 120 mg BI-201335 and about 2100 mg BI-207127, alternatively about 240 mg BI-201335 and about 1200 mg BI-207127, alternatively about 240 mg BI-201335 and about 1500 mg BI-207127, alternatively about 240 mg BI-201335 and about 1800 mg BI-207127, alternatively about 240 mg BI-201335 and about 2100 mg BI-207127. Suitably, in some embodiments, ritonavir or a suitable equivalent can be added to the at least two DAAs comprising at least one protease inhibitor, suitably in an amount of about 100 mg per day. Suitably, in some embodiments, ritonavir or a suitable equivalent can be added to the at least two DAAs comprising at least one protease inhibitor, suitably in an amount from about 100 mg to about 400 mg per day, preferably about 100 mg per day. In yet another example, the combination of two or more DAAs comprises telaprevir (VX-950, protease inhibitor) and VX-222 (non-nucleoside polymerase inhibitor). In some examples, the telaprevir is provided in total daily doses from about 1000 mg to about 2500 mg, alternatively from about 2000 mg to about 2500 mg, including, but not limited to, for example, about 1000 mg, about 1200 mg, about 1300 mg, about 1500 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, about 2100 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2400 mg, about 2500 mg. VX-222 can be administered with telaprevir in any combination with the dosage amounts of telaprevir provided above. VX-222 can be provided in a total daily dosage from about 100 mg to about 1000 mg, alternatively from about 200 mg to about 800 mg, including, but not limited to, for example, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg. In some examples, telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 100 mg, alternatively telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 200 mg, alternatively telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 400 mg, alternatively telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 600 mg, alternatively telaprevir can be a total daily dose of about 2250 mg and VX-222 can be a total daily dose of about 800 mg, alternatively telaprevir can be a total daily dose of about 1500 mg and VX-222 can be a total daily dose of about 200 mg, alternatively telaprevir can be a total daily dose of about 1500 mg and VX-222 can be a total daily dose of about 400 mg, alternatively telaprevir can be a total daily dose of about 1500 mg and VX-222 can be a total daily dose of about 800 mg. Suitably, telaprevir can be administered three times a day (TID), for example 3 times a day with 750 mg per dose. Other suitable daily dosage of telaprevir is 1125 mg twice a day (BID). Suitably, in some embodiments, ritonavir or a suitable equivalent can be added to the at least two DAAs comprising at least one protease inhibitor, suitably in an amount of about 100 mg to about 400 mg per day, preferably about 100 mg per day.

In yet another example, the combination of two or more DAAs includes danoprevir (protease inhibitor) and R7128 (nucleoside polymerase inhibitor). In some embodiments, danoprevir can be administered in a total daily dosage from about 100 mg to about 2000 mg, alternatively from about 200 mg to about 1800 mg, alternatively from about 400 mg to about 1800 mg, including, but not limited to, for example, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, and other amounts therebetween. R7128 can be administered in a total daily dose from about 100 mg to about 2000 mg, alternatively from about 200 mg to about 2000 mg, alternatively from about 1000 mg to about 2000 mg, including, but not limited to, for example, about 150 mg, about 200 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, or about 2000 mg. In some examples, the total daily dose of the danoprevir is about 200 mg and the total daily dose of R7128 is about 200 mg, alternatively the total daily dose of the danoprevir is about 400 mg and the total daily dose of R7128 is about 200 mg, alternatively, the total daily dose of the danoprevir is about 1000 mg and the total daily dose of R7128 is about 200 mg, alternatively the total daily dose of the danoprevir is about 1800 mg and the total daily dose of R7128 is about 200 mg, alternatively the total daily dose of the danoprevir is about 2000 mg and the total daily dose of R7128 is about 200 mg, alternatively the total daily dose of the danoprevir is about 400 mg and the total daily dose of R7128 is about 400 mg, alternatively, the total daily dose of the danoprevir is about 1000 mg and the total daily dose of R7128 is about 400 mg, alternatively the total daily dose of the danoprevir is about 2000 mg and the total daily dose of R7128 is about 400 mg, alternatively the total daily dose of the danoprevir is about 1800 mg and the total daily dose of R7128 is about 400 mg, alternatively the total daily dose of the danoprevir is about 400 mg and the total daily dose of R7128 is about 1000 mg, alternatively the total daily dose of the danoprevir is about 1000 mg and the total daily dose of R7128 is about 1000 mg, alternatively the total daily dose of the danoprevir is about 2000 mg and the total daily dose of R7128 is about 1000 mg, alternatively the total daily dose of the danoprevir is about 1800 mg and the total daily dose of R7128 is about 1000 mg, alternatively the total daily dose of the danoprevir is about 400 mg and the total daily dose of R7128 is about 2000 mg, alternatively, the total daily dose of the danoprevir is about 1000 mg and the total daily dose of R7128 is about 2000 mg, alternatively the total daily dose of the danoprevir is about 2000 mg and the total daily dose of R7128 is about 2000 mg, alternatively the total daily dose of the danoprevir is about 1800 mg and the total daily dose of R7128 is about 2000 mg. In suitable embodiments, danoprevir and R7128 can be administered with ritonavir, suitably in an amount of about 100 mg to about 400 mg per day, preferably about 100 mg per day.

In some other instances of the present technology, the combinations of two or more DAAs may be at least one

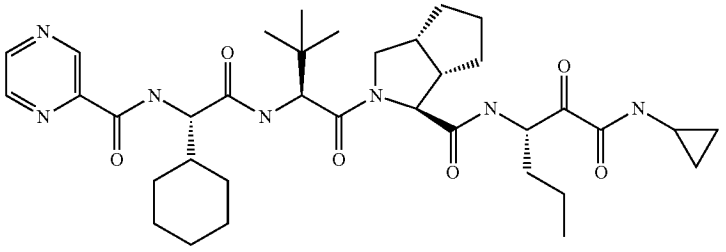
protease inhibitor and at least one NS5A inhibitor. In some examples, the at least one protease inhibitor is an NS3 protease inhibitor. In some embodiments, the at least one protease inhibitor and at least one NS5A inhibitor comprises BMS-650032 (BMS) and BMS-790052 (BMS) respectively. In suitable embodiments, BMS-650032 can be administered in a total daily dose from about 300 mg to about 1500 mg, alternatively from about 500 mg to about 1500 mg, including, but not limited to, for example, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, and about 1500 mg, and BMS-790052 (BMS) can have a total daily dose from about 10 mg to about 200 mg, alternatively from about 50 mg to about 100 mg, including, but not limited to, for example, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, or about 200 mg. In suitable examples, BMS-650032 (BMS) total daily dose is about 1200 mg and BMS-790052 (BMS) total daily dose is about 60 mg, alternatively BMS-650032 (BMS) total daily dose is about 300 mg and BMS-790052 (BMS) total daily dose is about 60 mg.

In some other instances of the present technology, the combinations of two or more DAAs may be at least one nucleoside or nucleotide polymerase inhibitor, at least one protease inhibitor, and at least one NS5A inhibitor. In some examples, the at least one protease inhibitor is an NS3 protease inhibitor. In some embodiments, the at least one nucleoside or nucleotide polymerase inhibitor is INX-189, the at least one protease inhibitor is BMS-650032 (asunaprevir), and the at least one NS5A inhibitor comprises is BMS-790052 (daclatasivr). Such embodiments are especially contemplated for treating a patient infected with HCV genotype 1, such as genotype 1a or 1b (particularly genotype 1a), as well as patients infected with other HCV genotypes, such as genotypes 2 or 3. In suitable embodiments, INX-189 can be administered in a total daily dose from about 5 mg to about 400 mg, alternatively from about 25 mg to about 200 mg, including but not limited to, for example, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, or about 300 mg. In suitable embodiments, BMS-650032 can be administered in a total daily dose from about 300 mg to about 1500 mg, alternatively from about 500 mg to about 1500 mg, including, but not limited to, for example, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, and about 1500 mg, and BMS-790052 (BMS) can have a total daily dose from about 10 mg to about 200 mg, alternatively from about 50 mg to about 100 mg, including, but not limited to, for example, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, or about 200 mg. In suitable examples, BMS-650032 (BMS) total daily dose is about 1200 mg and BMS-790052 (BMS) total daily dose is about 60 mg, alternatively BMS-650032 (BMS) total daily dose is about 300 mg and BMS-790052 (BMS) total daily dose is about 60 mg.

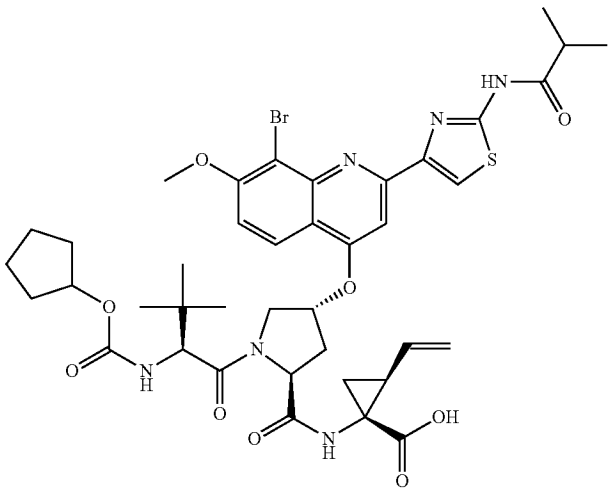
For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In an example, the combination of two or more DAAs comprises GS-5885 (an NS5A inhibitor), GS-9190 (tegobuvir, a non-nucleoside polymerase inhibitor), and GS-9451 (a protease inhibitor or a NS3 protease inhibitor). In some examples, GS-5885 is provided in a daily dose from about 3 mg to about 200 mg, alternatively from about 3 mg to about 100 mg, alternatively from about 30 mg to about 90 mg, including, but not limited to, for example, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, or about 200 mg, and GS-9190 is provided in a daily dose from about 10 mg to about 100 mg, alternatively from about 30 mg to about 90 mg, including, but not limited to, for example, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg; and GS-9451 can be administered in a daily dose from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, or about 500 mg. Suitably examples include about daily amounts of about 30 mg GS-5885, about 60 mg GS-9190 and about 200 mg GS-9451; alternatively about 60 mg GS-5885, about 60 mg GS-9190, and about 200 mg GS-9451; alternatively about 90 mg GS-5885, about 60 mg GS-9190, and about 200 mg GS-9451. In some embodiments the GS-9190, GS-9451, and GS-5885 is administered with ritonavir or a suitable equivalent, suitably in an amount of about 100 mg to about 400 mg per day, preferably about 100 mg per day. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor.

In another embodiment, the present technology provides interferon-free treatment comprising administering daily two DAAs without ribavirin, where the two DAAs include a HCV polymerase inhibitor, for example PSI-7977 and a NS5A inhibitor, for example BMS-790052 for a duration of no more than eleven weeks, preferably no more than eight weeks. PSI-7977 and BMS-790052 are administered in an effective amount to provide an SVR with a treatment duration of no more than eleven weeks, no more than ten weeks, no more than nine weeks, no more than eight weeks, no more than seven weeks, no more than six weeks, no more than five weeks, no more than four weeks or no more than three weeks. The patients can be treatment naïve patients or treatment experienced patients. In some embodiments, the patients can have HCV genotype 1, such as 1a or 1b. In some embodiments, the patients can have genotype 2 or 3, such as 2a, 2b or 3a. PSI-7977 can be provided in a total daily dose of from about 100 mg to about 500 mg, alternatively from about 200 mg to about 400 mg, including, but not limited to, for example, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg. BMS-790052 can be administered in combination with PSI-7977 at any daily dose of PSI-7977 provided above. BMS-790052 (BMS) can have a total daily dose of from about 10 mg to about 200 mg, alternatively from about 50 mg to about 100 mg, including, but not limited to, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, or about 200 mg. In one suitable example, PSI-7977 is administered in a total daily dose of 400 mg and BMS-790052 is administered in a total daily dose of 60 mg.

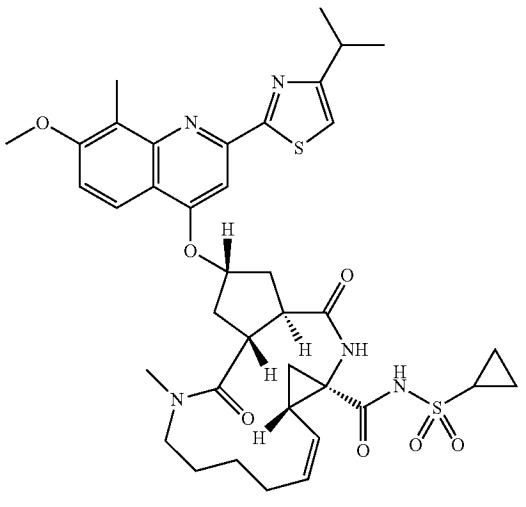
The chemical structures of some of these HCV inhibitors as reported by numerous sources are provided below:



Telaprevir

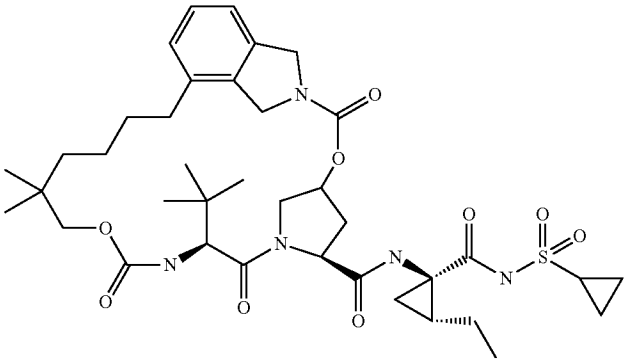


BI-201335

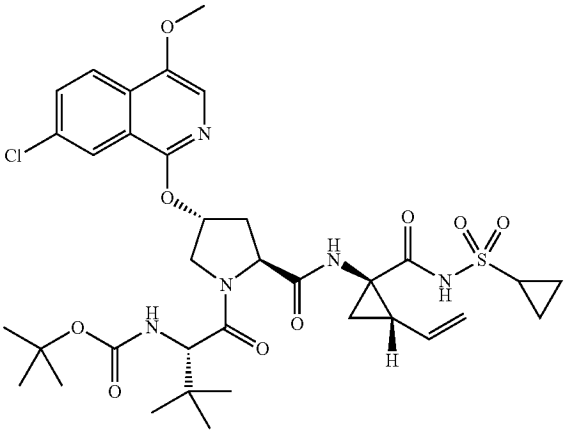


TMC-435 (TMC-435350)

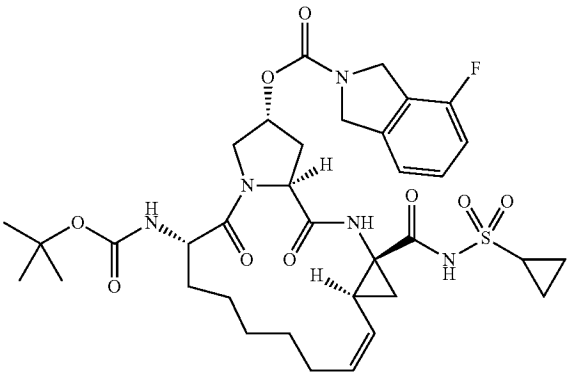
-continued



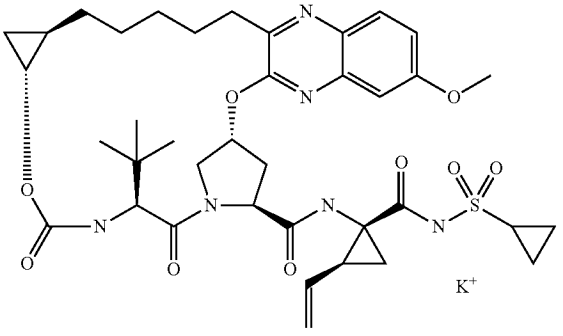
Vaniprevir, MK-7009



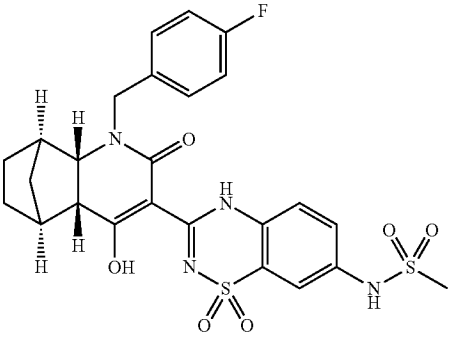
BMS-650032 (Asunaprevir)



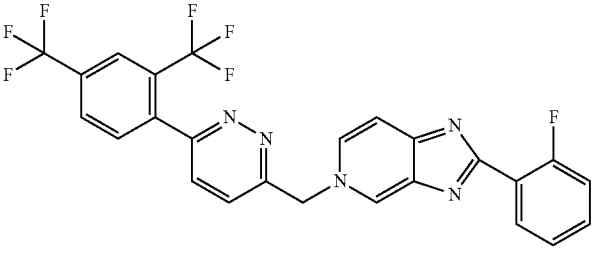
danoprevir



MK-5172

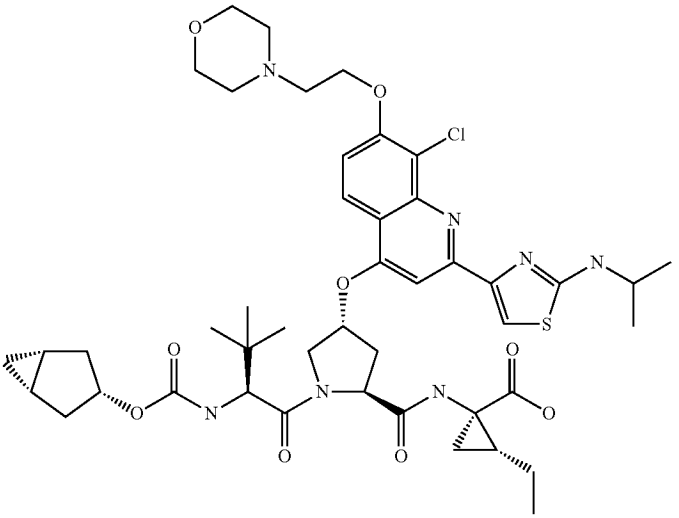


ANA-598 (Setrobuvir)

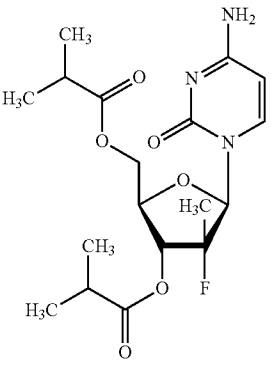


Tegobuvir
GS-333126 (GS-9190 or tegobuvir)

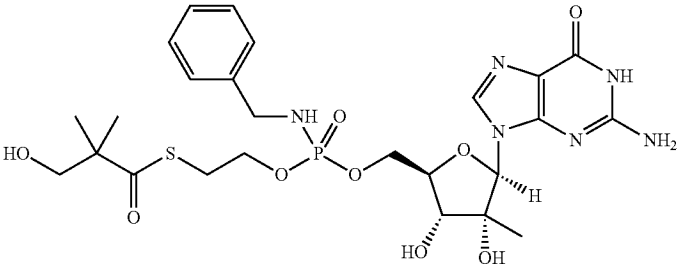
-continued



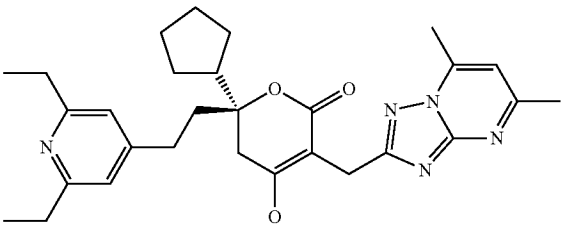
GS-9451
GS-9451



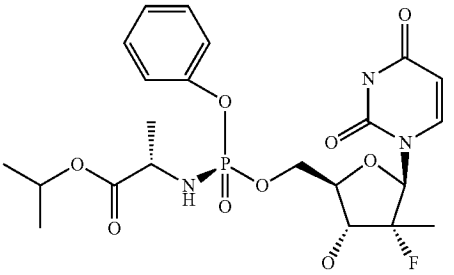
Mericitabine (R-4048 or RG7128)



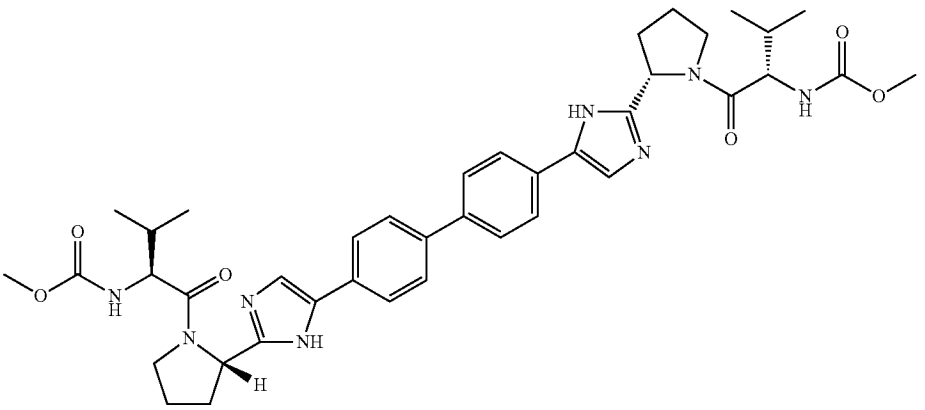
IDX-184



filibuvir (PF-00868554)

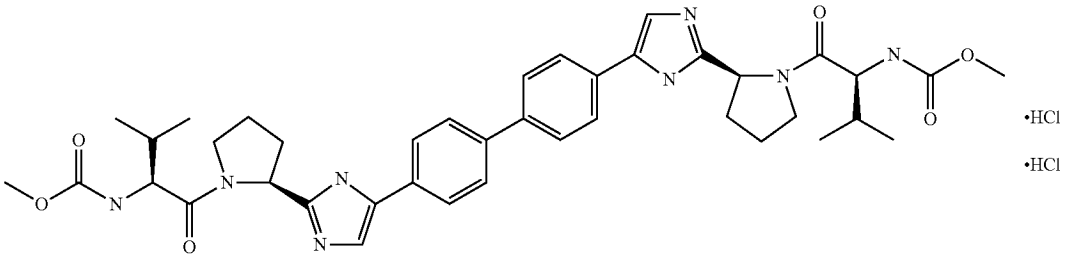


PSI-7977

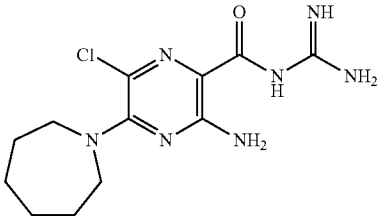


BMS-790052 (daclatasvir)

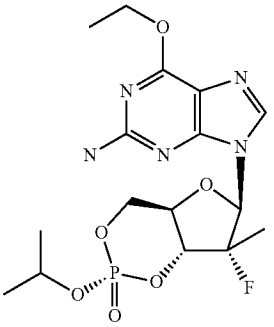
-continued



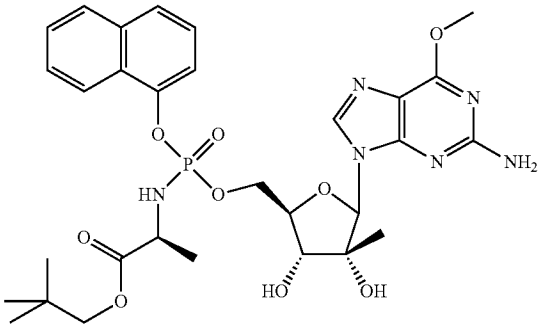
Daclatasvir dihydrochloride



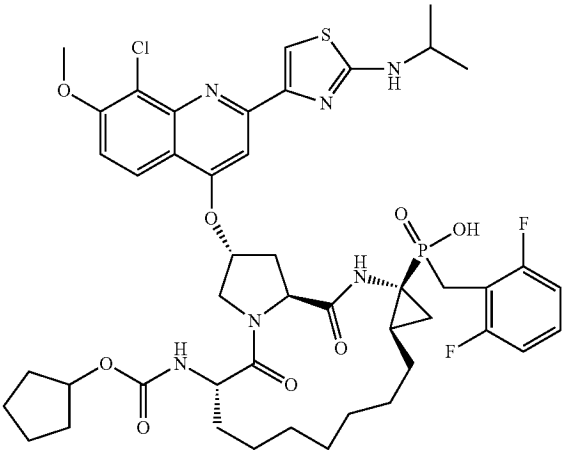
BIT-225



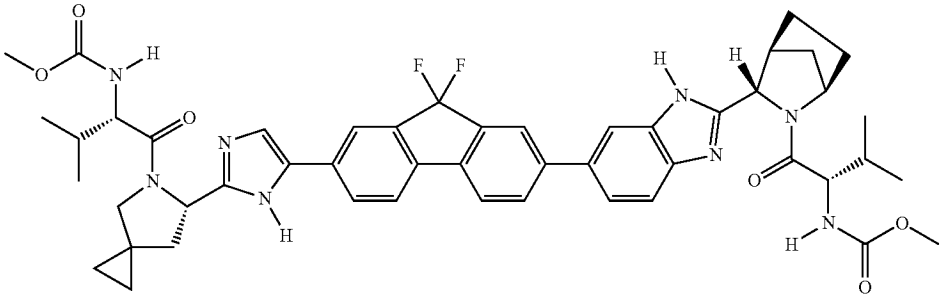
PSI-352938



INX-189

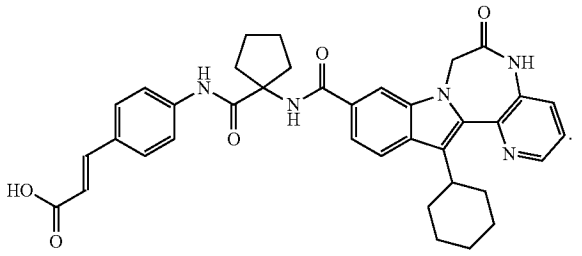


GS-9256



GS-5885

It has also been reported that BMS-791325 has the following structure:



See also publications at http://www1.eas1.eu/eas12011/program/Posters/Abstract680.htm; and http://clinicaltrials.gov/show/NCT00664625. For GS-5885, see publications at http://www.natap.org/2011/EASL/EASL_68.htm; http://www1.eas1.eu/eas12011/program/Posters/Abstract1097.htm; and http://clinicaltrials.gov/ct2/show/NCT01353248.

Any HCV inhibitor or DAA described herein encompasses its suitable salt forms when it is used in therapeutic treatments or pharmaceutical formulations.

The following table lists non-limiting examples of the treatment regimens of the present technology. In each treatment regimen, the at least two DAA with or without ritonavir, are administered daily to an HCV patient under such treatment. Each treatment is interferon-free and ribavirin-free. Each treatment regimen may also optionally comprise administering one or more other additional DAAs to the patient. The duration of each treatment regimen may last, for example and without limitation, no more than 12 weeks, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, no more than 8 weeks, alternatively no more than 7 weeks, alternatively no more than 6 weeks, alternatively no more than 5 weeks, alternatively no more than 4 weeks and may depend on the patient's response. In any given regimen described below, the drugs can be, for example and without limitation, co-formulated in a single solid dosage form when each has the same dosing frequency.

For instance, two or more drugs used in a regimen can be co-formulated in amorphous forms or molecularly dispersed in a matrix comprising a water-soluble polymer and optionally a surfactant; for another instance, therapeutic agent 1 and ritonavir (RTV) are formulated in an amorphous form or molecularly dispersed in a matrix comprising a water-soluble polymer and optionally a surfactant, and therapeutic agent 3 can be combined with amorphous Compound 1 and RTV in a single solid dosage form. For yet another instance, Compound 1 and RTV are formulated in a different dosage form than that of therapeutic agent 3.

TABLE 1

Non-Limiting Examples of Interferon-free Treatment Regimens with two or more DAAs (without ribavirin and with or without ritonavir)

Regimen	Drugs Used in Treatment	Suitable total daily dosages
1	Therapeutic Agent 1* + Therapeutic Agent 4	150 to 250 mg (pref. 150, 200, 250 mg) 5 mg to 300 mg (pref. 25 mg)
2	Therapeutic Agent 1* + Therapeutic Agent 4 + Therapeutic Agent 2	150 to 250 mg (pref. 150, 200, 250 mg) 5 mg to 300 mg (pref. 25 to 200 mg) 300 to 1800 mg (pref. 400 mg or 800 mg)

TABLE 1-continued

Non-Limiting Examples of Interferon-free Treatment Regimens with two or more DAAs (without ribavirin and with or without ritonavir)

Regimen	Drugs Used in Treatment	Suitable total daily dosages
3	Therapeutic Agent 1* + Therapeutic Agent 3 + Therapeutic Agent 4	150-250 mg (pref. 150 mg or 250 mg) 50 mg-1000 mg (pref. 400 mg) 5 mg-300 mg (pref. 25 mg-200 mg, more pref. 25 mg)
4	Therapeutic Agent 1* + Therapeutic Agent 2	150-250 mg (150 mg, 200 mg or 250 mg) 300-1800 mg (pref. 200 mg, 800 mg)
5	Therapeutic Agent 1* + Therapeutic Agent 3	50 mg to 250 mg (pref. 50 mg or 250 mg) 50 mg to 1000 mg (pref. 400 mg to 800 mg)
6	PSI-7977 + PSI-938	100 mg to 500 mg (pref. 200, 400 mg) 100 mg to 500 mg (pref. 300 mg)
7	BMS-790052 + BMS-650032	10 mg to 200 mg (pref. 60 mg) 300 mg to 1500 mg (pref. 1200 mg)
8	GS-5885 + GS-9190 + GS-9451	3 mg to 200 mg (pref. 30 mg to 90 mg) 30 mg to 90 mg (pref. 60 mg) 100 mg to 500 mg (pref. 200 mg)
9	GS-5885 + GS-9451	3 mg to 200 mg (pref. 30 to 90 mg) 100 mg to 500 mg (pref. 200 mg)
10	BI-201335 + BI-207127	100 mg to 400 mg (pref. 120 mg or 240 mg) 300 mg to 3600 mg (pref. 1200 mg to 2100 mg)
11	PSI-7977 + TMC-435	100 mg to 500 mg (pref. 400 mg) 25 mg to 200 mg (pref. 75 mg to 150 mg)
12	telaprevir + VX-222	1000 mg to 2500 mg (pref. 2250 mg) 200 mg to 800 mg
13	Danoprevir* + R7128	100 mg to 2000 mg (pref. 200 mg or 400 mg) 100 mg to 2000 mg (pref. 200 mg, 400 mg, 1000 mg or 2000 mg)
14	Danoprevir + R7128	100 mg to 2000 mg (pref. 800 mg or 1000 mg, or 1800 mg or 2000 mg) 100 mg to 2000 mg (pref. 200 mg, 400 mg, 1000 mg or 2000 mg)
15	PSI-7977 + daclatasvir (BMS-790052)	100 mg to 500 mg (pref. 400 mg) 10-200 mg (pref. 60 mg)
16	PSI-7977 + asunaprevir (BMS-650032)	100 mg to 2000 mg (pref. 1800 mg or 2000 mg) 300-1500 mg (pref. 1200 mg)
17	PSI-7977 + daclatasvir (BMS-790052) asunaprevir (BMS-650032)	100 mg to 500 mg (pref. 400 mg) 10-200 mg (pref. 60 mg) 300-1500 mg (pref. 1200 mg)

*ritonavir or a suitable equivalent can be added to any one of these treatments as described and may be added to any of these treatments at a daily total dosage as described in the present technology; preferably ritonavir is co-formulated with therapeutic agent 1 or danoprevir; the dose of ritonavir preferably is 100 mg. Pref. = preferred

Additional non-limiting examples of interferon-free treatment regimens with two or more DAAs, without ribavirin, and with or without ritonavir or a suitable equivalent, including the following: (a) Therapeutic Agent 1 at a total daily dose of 5 mg to 150 mg (pref. 5 mg, 25 mg, 50 mg, or 100 mg) with ritonavir or a suitable equivalent, and Therapeutic Agent 4 at a total daily dose of 5 mg to 150 mg (pref. 5 mg, 25 mg, 50 mg, or 100 mg); (b) Therapeutic Agent 1 at a total daily dose of 5 mg to 200 mg (pref. 5 mg, 25 mg, 50 mg, 100 mg) with ritonavir or a suitable equivalent, Therapeutic Agent 4 at a total daily dose of 5 mg to 200 mg (pref. 25 mg or 100 mg), and Therapeutic Agent 2 at a total daily dose of 200 mg to 800 mg (pref. 400 mg or 800 mg); (c) Therapeutic Agent 1 at a total daily dose of 5 mg to 150 mg (pref. 5 mg, 25 mg, 50 mg, or 100 mg) with ritonavir or a suitable equivalent, Therapeutic Agent 3 at a total daily dose of 100 mg to 600 mg (pref. 400 mg), and Therapeutic Agent 4 at a total daily dose of 5 mg to 300 mg (pref. 25 mg to 200 mg, more pref. 25 mg); (d)

Therapeutic Agent 1 at a total daily dose of 5 mg to 150 mg (pref. 5 mg, 25 mg, 50 mg, 100 mg) with ritonavir or a suitable equivalent, and Therapeutic Agent 2 at a total daily dose of 200-800 mg; (e) GS-5885 at a total daily dose of 3-200 mg (pref. 30-90 mg). GS-9190 at a total daily dose of 30-90 mg (pref. 60 mg), and GS-9451 at a total daily dose of 100-500 mg (pref. 200 mg); (f) GS-5885 at a total daily dose of 3 mg to 200 mg (pref. 30 mg, 60 mg, or 90 mg), and GS-9451 at a total daily dose of 100 mg to 500 mg (pref. 200 mg); (g) BI-201335 at a total daily dose of 100 mg to 400 mg (pref. 120 mg, 240 mg), and BI-207127 at a total daily dose of 300 mg to 3600 mg (pref. 1200 or 1500 mg, 1800 mg or 2100 mg); (h) PSI-7977 at a total daily dose of 100 mg to 500 mg (pref. 100, 200 mg), and TMC-435 at a total daily dose of 25 mg to 200 mg (pref. 75 mg, 100 mg, or 150 mg); (i) telaprevir at a total daily dose of 1000 mg to 2500 mg (pref. 1500 mg or 2250 mg), and VX-222 at a total daily dose of 100 mg to 800 mg (pref. 100 mg, 200 mg, 400 mg, 600 mg or 800 mg); (j) INX-189 at a total daily dose of 5 mg to 400 mg (pref. 50 mg, 100 mg or 200 mg), and daclatasvir (BMS-790052) at a total daily dose of 10 mg to 200 mg (pref. 60 mg); (k) INX-189 at a total daily dose of 5 mg to 400 mg (pref. 50 mg, 100 mg or 200 mg), and asunaprevir (BMS-650032) at a total daily dose of 300 mg to 1500 mg (pref. 1200 mg); and (1) INX-189 at a total daily dose of 5 mg to 400 mg (pref. 50 mg, 100 mg or 200 mg), daclatasvir (BMS-790052) at a total daily dose of 10 mg to 200 mg (pref. 60 mg), and asunaprevir (BMS-650032) at a total daily dose of 300 mg to 1500 mg (pref. 1200 mg). In any of these examples, ritonavir or a suitable equivalent can be added to any one of these treatments as described and may be added to any of these treatments at a daily total dosage as described in the present technology; preferably ritonavir is co-formulated with therapeutic agent 1 or danoprevir; the dose of ritonavir preferably is 100 mg.

The treatments of the present technology may be effective in treating HCV infection against HCV genotypes 1, 2, 3, 4, 5, 6, including subgenotypes, such as 1a, 1b, 2a, and 3a.

In general and depending on patients' conditions, the total daily dose of the DAAs of the present technology may be administered (either as a single or divided dose) in amounts from about 0.001 mg/kg to about 200 mg/kg, or from about 0.001 mg/kg to about 30 mg/kg, or from about 0.001 mg/kg to about 30 mg/kg, or from about 0.01 mg/kg, to about 10 mg/kg (i.e. mg of the compound or salt per kg body weight), and include any amounts or ranges there between, including, but not limited to increments of 0.001 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.05 mg/kg, and multiple factors thereof (e.g. 0.25×, 0.5×, 1×, 2×, 3×, 5×, 10×, 100×, etc.). Suitable dosages of the DAAs of the present technology include, but are not limited to, from about 25 mg to about 2000 mg, from about 25 mg to about 1500 mg, from about 25 mg to about 1600 mg, from about 25 mg to about 1000 mg, from about 25 mg to about 800 mg, from about 25 mg to about 500 mg, from about 25 mg to about 250 mg, from about 50 mg to about 2000 mg, from about 50 mg to about 1500 mg, from about 50 mg to about 1600 mg, from about 50 mg to about 1000 mg, from about 50 mg to about 800 mg, from about 50 mg to about 500 mg, from about 50 mg to about 250 mg, and include, but are not limited to, for example, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 80 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 165 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 250 mg, and includes any increments there between, including increments of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 10 mg, about 15 mg, about 20 mg, about 25, and multiples thereof (e.g. 0.25×, 0.5×, 1×, 2×, 3×, 5×, 10×, 100×, etc.). It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the disease undergoing therapy.

The cytochrome P-450 inhibitor may be administered in any suitable amount such as, for example, in doses of from about 0.3 mg/kg to about 2 mg/kg or from about 0.6 mg/kg to about 1.5 mg/kg. As non-limiting examples, the cytochrome P-450 inhibitor may be administered in a total daily dose amount of from about 25 mg to about 300 mg, or from about 50 mg to about 250 mg, or from about 100 mg to about 200 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose of about 100 mg to about 400 mg, preferably about 100 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 25 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 50 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 75 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 100 mg. In some embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 125 mg.

The one or more DAAs can be administered, for example and without limitation, concurrently or sequentially, and at the same or different frequencies. For instance, For example, one DAA can be administered immediately before or after the administration of another DAA. A short delay or time gap may exist between the administration of one DAA and that of another DAA. The frequency of administration may also be different. For example, a first DAA may be administered once a day and a second DAA may be administered twice or three times a day. For example, a first DAA with or without ritonavir may be administered once daily, and a second DAA may be administered twice daily.

The DAAs of the present technology can be co-formulated in a single dosage form. Non-limiting examples of suitable dosage forms include liquid or solid dosage forms. For example, a dosage form of Compound 1 as a solid dosage form is described in U.S. Patent Application Publication No. 2011/0312973, filed Mar. 8, 2011 and entitled "Solid Compositions", the entire content of which is incorporated herein by reference. More preferably, the dosage form is a solid dosage form in which at least one of the DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. The other DAAs can also be in an amorphous form or molecularly dispersed in the matrix, or formulated in different form(s) (e.g., in a crystalline form).

The DAAs of the present technology can be formulated in different dosage forms. It will be understood that the total daily dosage of the compounds and compositions to be administered will be decided by the attending physician within the scope of sound medical judgment.

In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 150 mg, and ritonavir at a dose of 100 mg, once a day; and Therapeutic agent 2 at a dose of 400 mg or 800 mg twice a day. The treatment lasts for 12 weeks, and at the end of treatment, the subject has no detectable virus.

In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 50 mg, and ritonavir at a dose of 100 mg, once a day; Therapeutic agent 2 at a dose of 400 mg or 800 mg twice a day. The treatment lasts for 12 weeks, and the end of treatment, the subject has no detectable virus.

In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 250 mg, and ritonavir at a dose of 100 mg, once a day; and Therapeutic agent 2 at a dose of 400 mg BID. The treatment lasts for 12 weeks, and the end of treatment, the subject has no detectable virus.

In another embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 150 mg, and ritonavir at a dose of 100 mg, once a day; and Therapeutic agent 2 at a dose of 400 mg BID. The treatment lasts for 12 weeks, and the end of treatment, the subject has no detectable virus.

In yet another embodiment, a method for treating a peginterferon+ribavirin (P/RBV) non-responder comprises administering Therapeutic agent 1 at a dose of 150 mg, and ritonavir at a dose of 100 mg, once a day; and Therapeutic agent 2 at a dose of 400 mg BID. The treatment lasts for 12 weeks, and the end of treatment, the subject has no detectable virus.

In yet another embodiment, a method for treating a peginterferon+ribavirin (P/RBV) non-responder comprises administering Therapeutic agent 1 at a dose of 50 mg QD, Therapeutic agent 2 at a dose of 400 mg BID, and ritonavir at a dose of 100 mg QD for 12 weeks. At the end of treatment, the subject has no detectable virus.

In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a total daily dose of 150 mg, Therapeutic agent 3 at a total daily dose of 400 mg, and ritonavir at a dose of 100 mg once a day for 12 weeks. At the end of treatment, the subject has no detectable virus.

In another embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a total daily dose of 100 mg or 200 mg QD, Therapeutic agent 4 at a total daily dose of 25 mg, ritonavir at a dose of 100 mg QD for 12 weeks. At the end of treatment, the subject has no detectable virus.

In yet another embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a total daily dose of 100 mg or 150 mg QD, Therapeutic agent 2 at a dose of 400 mg BID, Therapeutic agent 4 at a total daily dose of 25 mg, ritonavir at a dose of 100 mg QD for 12 weeks. At the end of treatment, the subject has no detectable virus.

It should be understood that the above-described embodiments and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

EXAMPLE 1

Synergistic Concentrations of Compound 1 and Compound 2 in Genotype 1b HCV Replicon Assay

Examples 1-3 are for illustration and do not limit the scope of this disclosure in any way. Not to be bound by any theory, the unexpected synergistic effects from combining different classes of HCV inhibitors (e.g., a combination of a protease inhibitor (such as Compound 1) and a polymerase inhibitor (such as Compound 2), or a combination of a protease inhibitor (such as Compound 1) and a NS5A inhibitor (such as Compound 4)) may contribute to the effectiveness of the short-duration, interferon- and ribavirin-free therapies of the present technology.

Materials:

A replicon cell line was derived from the human hepatoma cell line Huh7. It was derived from HCV genotype 1b (Con1), and is a bicistronic subgenomic replicon, essentially similar to those described in Science 285(5424):110-3 (1999). The first cistron of the construct contains a firefly luciferase reporter and a neomycin phosphotransferase selectable marker. Replicon cells were maintained in Dulbecco's Modified Eagle Media (DMEM) containing 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen), 200 mg/ml G418, an aminoglycoside antibiotic (Invitrogen) and 10% fetal bovine serum (FBS) at 37° C. and 5% CO2.

Replicon Cell Culture:

Replicon cells were seeded at a density of 5000 cells per well of a 96-well plate in 100 μl DMEM containing 5% FBS. The following day, Compounds 1 and 2 were diluted in dimethyl sulfoxide (DMSO) to generate a 200× stock in a series of 6 two-fold dilutions. The dilution series was then further diluted 100-fold in the medium containing 5% FBS.

Combination Studies:

Combination studies were performed to evaluate the interaction effects of therapeutic agent 1 and therapeutic agent 2 in the replicon assay described above. The purpose of these studies was to determine whether there are doses or concentrations of each compound where synergy or antagonism is demonstrated with the other compound. Three experiments with three plates in each experiment were performed on three separate days. Six concentrations of Compound 1 alone and six concentrations of Compound 2 alone were assayed in each plate. In addition, 36 combinations of concentrations of the two compounds were assayed for each plate. The variable analyzed was the fraction of inhibition of the luciferase signal.

The dilutions of each compound were combined with the dilutions of the other compound in a checkerboard fashion. The concentrations tested were chosen to ensure that the EC_{50} for each compound alone is in the middle of the serial dilution range. Medium with inhibitor(s) was added to the cell culture plates already containing 100 μl of DMEM with 5% FBS. The cells were incubated in a tissue culture incubator at 37° C. and 5% CO_2 for three days. The inhibitor effects of compounds on HCV replication were determined by measuring activity of a luciferase reporter gene using a Luciferase Assay System kit (Promega) following the manufacturer's instructions. Passive Lysis buffer (30 μl, Promega) was added to each well, and the plates were incubated for 15 minutes with rocking to lyse the cells. Luciferin solution (100 μl, Promega) was added to each well and the luciferase activity was measured using a Victor II luminometer (Perkin-Elmer). To determine the EC_{50}, the luciferase inhibition data were analyzed using GraphPad Prism 4 software. Three experiments were performed with three replicates per experiment. The percent inhibition results were analyzed for synergy, additivity and antagonism according to the Pritchard and Shipman model (Antiviral Research 14:181-206 (1990)).

Combination Analysis:

Prichard and Shipman proposed a direct approach to solve this drug-drug interaction problem. The method was able to calculate theoretical additive effects directly from the individual dose-response curves determined in the assay. The calculated theoretical additivity was then compared to the experimental dose-response surface, and subsequently sub-

tracted to reveal any areas of aberrant interaction. The following equation was used to calculate the theoretical additive effects:

$$Z=X+Y(1-X)=X+Y-XY,$$

where Z is the total inhibition produced by the combination of drugs X and Y, with X and Y representing the inhibition produced by drugs X and Y alone respectively.

A difference between the actual observed fraction of inhibition and the predicted value was calculated for each concentration combination for each plate in each experiment to determine whether the observed combined effect was greater than the theoretical additive effect Z calculated from the equation above. For each concentration combination, the replicates (across all plates and experiments) were used to calculate a mean difference between observed and predicted fraction of inhibition, its standard error and its two-sided 95% confidence interval.

Synergy or antagonism for a concentration combination was determined based on the following 2 rules: First, the 95% CI of the mean difference between observed and predicted fraction of inhibition at each concentration combination is calculated. If the lower bound of 95% CI is larger than zero, then the drug combination would be considered having a synergistic effect; if the upper bound of 95% CI is less than zero, then the drug combination would be considered having an antagonistic effect; otherwise, no significant antagonism or synergy at this concentration combination.

Second, the synergistic or antagonistic effect must have its relative mean difference, the absolute mean difference divided by its corresponding observed mean inhibition, greater than 1%. By doing this, small differences of statistical significance caused by very small variance could be excluded.

Combination of Therapeutic Agent 1 and Therapeutic Agent 2:

The inhibitory effects on replicons produced by each drug alone or in combination with the other at concentrations up to ten-fold above the EC_{50} were examined in the genotype 1b (Con1) replicon using a checkerboard titration pattern (two-fold serial dilutions) in a standard three-day antiviral assay. The concentrations tested were chosen to ensure that the EC_{50} values of the compounds were in the middle of the serial dilution range. For Compound 1, concentrations ranged from 0.031 nM to 1.0 nM. For Compound 2, concentrations ranged from 0.125 nM to 4.0 nM. Synergy, additivity, and antagonism were evaluated using the Pritchard and Shipman model.

Results:

The results of the assay analysis are illustrated in FIGS. **1** and **2** and Table 2. In the 3-D surface plot of FIG. **1**, deviations from expected interactions between Compound 1 and Compound 2 are purely additive at concentrations associated with a horizontal plane at 0%. Synergistic interactions between Compound 1 and Compound 2 appear as a peak above the horizontal plane with a height corresponding to the percent above calculated additivity. Antagonistic interactions between Compound 1 and Compound 2 appear as a pit or trough below the horizontal plane with a negative value signifying the percent below the calculated additivity. Synergistic interactions appear as dark grey, additive interactions appear white, and antagonistic interactions appear as speckled.

As illustrated in the 3-D surface plot of FIG. **1** and the contour plot of FIG. **2**, an additive or synergistic effect exists at most of the concentrations for Compound 1 and Compound 2. In particular, there is a concentration region showing synergy at most concentrations of Compound 1 and at the lower to mid-range dose concentrations of Compound 2.

Table 2 below lists combinations of concentrations of Compound 1 and Compound 2 with statistically significant synergistic or antagonistic effects based on the Prichard and Shipman model analysis. For each combination of concentrations, Table 2 includes the mean difference in the observed and predicted fraction of inhibition, the standard deviation or error of the mean difference, and the upper and lower limits of the 95% confidence interval.

According to Table 2, all of the combinations of Compound 1 and Compound 2 listed in the table have statistically significant synergistic effects.

The results presented in FIGS. **1** and **2** and Table 2 demonstrate that the combination of therapeutic agent 1 and therapeutic agent 2 achieves additivity or synergy at most of the concentration combinations of the two agents. Taken together, these in vitro replicon results suggest that therapeutic agent 2 should produce a significant antiviral effect in patients when administered in combination with therapeutic agent 1 in patients infected with HCV.

TABLE 2

Compound 2, nM	Compound 1, nM	Mean difference in fraction of inhibition: Observed – Predicted	Standard error of mean difference	Lower 95% confidence limit	Upper 95% confidence limit
.125	.12500	0.06176	0.023352	0.007912	0.11561
.125	.25000	0.05321	0.022199	0.002024	0.10440
.125	.50000	0.01176	0.002680	0.005583	0.01794
.250	.25000c	0.06626	0.020630	0.018692	0.11384
.250	.50000	0.01061	0.002677	0.004438	0.01679
.500	.06250	0.04373	0.014897	0.009375	0.07808
.500	.12500	0.10416	0.026757	0.042454	0.16586
.500	.25000	0.09327	0.019859	0.047471	0.13906
.500	.50000	0.01422	0.003333	0.006535	0.02191
1.00	.06250	0.06696	0.020488	0.019715	0.11421
1.00	.12500	0.14103	0.021289	0.091939	0.19013
1.00	.25000	0.11027	0.016762	0.071617	0.14892
1.00	.50000	0.01365	0.002312	0.008315	0.01898
2.00	.06250	0.05974	0.007690	0.042004	0.07747
2.00	.12500	0.10032	0.011820	0.073066	0.12758
2.00	.25000	0.07117	0.009428	0.049428	0.09291
4.00	.03125	0.03235	0.003950	0.023236	0.04145
4.00	.06250	0.05141	0.004313	0.041470	0.06136
4.00	.12500	0.06572	0.004692	0.054901	0.07654
4.00	.25000	0.03452	0.004775	0.023509	0.04553

EXAMPLE 2

Synergistic Concentrations of Compound 1 and Compound 4 in Genotype 1b HCV Replicon Assay

Materials:

The replicon cell line was derived from the human hepatoma cell line Huh7. It was derived from HCV genotype 1b (Con1), and is a bicistronic subgenomic replicon, essentially similar to those described in Science 285(5424):110-3 (1999). The first cistron of the construct contains a firefly luciferase reporter and a neomycin phosphotransferase selectable marker. Replicon cells were maintained in Dulbecco's Modified Eagle Media (DMEM) containing 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen), 200 mg/ml G418 (Invitrogen) and 10% fetal bovine serum (FBS) at 37° C. and 5% CO_2.

Replicon Cell Culture:

Replicon cells were seeded at a density of 5000 cells per well of a 96-well plate in 100 μl DMEM containing 5% FBS. The following day, compounds were diluted in dimethyl sulfoxide (DMSO) to generate a 200× stock in a series of 6 two-fold dilutions. The dilution series was then further diluted 100-fold in the medium containing 5% FBS.

Combination Studies:

Combination studies were performed to evaluate the interaction effects of therapeutic agent 1 and therapeutic agent 4 in the replicon assay described above. The purpose of these studies was to determine doses or concentrations of each compound where synergy or antagonism is demonstrated with the other compound. Three experiments with three plates in each experiment were performed on three separate days. Six concentrations of Compound 1 alone and six concentrations of Compound 2 alone were assayed in each plate. In addition, 36 combinations of concentrations of the two compounds were assayed for each plate. The variable analyzed was the fraction of inhibition of the luciferase signal.

The dilutions of each compound were combined with the dilutions of the other compound in a checkerboard fashion. The concentrations tested were chosen to ensure that the EC_{50} for each compound alone is in the middle of the serial dilution range. Medium with inhibitor(s) was added to the cell culture plates already containing 100 μl of DMEM with 5% FBS. The cells were incubated in a tissue culture incubator at 37° C. and 5% CO_2 for three days. The inhibitor effects of compounds on HCV replication were determined by measuring activity of a luciferase reporter gene using a Luciferase Assay System kit (Promega) following the manufacturer's instructions. Passive Lysis buffer (30 μl, Promega) was added to each well, and the plates were incubated for 15 minutes with rocking to lyse the cells. Luciferin solution (100 μl, Promega) was added to each well and the luciferase activity was measured using a Victor II luminometer (Perkin-Elmer). To determine the EC_{50}, the luciferase inhibition data were analyzed using GraphPad Prism 4 software. Three experiments were performed with three replicates per experiment. The percent inhibition results were analyzed for synergy, additivity and antagonism according to the Pritchard and Shipman model (Antiviral Research 14:181-206 (1990)).

Combination Analysis:

The Prichard and Shipman approach to calculating theoretical additive effects (described in Example 1) was used for the present example.

The difference between the actual observed fraction of inhibition and the predicted value was calculated for each concentration combination for each plate in each experiment to determine whether the observed combined effect was greater than the theoretical additive effect Z calculated from the Prichard and Shipman equation. For each concentration combination, the replicates (across all plates and experiments) were used to calculate a mean difference between observed and predicted fraction of inhibition, its standard error and its two-sided 95% confidence interval.

Synergy or antagonism for a concentration combination was determined based on the same rules set forth in Example 1.

Combination of Therapeutic Agent 1 and Therapeutic Agent 4:

The inhibitory effects in replicon produced by each drug alone or in combination with the other at concentrations up to ten-fold above the EC_{50} were examined in the genotype 1b (Con1) replicon using a checkerboard titration pattern (two-fold serial dilutions) in the standard three-day antiviral assay. The concentrations tested were chosen to ensure that the EC_{50} values of the compounds were in the middle of the serial dilution range. For Compound 4, concentrations ranged from 0.0002 nM to 0.0063 nM, and for Compound 1, concentrations ranged from 0.023 nM to 0.75 nM. Synergy, additivity, and antagonism were evaluated using the Pritchard and Shipman model.

Results:

The results of the assay analysis are illustrated in FIGS. **3** and **4** and Table 3. In the 3-D surface plot of FIG. **3**, deviations from expected interactions between Compound 1 and Compound 4 are purely additive at concentrations associated with a horizontal plane at 0%. Synergistic interactions between Compound 1 and Compound 4 appear as a peak above the horizontal plane with a height corresponding to the percent above calculated additivity. Antagonistic interactions between Compound 1 and Compound 4 appear as a pit or trough below the horizontal plane with a negative value signifying the percent below the calculated additivity. Synergistic interactions appear as shades of dark grey, additive interactions appear white, and antagonistic interactions appear as speckled.

As illustrated in the 3-D surface plot of FIG. **3** and the contour plot of FIG. **4**, an additive or synergistic effect exists at most of the concentrations for Compound 1 and Compound 4. In particular, there is a concentration region showing synergy at the lower dose concentrations of Compound 4 and mid-range dose concentrations of Compound 1.

Table 3 below lists combinations of concentrations of Compound 1 and Compound 4 with statistically significant synergistic or antagonistic effects based on the Prichard and Shipman Model analysis. For each combination of concentrations, Table 3 includes the mean difference in the observed and predicted fraction of inhibition, the standard deviation or error of the mean difference, and the upper and lower limits of the 95% confidence interval.

According to Table 3, most of the combinations of Compound 1 and Compound 4 listed in the table have statistically significant synergistic effects. A small amount of antagonism was observed at the lowest concentrations of Compound 1.

The results presented in FIGS. **3** and **4** and Table 3 demonstrate that the combination of therapeutic agent 4 and therapeutic agent 1 achieves additivity at most of the concentration combinations of the two agents and achieves synergy at certain concentration combinations, in particular, at low concentrations of therapeutic agent 4 and mid-range concentrations of therapeutic agent 1. Taken together, these in vitro replicon results suggest that therapeutic agent 4 should produce a significant antiviral effect in patients when administered in combination with therapeutic agent 1 in patients infected with HCV.

TABLE 3

Compound 4, nM	Compound 1, nM	Mean difference in fraction of inhibition: Observed – Predicted	Standard error of mean difference	Lower 95% confidence limit	Upper 95% confidence limit
0.000197	0.375000	0.09895	0.033975	0.02060	0.17729
0.000394	0.187500	0.16900	0.038934	0.07922	0.25878
0.000394	0.375000	0.11401	0.027710	0.05011	0.17791
0.000788	0.187500	0.15349	0.038860	0.06388	0.24310
0.000788	0.375000	0.09992	0.027266	0.03704	0.16279
0.001575	0.023438	−0.08326	0.027126	−0.14582	−0.02071
0.001575	0.046875	−0.11894	0.026099	−0.17913	−0.05876
0.001575	0.187500	0.07958	0.020080	0.03328	0.12588
0.003150	0.023438	−0.10156	0.018406	−0.14401	−0.05912
0.003150	0.046875	−0.08091	0.014615	−0.11462	−0.04721

Similar results were also demonstrated for the combination of therapeutic agent 2 and therapeutic agent 4, where additivity was observed at most of the concentration combinations of the two agents and synergy was observed at low concentrations of therapeutic agent 2 and therapeutic agent 4.

EXAMPLE 3

Reduction of HCV-Infected Cells with Combinations of Therapeutic Agents 1, 2 and 4

In order to quantify the frequency of resistant replicon colonies selected by therapeutic agent 1, therapeutic agent 2, therapeutic agent 4, or various combinations of these agents, the stable subgenomic replicon cell line derived from HCV genotype 1a (H77; Genbank accession number AF011751) was utilized. The replicon construct was bicistronic and the cell line was generated by introducing the constructs into cell lines derived from the human hepatoma cell line Huh-7. The replicon also has a firefly luciferase reporter and a neomycin phosphotransferase (Neo) selectable marker. The two coding regions, separated by the FMDV 2a protease, comprise the first cistron of the bicistronic replicon construct, with the second cistron containing the HCV NS3-NS5B coding region with addition of adaptive mutations E1202G, K1691R, K2040R and S2204 I. This HCV replicon cell line was maintained in Dulbecco's modified Eagles medium (DMEM; Invitrogen) containing 10% (v/v) fetal bovine serum, 100 IU/ml penicillin, 100 μg/ml streptomycin, and 200 μg/ml G418 (all from Invitrogen). 1a-H77 replicon cells (10^5-10^6) were plated in 150 mm cell culture plates and grown in the presence of G418 (400 μg/ml) and Compound 1, Compound 2, and/or Compound 4 at concentrations that were either 10-fold (10×) or 100-fold (100×) above the EC_{50} value for the HCV genotype 1a replicon cell line. The EC_{50} values for Compound 1, Compound 2, and Compound 4 used for this experiment were 0.9, 7.7, and 0.01 nM, respectively. After three weeks of treatment, the majority of replicon cells were cleared of replicon RNA and, therefore, were unable to survive in the G418-containing medium since the replicon RNA included the neo marker conferring G418 resistance. The cells containing resistant replicon variants survived and formed colonies, and these colonies were stained with 1% crystal violet in 10% Protocol SafeFix II reagent (Fisher Scientific), and counted. As shown in FIG. **5**A, the combination of Compound 4 plus either Compound 1 or Compound 2 at either 10-fold or 100-fold above their respective EC_{50} value resulted in significantly fewer colonies than either Compound 1, Compound 2, or Compound 4 alone at 10-fold or 100-fold above their respective EC_{50} value.

FIG. **5**B illustrates the percentage of colonies surviving two vs. three DAA combinations. In colony survival assays, 1a-H77 replicon cells were grown in the presence of a DAA combination and G418 for approximately three weeks, after which time the cells containing resistant replicon variants had formed colonies. The cells were stained with crystal violet and counted. "Triple Combination" is either a combination of Compounds 1, 2 and 4 at concentrations of 5-fold (5×) over their respective EC50 values, or a combination of Compounds 1, 2 and 4 at concentrations of 10-fold (10×) over their respective EC50 values.

FIGS. **5**C and **5**D show the effect of a combination of Compounds 1 and 4 in long-term HCV RNA reduction assays in genotype 1 replicon cell lines. In long-term replicon RNA reduction assays, 106 replicon cells were plated in the absence of G418. The inhibitors at concentrations of either 10-fold (10×) or 100-fold (100×) over their respective EC50 values were added, and the cells were grown to approximately 95% confluence (4 days). At each passage, 106 cells were removed and frozen, and an additional 106 cells were passed into another flask with fresh media and inhibitors. RNA was extracted from 106 cells and HCV RNA was measured in a Real-Time RT-PCR assay. FIGS. **5**C and **5**D show that in both 1a and 1b replicon cells, the combination of Compounds 1 and 4, each at 10-fold over EC50, is more effective at clearing cells of replicon than 100-fold over EC50 of either inhibitor alone.

Predominant resistant variants selected by Compound 1, 2, or 4 in genotype 1 replicons were also determined. For Compound 1, the predominant resistance variants in 1a-H77 replicons include R155K, D168A and D168V with fold resistance of 26, 48 and 128, respectively; and the predominant resistance variants in 1b-Con1 replicons include R155K, A156T and D168V with fold resistance of 48, 9 and 190, respectively. For Compound 2, the predominant resistance variants in 1a-H77 replicons include C316Y, M414T, Y448C and S556G with fold resistance of 1600, 36, 980 and 15, respectively; and the predominant resistance variants in 1b-Con1 replicons include C316Y, M414T and D559G with fold resistance of 1400, 26 and 100, respectively. For Compound 4, the predominant resistance variants in 1a-H77 replicons include M28T, M28V, Q30R, Y93C and Y93H with fold resistance of 9000, 60, 800, 1700 and 41000, respectively; and the predominant resistance variants in 1b-Con1 replicons include Y93H with fold resistance of 55. These experiments also showed that in genotype 1a, a number of variants selected by Compounds 2 or 4 conferred higher levels of resistance than those selected by Compound 1, and that in genotype 1b, one variant (C316Y) selected by Compound 2 conferred a higher level of resistance than those selected by either Compound 1 or Compound 4.

The above examples show that the combination of two different classes of DAAs (e.g., a combination of a HCV protease inhibitor and a HCV polymerase inhibitor, or a combination of a HCV protease inhibitor and a HCV NS5A inhibitor, or a combination of a HCV polymerase inhibitor and a HCV NS5A inhibitor) can lead to an improved resistance barrier in patients relative to a single DAA alone, while the combination of three different classes of DAAs (e.g., a combination of a HCV protease inhibitor, a HCV polymerase inhibitor, and a HCV NS5A inhibitor) can lead to even more significant barrier to resistance. Improvement in the barrier to resistance achieved through co-administration of multiple DAAs of different classes or with different mechanism of action is expected to correlate with enhanced efficacy in patients.

EXAMPLE 4

Use of 2-DAA Combination without Interferon and Ribavirin to Treat Treatment-Naïve Subjects Infected with Genotype 1, 2 or 3

Genotype 1

Ten previously untreated subjects infected with HCV genotype 1 were treated with a 2-DAA combination for 12 weeks. The treatment was interferon- and ribavirin-free and was designed to last for 12 weeks. The 2-DAA combination included Compound 1/r (200/100 mg QD) and Compound 4 (25 mg QD). At week 3 the treatment, seven of the ten subjects showed no detectable HCV RNA; and the remaining three subjects had HCV RNA levels of less than 25 IU/mL. At week 4, eight subjects showed no detectable HCV RNA, and the remaining two showed (or were believed to have) an HCV RNA level of less than 25 IU/mL. At week 5, nine subjects had no detectable HCV RNA and the remaining one had an HCV RNA level of less than 25 IU/mL. At weeks 6 and 7 of the treatment, all ten subjects were tested and found no detectable HCV RNA. At weeks 9, 10, 11 and 12 of the treatment, one subject showed viral rebound (breakthrough), and the remaining nine subjects showed no detectable HCV RNA.

At post-treatment week 2, at least seven subjects were tested and found no detectable HCV RNA. At post-treatment week 4, at least seven subjects were tested and found no detectable HCV RNA. At post-treatment week 8, at least three subjects were tested and found no detectable HCV RNA.

Genotype 2

Ten previously untreated subjects infected with HCV genotype 2 were treated with the same regimen of this Example. At week 3 of the treatment, eight of the ten subjects showed no detectable HCV RNA, one had viral rebound, and one had HCV RNA levels of less than 25 IU/mL. At week 5 of the treatment, nine of the ten subjects showed no detectable HCV RNA, and one had breakthrough. At weeks 10, 11 and 12 of the treatment, at least seven of the ten subjects were tested and found no detectable HCV RNA.

At post-treatment week 2, at least five subjects found no detectable HCV RNA; and two more subjects had breakthrough. At post-treatment week 4, at least four subjects found no detectable HCV RNA.

Genotype 3

Similarly, ten previously untreated subjects infected with HCV genotype 3 were treated with the same regimen of this Example. At weeks 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 of the treatment, two subjects showed no detectable HCV RNA. At post-treatment weeks 2 and 4, the same two subjects were confirmed with no detectable HCV RNA. A number of subjects appeared to have breakthrough during the treatment.

EXAMPLE 5

Use of 3-DAA Combination without Interferon and Ribavirin to Treat Treatment-Naïve Subjects Infected with Genotype 1

Twelve previously untreated subjects with HCV genotype 1 infection were treated with a 3-DAA combination for 12 weeks. The treatment was interferon- and ribavirin-free. The 3-DAA combination included Compound 1/r (150/100 mg QD), Compound 2 (400 mg BID), and Compound 4 (25 mg QD). The weight based dosing of ribavirin ranged from 1000 to 1200 mg divided twice daily.

At week 3 of the treatment, seven of the twelve subjects had no detectable HCV RNA, and the five remaining subjects had HCV RNA levels of less than 25 IU/mL. At week 4 of the treatment, nine of the twelve subjects had no detectable HCV RNA, and the three remaining subjects had HCV RNA levels of less than 25 IU/mL. At weeks 6 and 8, all twelve subjects had no detectable HCV RNA. At weeks 10 and 12, eleven of the twelve subjects showed no detectable HCV RNA, and one subject had detectable HCV RNA.

At post-treatment weeks 2 and 4, at least ten of the twelve subjects were tested and found no detectable HCV RNA. At post-treatment week 8, at least seven of the twelve subjects were tested and found no detectable HCV RNA. Two subjects appeared to have breakthrough during or after the treatment.

EXAMPLE 6

Clinical Modeling for Interferon-Free DAA Combination Therapies

This example describes a novel clinical model for evaluating optimal doses and durations of interferon-free HCV therapies using combinations of different DAAs. This model reasonably predicted the effectiveness of numerous DAA combinations in interferon-free, short-duration therapies.

A mechanistic model was used to model the relationship between DAA exposures and antiviral efficacy in HCV-infected subjects. This model was used to conduct clinical trial simulations of clinical outcomes following administration of various DAA combination regimens (e.g., specific DAA combinations and different doses of DAAs) and durations of therapy.

Numerous DAAs have been extensively documented to select mutants following short duration of monotherapy (e.g., less than 1 week). The viral dynamic model of this Example included single and double mutants. Specifically, the model included 2 single mutants and one double mutant for each of the 2-DAA combination regimens. Thus, a 2-DAA combination regimen (e.g., a combination of a protease inhibitor and a NS5A inhibitor) included 2 single mutants and one double mutant. A 3-DAA combination (e.g., a combination of a protease inhibitor, a polymerase inhibitor and a NS5A inhibitor, such as a combination of a protease inhibitor, a non-nucleoside polymerase inhibitor (NNPI) and a NS5A inhibitor) included 3 single and 2 double mutants.

The model has 3 components: hepatocytes (uninfected or target cell), infected cell and viral dynamics. The differential equations describing the dynamics of the 3 components are as follows:

(1) Hepatocytes (Uninfected or Target Cell) Dynamics

$$dT/dt = s - de*T - (1-\eta)*\beta*T*(VLWT + VLPoly + VLProt + VLNS5A + VLNS5AProt + VLPolyProt)$$

(2) Infected Cell Dynamics

(a) Infected with Wild Type Virus

$$dIWT/dt = (1-\eta)*\beta*T*VLWT - \delta*IWT$$

(b) Infected with Polymerase Mutant Virus

$$dIPoly/dt = (1-\eta)*\beta*T*VLPoly - \delta*IPoly$$

(c) Infected with Protease Mutant Virus

$$dIProt/dt = (1-\eta)*\beta*T*VLProt - \delta*IProt$$

(d) Infected with NS5A Mutant Virus

$$dINS5A/dt = (1-\eta)*\beta*T*VLNS5A - \delta*INS5A$$

(e) Infected with Protease-NS5A Double Mutant Virus

$$dINS5AProt/dt = (1-\eta)*\beta*T*VLNS5AProt - \delta*INS5AProt$$

(f) Infected with Protease-Polymerase Double Mutant Virus

$$dIPolyProt/dt = (1-\eta)*\beta*T*VLPolyProt - \delta*IPolyProt$$

(3) Viral Dynamics

(a) Wild Type Virus

$$dVLWT/dt = (1-3*\mu)*\rho*(1-Eff1)*IWT + \mu*(\rho*(1-Eff2)*Fit1*IPoly + \rho*(1-Eff3)*Fit2*IProt + \rho*(1-Eff4)*Fit3*INS5A) - c*VLWT$$

(b) Polymerase Mutant Virus

$$dVLPoly/dt = (1-\mu-\phi)*\rho*(1-Eff2)*Fit1*IPoly + \mu*\rho*(1-Eff1)*IWT + \phi*\rho*(1-Eff5)*Fit4*IPoly-Prot - c*VLPoly$$

(c) Protease Mutant Virus

$$dVLProt/dt = (1-\mu-2*\phi)*\rho*(1-Eff3)*Fit2*IProt + \mu*\rho*(1-Eff3)*IWT + \phi*(\rho*(1-Eff5)*Fit4*IPolyProt + \rho*(1-Eff6)*Fit5*INS5AProt) - c*VLProt$$

(d) NS5A Mutant Virus

$$dVLNS5A/dt = (1-\mu-\phi)*\rho*(1-Eff4)*Fit3*INS5A + \mu*\rho*(1-Eff1)*IWT + \phi*\rho*(1-Eff6)*Fit5*INS5AProt - c*VLNS5A$$

(e) NS5A and Protease Double Mutant Virus

$$dVLNS5AProt/dt = (1-2*\phi)*\rho*(1-Eff6)*Fit5*INS5AProt + \phi*(\rho*(1-Eff4)*Fit3*INS5A + \rho*(1-Eff3)*Fit2*IProt) - c*VLNS5AProt$$

(f) Poly and Protease Mutant Double Mutant Virus

$$dVLPolyProt/dt = (1-2*\phi)*\rho*(1-Eff5)*Fit4*IPolyProt + \phi*(\rho*(1-Eff2)*Fit1*IPoly + \rho*(1-Eff3)*Fit2*IProt) - c*VLPolyProt$$

The parameters used in the above equations are described in Table 5.

TABLE 5

Viral Dynamic Parameters

Parameter	Description
s	zero-order production of hepatocytes
T	number of Target or uninfected hepatocytes
de	first-order rate constant for the death of hepatocytes
β	rate-constant for the infection of hepatocytes by virus
δ	first-order rate constant for the death of infected hepatocytes
η	fractional reduction of the rate-constant for the infection of hepatocytes by virus

TABLE 5-continued

Viral Dynamic Parameters

Parameter	Description
μ	probability of the formation of single mutants and mutation back to Wild-Type
φ	probability of the formation of double mutants and mutation back to single mutant
ρ	production rate of the Wild-Type virus
c	clearance rate of the virus
Eff1, Eff2, Eff3, Eff4	inhibition of production of Wild Type, polymerase, protease, and NS5A mutant, respectively
Eff5, Eff6	inhibition of production of polymerase-protease and NS5A-protease double mutant, respectively
Fit1, Fit2, Fit3	fitness of polymerase, protease and NS5A mutant relative to wild type virus, respectively
Fit4, Fit5	fitness of polymerase-protease and NS5A-protease double mutant relative to wild type virus, respectively
IWT, IPoly, Iprot, INS5A	number of cells infected with wild type, polymerase, protease and NS5A mutants, respectively
IPoly-Prot, INS5A-Prot	number of cells infected with polymerase-protease and NS5A-protease double mutant, respectively
VLWT, VLPoly, VLProt, VLNS5A	viral load for wild type virus, polymerase, protease and NS5A mutant virus, respectively
VLPoly-Prot, VLNS5A-Prot	viral load for polymerase-protease and NS5A-protease double mutant, respectively

As shown in the differential equations for viral dynamics, the effect of DAA is included as an inhibition of viral load production. For example, the effect of DAA(s) on production of wild type virus is given as (1−Eff1)*ρ where Eff1 is the fraction of viral production that is inhibited. In the absence of drug Eff1=0 and in the presence of drug Eff1 takes a value between 0 and 1. Eff1 is described using an Emax model:

$$Eff1 = Emax*Conc/(EC_{50}+Conc)$$

where Emax represents maximum inhibition, Conc is the plasma DAA concentration and EC_{50} is the concentration that inhibits viral load production by 50%. As the fold-change in EC_{50} for the mutants compared to wild type virus was based on values obtained from in vitro replicon studies, EC_{50} was estimated only for wild type virus.

For DAA combinations, the effect was assumed to be multiplicative and incorporated as follows:

$$(1-Eff1) = (1-Eff_{DAA1})*(1-Eff_{DAA2})*(1-Eff_{DAA3})$$

The effect of ribavirin (RBV) can also be added on infection rate β as an Emax model. In presence of ribavirin, the infection rate decreases by a factor (1−η) where

$$\eta = Conc_{RBV}/(EC_{50\text{-}RBV}+Conc_{RBV})$$

The model does not include a double mutant to the polymerase+NS5A inhibitors. In a 3-DAA regimens, a polymerase+NS5A double mutant is often wild type for the protease inhibitor. Hence, this double mutant is not expected to significantly affect clinical outcomes for a 3-DAA regimen simulation. On the other hand, the model can be readily adapted to simulate a 2-DAA regimen containing a polymerase inhibitor and a NS5A inhibitor by treating the polymerase inhibitor (e.g., PSI-7977) as a protease inhibitor in the model.

The lowest available limit of detection (LOD) of viral load assays is 10 IU/mL. Assuming 3 virion particles per IU, this constitutes about 0.5 million viruses in the body at LOD. Hence, subjects have to be treated for significant period of time after their viral load falls below the LOD to achieve cure. This duration depends on the potency of the compounds and the individual response to therapy.

In order to predict the duration required for cure, a "threshold" concept was used. For simulations, an HCV-infected subject was assumed to achieve SVR when viral load reaches less than 1 virion in the total plasma and extracellular fluid volume (about 15000 mL), i.e., viral load measurement of <1 copy/15000 mL or <0.33 IU/15000 mL. This translates to about 5 log IU/mL. Cf. Snoeck E et al., CLIN PHARMACOL THER. 87(6):706-13 (2010), wherein based on data from patients treated with peg-IFN and ribavirin, subjects were estimated to achieve SVR when the predicted number of infected cells fell below 1. While such low viral loads cannot be measured experimentally, they can be simulated using the viral dynamic model.

The model can be used to predict SVR for any combination of DAAs, with or without interferon, and with or without ribavirin.

As non-limiting examples, various interferon-free treatment regimens using different combinations of Compound 1, Compound 2 and/or Compound 4, with or without ribavirin, were evaluated using the model of this Example. The following approach was used to include mutants in the model:

a. One single mutant per DAA

b. One double mutant per DAA combination

For a combination of two DAAs, e.g., a combination of Compound 1 and Compound 2, the model included one mutant resistant to Compound 1, one mutant resistant to Compound 2, and one double mutant resistant to both Compound 1 and Compound 2. Compound 1 is coadministered or co-formulated with ritonavir (or another pharmacokinetics enhancer) to improve its drug exposure.

A double mutant to Compound 2 and Compound 4 was not included in the modeling. In the 3-DAA regimens, a Compound 2/Compound 4 double mutant is likely wild type for Compound 1 due to the high potency and resistant profile of Compound 1. Hence, the Compound 2/Compound 4 double mutant is not expected to affect clinical outcomes for treatments containing Compound 1.

Single mutants included in the model were based on mutants observed for the individual DAAs in the Phase 1b and 2a studies (e.g., clinical studies M10-351, M12-116, and M11-602). For double mutants with resistance to 2 DAA classes, the sensitivity (EC_{50}) of double mutants to drug was assumed to be a combination of the 2 single mutants. Thus, for Compound 1 and Compound 2, the single mutants were D168V and M414T, respectively, and the double mutant was D168V-M414T. In this scenario, the D168V mutant would be less sensitive to Compound 1 but would be as sensitive to Compound 2 as wild type virus. Similarly, the M414T mutant would be less sensitive to Compound 2 but would be as sensitive to Compound 1 as wild type virus. The double mutant D168V-M414T would be less sensitive to both Compound 1 and Compound 2.

The fold change in EC_{50} for the mutants compared to wild type virus was based on values obtained from in vitro replicon studies. Since monotherapy data for Compound 4 indicated a variety of mutants with different EC_{50}s, a value of 1000× fold change in EC_{50} was used for Compound 4 for modeling and simulations.

Baseline prevalence of the mutants was estimated during model fitting, while the mutation rate was based on the literature values. Both baseline prevalence and mutation rate determined mutant fitness.

Pharmacokinetic data and viral load data from 140 treatment-naïve HCV-infected subjects were used to construct the model. For modeling, number of target cells at baseline, number of infected cells at baseline, death rate of target cells and mutation rates were based on literature values. See, e.g., Snoeck et al. supra; Rong et al. SCI TRANSL MED. 2(30):30ra32 (2000); Neal and Pravin, ACOP 2009 (http://2009.go-acop.org/sites/all/assets/webform/Lauren-Neal_ACoP_2009.pdf); Neumann et al. SCIENCE 282(5386):103-7 (1998); Shudo et al. ANTIVIR THER. 13(7):919-26 (2008); and Dahari et al. J THEOR BIOL. 247(2):371-81 (2007). The production rate of virus and infection rate of virus were derived from other parameters in the model. All other parameters were estimated. Exposure-antiviral response modeling was performed using NONMEM 7.2.

Clinical trial simulations were performed using Trial Simulator version 2.2.1. Fifty subjects and 50 replicates were simulated for each treatment. A subject drop out rate from the study due to any reason was assumed to be 8% over 24 weeks based on available literature on trials in subjects with HCV. All simulations were conducted assuming 100% compliance. Covariates included in the simulations were genotype 1a/1b status. Clinical outcomes simulated included: (1) percentage of subjects below limit of detection (LOD) of 10 IU/mL and (2) percentage of subjects achieving SVR.

Clinical trial simulations were conducted to determine optimal dose and duration for SVR. Over 80 scenarios were simulated to predict the percentage of subjects with SVR following administration of various 2- and 3-DAA combinations (e.g., Compound 1+Compound 2, or Compound 1+Compound 4, or Compound 1+Compound 2+Compound 4), without RBV, at a range of doses for each DAA (e.g., Compound 1/ritonavir at 250/100, 150/100 or 100/100 mg QD, Compound 4 at 5, 25 or 100 mg QD, and Compound 2 at 400 or 800 mg BID) and across a range of treatment durations (e.g., 2. 4, 6, 8, 10, 12, 16, and 24 weeks).

Optimal dose and duration were predicted based on percentage of subjects with viral load of less than −5 log IU/mL threshold for SVR. Selected and relevant results of simulation for the 2- and 3-DAA combinations of Compounds 1, 2 and/or 4 are shown in FIGS. **6**A, **6**B and **6**C for two different doses of Compound 1. FIG. **6**A shows the predicted median SVR percentage ("% SVR") and 90% confidence interval (the vertical bar at the top of each SVR percentage column) for different treatment durations using a combination of Compound 1 and Compound 2; FIG. **6**B shows the predicted median and 90% confidence interval for different treatment durations using a combination of Compound 1 and Compound 4; and FIG. **6**C shows the predicted median and 90% confidence interval for different treatment durations using a combination of Compound 1, Compound 2 and Compound 4. In each simulation, RBV was included, and Compound 1 was used with 100 mg ritonavir, and the subjects are HCV genotype 1, treatment-naïve patients. SVR24 is lower than SVR12 in some cases due to drop out; longer durations are not necessarily predicted to improve SVR but could result in more dropouts resulting in lower SVR.

The model predicted that with 8-12 weeks of dosing at least 80 to 90% subjects can achieve SVR with 2 and 3 DAA combinations. The model also predicted that durations shorter than 8 weeks can cure a significant number of subjects. A 2-DAA regimen was predicted to cure over 40% of the subjects and a 3-DAA regimen was predicted to cure about 60% of the subjects with only 6 weeks of dosing. Dosing for durations of over 12 weeks was not expected to increase the percentage of subjects with SVR significantly. Addition of the 3rd DAA was predicted to shorten treatment duration by 2 to 4 weeks as optimal durations for the 3-DAA combination of Compound 1, Compound 2 and Compound 4 were predicted to be 8-10 weeks.

FIGS. **6**A, **6**B and **6**C illustrate the predictions for DAA combinations without ribavirin. The model also predicts

similar or comparable SVR percentages for these DAA combinations when used with ribavirin. In addition, the effect of interferon (e.g., pegylated interferon) can also be added by incorporating interferon similar to a DAA but without any resistant mutants.

One of the advantages that the model provides is that it allows examination of various viral parameters and its effect on dose, duration and SVR. For example while experimentally determining the effect of mutants parameters is very difficult if not impossible, they can be examined using the model. Thus SVR in patient population that have different mutants can be predicted with the model.

The model was used to simulate a treatment regimen which included 150/100 mg Compound 1/ritonavir QD+400 mg Compound 3 QD+weight-based amounts of RBV BID for 12 weeks. Subjects under the treatment included 11 treatment naïve subjects between the ages of 18 and 65. All subjects completed 12 weeks of therapy with Compound 1 and ritonavir (Compound 1/r) dosed in combination with Compound 3 and ribavirin (RBV). Compound 1 (150 mg once daily (QD)) was dosed with 100 mg QD ritonavir, 400 mg QD Compound 3, and weight-based amounts of RBV in treatment naïve subjects infected with genotype (GT) 1 HCV. The percentage of subjects with HCV RNA less than LOD at 2, 4, 8, 10, and 12 weeks was summarized in FIG. **7**. The mean predicted versus observed percentage of subjects with below LOD ("% LOD") at respective weeks are shown FIG. **7**. 95% confidence intervals for the predicted data (the vertical bar at the top of each respective predicted LOD percentage column) were also indicated. As shown in FIG. **7**, the model reasonably predicted the clinical outcome of % LOD.

The model was also used to simulate another treatment regimen. The regimen included three groups of patients. In Group 1, previously untreated subjects having HCV infection were treated with a protease inhibitor (in combination with ritonavir), a polymerase inhibitor, and ribavirin. The treatment was without interferon. Subjects included 19 treatment naïve subjects between the ages of 18 and 65. One subject discontinued the study at week 3. All of the remaining 18 subjects completed 12 weeks of therapy with Compound 1/r dosed in combination with Compound 2 and RBV. Compound 1 (250 mg QD) was dosed with 100 mg QD ritonavir, 400 mg BID Compound 2, and RBV in treatment naïve subjects infected with GT1 HCV.

In Group 2, previously untreated subjects having HCV infection were treated with a protease inhibitor (in combination with ritonavir), a polymerase inhibitor, and ribavirin. The treatment was without interferon. Subjects included 14 treatment naïve subjects between the ages of 18 and 65. One subject discontinued the study at week 1. Therefore, a total of 13 subjects were under study. All of the thirteen subjects completed 12 weeks of therapy with Compound 1/r dosed in combination with Compound 2 and RBV. Compound 1 (150 mg QD) was dosed with 100 mg QD ritonavir, 400 mg BID Compound 2, and RBV in treatment naïve subjects infected with GT1 HCV.

In Group 3, peginterferon+ribavirin (P/RBV) non-responders were treated with a protease inhibitor (in combination with ritonavir), a polymerase inhibitor, and ribavirin. The treatment was without interferon. Subjects included 17 P/RBV non-responders between the ages of 18 and 65. Subjects were treated with Compound 1/r dosed in combination with Compound 2 and RBV for 12 weeks. Compound 1 (150 mg QD) was dosed with 100 mg QD ritonavir, 400 mg BID Compound 2, and RBV in P/RBV non-responders infected with GT1 HCV. During the treatment, four patients had breakthroughs and discontinued the study before week 7.

The mean predicted versus observed percentage SVR ("% SVR") after 12-week treatment are shown FIG. **8**. 95% confidence intervals for the predicted data (the vertical bar at the top of each respective predicted SVR percentage column) were also indicated. As shown in FIG. **8**, the predicted SVR percentages aligned well with the observed SVR percentages. Simulations also predict that the same treatment regimen but without ribavirin has similar or comparable LOD percentages for different treatment durations.

The exposure response viral dynamic model of this Example provided a quantitative method to reasonably predict SVR for various combination of antiviral compounds. Based on the exposure-antiviral response modeling and clinical trial simulations, it demonstrated that (1) addition of a 3rd DAA to a 2-DAA combination can reduce optimal duration of treatment and/or increase SVR; (2) 8-12 weeks of dosing is the optimal duration of therapy for 2 and 3 DAA combinations of Compound 1/r, Compound 2 and Compound 4; and (3) durations shorter than 8 weeks of interferon-free treatment have been predicted to cure a significant percent of the subjects.

EXAMPLE 7

Clinical Modeling for Interferon-Free DAA Combination Therapies Containing BMS-790052 and BMS-650032

The model described above was also used to predict the SVR percentage of interferon-free treatment regimens containing BMS-790052 and BMS-650032 without ribavirin, based on existing published clinical data including two Phase 1 and one Phase 2 study of BMS-790052 and one Phase 1 and one Phase 2a study of BMS-650032. FIG. **9** shows the predicted median SVR percentage and 90% SVR confidence interval for different treatment durations of a 2-DAA regimen containing BMS-790052 (60 mg QD) and BMS-650032 (600 BID) in genotype 1 naïve subjects. The combination of BMS-790052 (60 mg QD) plus BMS-650032 (600 mg BID) in genotype 1 subjects was predicted to achieve improved SVR for durations of 12 weeks or greater with predicted SVR rates of about 70% for 10 weeks of dosing. Similar regimens but containing ribavirin, or regimens with similar dosings of BMS-790052 and BMS-650032 with or without ribavirin, are expected to achieve similar SVR rates.

EXAMPLE 8

Clinical Modeling for Interferon-Free Therapies Containing PSI-7977

Likewise, a 3-DAA regimen without interferon and ribavirin was modeled for genotype 1 patients based on existing clinical data. The 3-DAA regimen contains 200/100 mg QD Compound 1/r, 50 mg QD Compound 4, and 400 mg QD PSI-7977. FIG. **10** depicts the predicted median SVR rates for different treatment durations of this 3-DAA combination. This 3-DAA combination was predicted to have over 60% SVR in 6 weeks and over 80% SVR at duration of 8-week, 10-week, 12-week or longer treatment. Similar regimens but containing ribavirin, or regimens with similar dosings of Compound 1/r, Compound 4 and PSI-7977 with or without ribavirin, are expected to achieve similar SVR rates.

The model can also be used to predict SVR for regimens containing single DAA or single DAA with ribavirin. For example, the model predictions for PSI-7977+ribavirin for various durations for treating HCV genotype 1 treatment-

naïve patients were obtained. FIG. **11** depicts the predicted median and 90% confidence interval of SVR percentage for different treatment durations of such a regimen containing PSI-7977 (as the sole DAA; 400 mg QD) and ribavirin (600 mg BID). The 90% confidence interval for the predicted SVR (the vertical bar at the top of each respective predicted SVR percentage column) is also indicated in FIG. **11**. The prediction was based on the already published clinical data for PSI-7977. SVR rate for PSI-7977+ribavirin was predicted to be around 75-90% following 12 weeks of dosing, and about 55-75% following 8 weeks dosing, in genotype 1 subjects. Similar SVR percentages for genotype 1 treatment-naïve patients are expected for similar regimens containing similar PSI-7977 QD dosing (e.g., 200-600 mg QD) but without ribavirin.

Data from two Phase 1 and one Phase 2 study of Daclatasvir (BMS-790052) and one Phase 1 and one Phase 2 study of PSI-7977 were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for a 2-DAA combination with Daclatasvir (BMS-790052) and PSI-7977 in genotype 1 naïve patients are shown in FIG. **12**. The model predicted that following 10-12 weeks of dosing with the combination of Daclatasvir and PSI-7977 without ribavirin, at least 90% of HCV genotype 1 naïve patients can achieve SVR.

Similarly, data from one Phase 1a study of TMC-435 and one Phase 1 and one Phase 2 study of PSI-7977 were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for a 2-DAA combination with the TMC-435 and PSI-7977 in genotype 1 naïve patients are shown in FIG. **13**. The model predicts that following 10-12 weeks of dosing with the combination of TMC-435 and PSI-7977 without ribavirin, at least 90% of HCV patients can achieve SVR.

EXAMPLE 9

Clinical Modeling for Interferon-Free DAA Combination Therapies Containing Danoprevir and Mercitabine

In addition, data from one Phase 1 and one Phase 2 study of Danoprevir and Mercitabine were used for estimating the pharmacokinetic and viral dynamic model parameters. Ritonavir was co-administered with danoprevir to improve the pharmacokinetics of danoprevir. Predictions for a 2-DAA combination with Danoprevir and Mercitabine in genotype 1 naïve patients are shown in FIG. **14**. The model predicts that following 16 weeks of dosing with the combination of Danoprevir and Mercitabine without ribavirin, at least 90% of HCV patients can achieve SVR.

EXAMPLE 10

Clinical Modeling for Interferon-Free DAA Combination Therapies Containing Tegobuvir (GS-9190), GS-9451 and GS-5885

Data from Phase 1 and Phase 2 studies of GS-9190 (tegobuvir), GS-9451 and GS-5885 were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for the combination with GS-9190 (tegobuvir), GS-9451 and GS-5885 and without ribavirin in genotype 1 naive patients are shown in FIG. **15**. The model predicts that following 12 weeks of dosing with the combination of GS-9190 (tegobuvir)+GS-9451+GS-5885+RBV and without ribavirin, about 70% of genotype 1 naïve patients can achieve SVR and following 24 weeks of treatment >80% of genotype 1 naïve patients can achieve SVR.

EXAMPLE 11

Clinical Modeling for Interferon-Free DAA Combination Therapies Containing PSI-7977 (GS-7977)

Data from Phase 1 and Phase 2 studies of GS-9451 and GS-7977 (PSI-7977) were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for the combination with GS-9451 and GS-7977 (PSI-7977) and without ribavirin in genotype 1 naive patients are shown in FIG. **16**.

Data from Phase 1 and Phase 2 studies of GS-5885 and GS-7977 (PSI-7977) were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for the combination with GS-5885 and GS-7977 (PSI-7977) and without ribavirin in genotype 1 naive patients are shown in FIG. **16**.

Data from Phase 1 and Phase 2 studies of GS-9451, GS-5885 and GS-7977 (PSI-7977) were used for estimating the pharmacokinetic and viral dynamic model parameters. Predictions for the combination with GS-9451, GS-5885 and GS-7977 (PSI-7977) and without ribavirin in genotype 1 naive patients are shown in FIG. **16**.

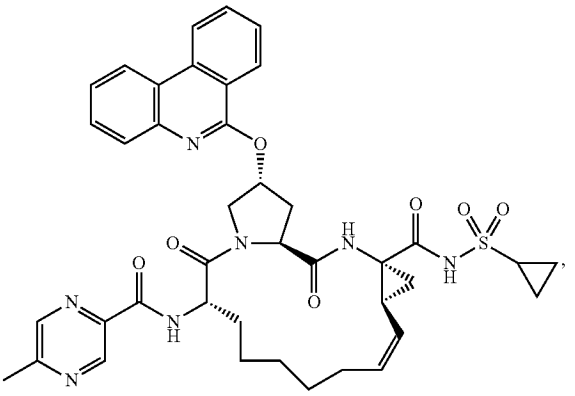
The model predicts that following 12 weeks of dosing with the combination of GS-9451 and GS-7977 (PSI-7977), or the combination of GS-5885 and GS-7977 (PSI-7977), or the combination of GS-9451, GS-5885 and GS-7977 (PSI-7977), and in the absence of ribavirin, at least 90% of genotype 1 naïve patients can achieve SVR.

The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

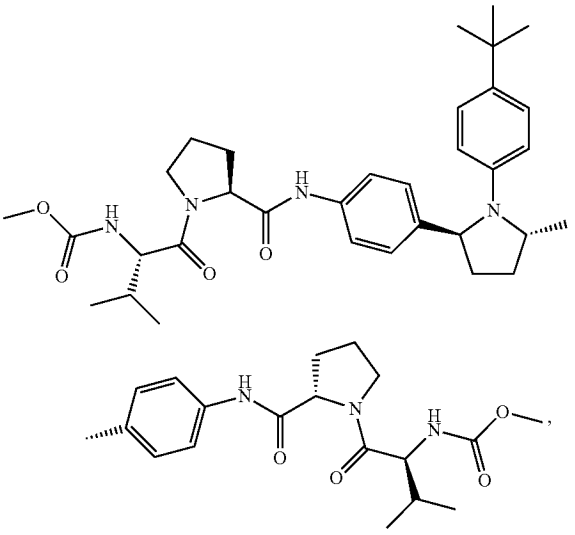
1. A method of treatment for HCV, comprising administering at least two direct acting antiviral agents (DAAs) to an HCV patient infected with HCV genotype 1, wherein said treatment does not include administration of either interferon or ribaviron to said patient, and said treatment lasts for 12 weeks, and wherein said at least two DAAs comprise:

Compound 1 having formula of



or a pharmaceutically acceptable salt thereof, and

Compound 4 having formula of

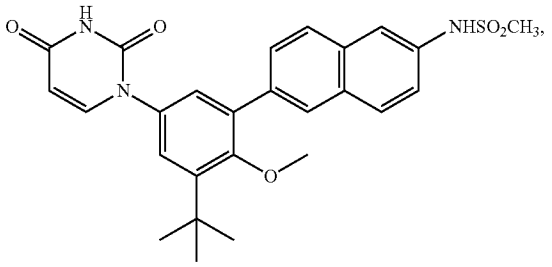


or a pharmaceutically acceptable salt thereof,

wherein Compound 1 or the salt thereof is co-administered with ritonavir.

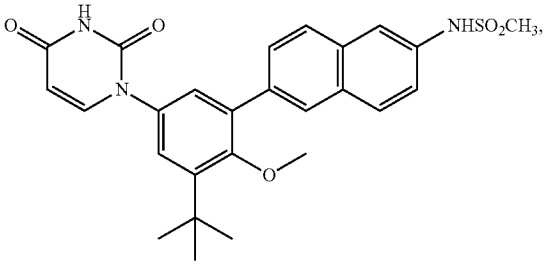
2. The method of claim **1**, wherein said patient is a treatment-naïve patient.

3. The method of claim **1**, wherein said at least two DAAs further comprise compound 2 having formula of



or a pharmaceutically acceptable salt thereof.

4. The method of claim **2**, wherein said at least two DAAs further comprise compound 2 having formula of



or a pharmaceutically acceptable salt thereof.

5. The method of claim **1**, wherein said patient is infected with HCV genotype 1a.

6. The method of claim **2**, wherein said patient is infected with HCV genotype 1a.

7. The method of claim **3**, wherein said patient is infected with HCV genotype 1a.

8. The method of claim **4**, wherein said patient is infected with HCV genotype 1a.

9. A method of treatment for HCV, comprising administering at least two direct acting antiviral agents (DAAs) to an HCV patient infected with HCV genotype 1, wherein said treatment does not include administration of either interferon or ribavirin to said patient, wherein said at least two DAAs comprise PSI-7977 and TMC-435, and wherein said treatment lasts for 12 weeks.

10. The method of claim **9**, wherein said patient is a treatment-naïve patient.

11. The method of claim **9**, wherein said patient is infected with HCV genotype 1a.

12. The method of claim **10**, wherein said patient is infected with HCV genotype 1a.

13. A method of treatment for HCV, comprising administering at least two direct acting antiviral agents (DAAs) to an HCV patient infected with HCV genotype 1, wherein said treatment does not include administration of either interferon or ribavirin to said patient, wherein said at least two DAAs comprise PSI-7977 and GS-5885, and wherein said treatment as for 12 weeks.

14. The method of claim **13**, wherein said patient is a treatment-naïve patient.

15. The method of claim **13**, wherein said patient is infected with HCV genotype 1a.

16. The method of claim **14**, wherein said patient is infected with HCV genotype 1a.

* * * * *

Exhibit C

REDACTED
IN ITS ENTIRETY

Exhibit D

REDACTED
IN ITS ENTIRETY

Exhibit E

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of Earliest Event Reported): November 21, 2011

Gilead Sciences, Inc.

(Exact name of registrant as specified in its charter)

Delaware	0-19731	94-3047598
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

333 Lakeside Drive, Foster City, California	94404
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code (650) 574-3000

Not Applicable
Former name or former address, if changed since last report

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☒ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 8.01 Other Events.

On November 21, 2011, Gilead Sciences, Inc. ("Gilead") announced that it had signed a definitive agreement under which Gilead will acquire Pharmasset, Inc. ("Pharmasset") for $137 cash per Pharmasset share. The transaction, which values Pharmasset at approximately $11 billion, was unanimously approved by Pharmasset's Board of Directors. A copy of the Press Release is attached as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

Investor Presentation Slides to be reviewed by Gilead executives with investors are attached as Exhibit 99.2 to this Current Report on Form 8-K.

Item 9.01. Financial Statements and Exhibits.

Exhibit No.	Description
99.1	Joint Press Release of Gilead and Pharmasset dated November 21, 2011
99.2	Investor Presentation Slides

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, hereunto duly authorized.

GILEAD SCIENCES, INC.
(Registrant)

By: /s/ John F. Milligan, Ph.D.
Name: John F. Milligan, Ph.D.
Title: President and Chief Operating Officer

Dated: November 21, 2011

EXHIBIT LIST

Exhibit No.	Description
99.1	Joint Press Release of Gilead and Pharmasset dated November 21, 2011
99.2	Investor Presentation Slides

Exhibit 99.1

Gilead Contacts
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Amy Flood, Media
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Pharmasset Contacts
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Sard Verbinnen & Co
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GILEAD SCIENCES TO ACQUIRE PHARMASSET, INC. FOR $11 BILLION

- Accelerates Development of All-Oral Regimen for the Treatment of HCV -
- Leverages Gilead's Infrastructure and Expertise in Antiviral Drug Development, Manufacturing and Commercialization -

Foster City, California and Princeton, New Jersey, November 21, 2011 — Gilead Sciences, Inc. (Nasdaq: GILD) and Pharmasset, Inc. (Nasdaq: VRUS) announced today that the companies have signed a definitive agreement under which Gilead will acquire Pharmasset for $137 per share in cash. The transaction, which values Pharmasset at approximately $11 billion, was unanimously approved by Pharmasset's Board of Directors. Gilead plans to finance the transaction with cash on hand, bank debt and senior unsecured notes. The company expects the transaction, when completed, to be dilutive to Gilead's earnings through 2014 and accretive in 2015 and beyond. Further guidance will be provided when the transaction closes, which is expected to be in the first quarter of 2012.

Pharmasset currently has three clinical-stage product candidates for the treatment of chronic hepatitis C virus (HCV) advancing in trials in various populations. The company's lead product candidate, PSI-7977, an unpartnered uracil nucleotide analog, has recently been advanced into two Phase 3 studies in genotype 2 and 3 patients. Both studies will utilize 12 weeks of treatment with PSI-7977 in combination with ribavirin. One study will compare this all-oral regimen against 24 weeks of the standard-of-care pegylated interferon/ribavirin in treatment-naïve patients, and the second study will compare the all-oral regimen to placebo in interferon-intolerant/ineligible patients. A third Phase 3 study in genotype 1 patients will be initiated in the second half of 2012, the design of which is dependent on the outcome of Phase 2 studies which are evaluating PSI-7977 in various combinations in genotype 1-infected patients. If successful, this strategy could lead to an initial U.S. regulatory approval of PSI-7977 in 2014. PSI-938, an unpartnered guanosine nucleotide analog, is being tested in a Phase 2b interferon-free trial as monotherapy and in combination with PSI-7977 in subjects with HCV of all viral genotypes. Mericitabine (RG7128), a cytidine nucleoside analog, is partnered with Roche and is being evaluated in three Phase 2b trials. Roche is responsible for all aspects of the development of mericitabine.

"The acquisition of Pharmasset represents an important and exciting opportunity to accelerate Gilead's effort to change the treatment paradigm for HCV-infected patients by developing all-oral regimens for the treatment of the disease regardless of viral genotype," said John C. Martin, PhD, Chairman and Chief Executive Officer of Gilead. "Pharmasset presented compelling Phase 2 data earlier this month further characterizing the strong efficacy and safety profile of PSI-7977. The compound, together with Pharmasset's other pipeline candidates, represents a strong strategic fit with Gilead's vision, pipeline and capabilities. This transaction will serve to drive the long-term growth of our business, and we look forward to working closely with the Pharmasset team to advance a broad clinical program in HCV to address the unmet needs of patients and the medical community."

- more -

"We are excited to join together with Gilead, which shares our commitment to providing HCV patients with new, highly efficacious and safe oral therapies," said Schaefer Price, President and Chief Executive Officer, Pharmasset. "We are very encouraged by the data from our Phase 2 studies of PSI-7977 and believe strongly in the potential of this compound to be a component in the transformation of the treatment of chronic HCV. Gilead's established expertise and leadership in the field of antiviral drug development and commercialization, coupled with the company's existing portfolio of promising compounds for HCV, make this partnership an ideal step to fully realize the potential of our promising molecules as part of future all-oral combination therapies for millions of patients in need around the world."

Gilead's research and development portfolio includes seven unique molecules in various stages of clinical development for the treatment of HCV. Pegylated interferon in combination with ribavirin is currently part of the standard of care treatment for patients with chronic hepatitis C. Gilead is focused on advancing multiple compounds with different mechanisms of action and resistance profiles in combinations that will support delivery of an all-oral regimen that would eliminate the need for pegylated interferon. Three separate all-oral Phase 2 studies are currently ongoing, and Gilead expects clinical data from these studies to become available in 2012 and early 2013. Pharmasset's compounds are complementary to Gilead's existing HCV portfolio, and the transaction will help advance Gilead's effort to develop an all-oral regimen for the treatment of HCV.

Terms of the Transaction

Under the terms of the merger agreement, a wholly-owned subsidiary of Gilead will promptly commence a tender offer to acquire all of the outstanding shares of Pharmasset's common stock at a price of $137 per share in cash. Following successful completion of the tender offer, Gilead will acquire all remaining shares not tendered in the offer through a second step merger at the same price as in the tender offer.

The consummation of the tender offer is subject to various conditions, including a minimum tender of at least a majority of outstanding Pharmasset shares on a fully diluted basis, the expiration or termination of the waiting period under the Hart Scott Rodino Antitrust Improvements Act, and other customary conditions. The tender offer is not subject to a financing condition.

The $137 per share price in the transaction represents an 89% premium to Pharmasset's closing share price on Friday, November 18, 2011, the last trading day prior to announcement, and 59% to Pharmasset's all time high closing stock price.

Gilead has received commitments from Bank of America Merrill Lynch and Barclays Capital in connection with financing of the transaction.

Barclays Capital and Bank of America Merrill Lynch are acting as financial advisors to Gilead in the transaction. Morgan Stanley & Co. LLC is acting as the financial advisor to Pharmasset. Skadden, Arps, Slate, Meagher & Flom LLP is serving as legal counsel to Gilead and Sullivan & Cromwell LLP is serving as legal counsel to Pharmasset.

Conference Call

Gilead will host a conference call today, Monday, November 21, 2011, at 8:00 a.m. Eastern Time, to discuss the proposed acquisition. To access the live call, please dial 1-800-599-9829 (U.S.) or 1-617-847-8703 (international). The conference passcode number is 61526607. Telephone replay is available approximately one hour after the call through 11:00 a.m. Eastern Time, November 24, 2011. To access, please call 1-888-286-8010 (U.S.) or 1-617-801-6888 (international). The conference passcode number for the replay is 39677531. The information provided on the teleconference is only accurate at the time of the conference call, and Gilead will take no responsibility for providing updated information.

About Pharmasset

Pharmasset is a clinical-stage pharmaceutical company committed to discovering, developing and commercializing novel drugs to treat viral infections. Pharmasset's primary focus is the development of oral therapeutics for the treatment of hepatitis C virus (HCV) infection. Pharmasset's research and development efforts are focused on nucleoside/tide analogs, a class of compounds which act as alternative substrates for the viral polymerase, thus inhibiting viral replication.

About Gilead Sciences

Gilead Sciences is a biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need. Gilead's mission is to advance the care of patients suffering from life-threatening diseases worldwide. Headquartered in Foster City, California, Gilead has operations in North America, Europe and Asia Pacific.

Forward-Looking Statement

This press release includes forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995, that are subject to risks, uncertainties and other factors. All statements other than statements of historical fact are statements that could be deemed forward-looking statements, including all statements regarding the intent, belief or current expectation of the companies' and members of their senior management team. Forward-looking statements include, without limitation, statements regarding business combination and similar transactions, prospective performance and opportunities and the outlook for the companies' businesses, including, without limitation, the ability of Gilead to advance Pharmasset's product pipeline or develop an all-oral antiviral regimen for HCV, performance and opportunities and regulatory approvals, the anticipated timing of data from clinical data; the possibility of unfavorable results of the companies' clinical trials; filings and approvals relating to the transaction; the expected timing of the completion of the transaction; the ability to complete the transaction considering the various closing conditions; and any assumptions underlying any of the foregoing. Investors are cautioned that any such forward-looking statements are not guarantees of future performance and involve risks and uncertainties and are cautioned not to place undue reliance on these forward-looking statements. Actual results may differ materially from those currently anticipated due to a number of risks and uncertainties. Risks and uncertainties that could cause the actual results to differ from expectations contemplated by forward-looking statements include: uncertainties as to the timing of the tender offer and merger; uncertainties as to how many of Pharmasset's stockholders will tender their stock in the offer; the possibility that competing offers will be made; the possibility that various closing conditions for the transaction may not be satisfied or waived, including that a governmental entity may prohibit, delay or refuse to grant approval for the consummation of the transaction; the effects of the transaction on relationships with employees, customers, other business partners or governmental entities; other business effects, including the effects of industry, economic or political conditions outside of the companies' control; transaction costs; actual or contingent liabilities; and other risks and uncertainties detailed from time to time in the companies' periodic reports filed with the Securities and Exchange Commission, including current reports on Form 8-K, quarterly reports on Form 10-Q and annual reports on Form 10-K. All forward-looking statements are based on information currently available to the companies, and the companies assume no obligation to update any such forward-looking statements.

Additional Information and Where to Find It

The tender offer described in this document has not yet commenced. This announcement is neither an offer to purchase nor a solicitation of an offer to sell shares of Pharmasset. At the time the offer is commenced, Gilead will file a Tender Offer Statement on Schedule TO with the U.S. Securities and Exchange Commission, and Pharmasset will file a Solicitation/Recommendation Statement on Schedule 14D-9 with respect to the offer. Pharmasset stockholders and other investors are urged to read the tender offer materials (including an Offer to Purchase, a related Letter of Transmittal and certain other offer documents) and the Solicitation/Recommendation Statement because they will contain important information which should be read carefully before any decision is made with respect to the tender offer. The Offer to Purchase, the related Letter

of Transmittal and certain other offer documents, as well as the Solicitation/Recommendation Statement, will be made available to all stockholders of Pharmasset at no expense to them. The Tender Offer Statement and the Solicitation/Recommendation Statement will be made available for free at the Commission's web site at www.sec.gov. Free copies of these materials and certain other offering documents will be made available by Gilead by mail to Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404, attention: Investor Relations.

In addition to the Offer to Purchase, the related Letter of Transmittal and certain other offer documents, as well as the Solicitation/Recommendation Statement, Gilead and Pharmasset file annual, quarterly and special reports, proxy statements and other information with the Securities and Exchange Commission. You may read and copy any reports, statements or other information filed by Gilead or Pharmasset at the SEC public reference room at 100 F Street, N.E., Washington, D.C. 20549. Please call the Commission at 1-800-SEC-0330 for further information on the public reference room. Gilead's and Pharmasset's filings with the Commission are also available to the public from commercial document-retrieval services and at the website maintained by the Commission at www.sec.gov.

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For more information on Gilead Sciences, please visit the company's website at www.gilead.com or call Gilead Public Affairs at 1-800-GILEAD-5 or 1-650-574-3000.

Exhibit 99.2

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Advancing Therapeutics.
Improving Lives.

Gilead to Acquire Pharmasset

November 21, 2011

Safe Harbor Disclaimer

Statements included in this presentation that are not historical in nature are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. Gilead cautions readers that forward-looking statements are subject to certain risks and uncertainties, which could cause actual results to differ materially. These risks and uncertainties include: Gilead’s ability to consummate the acquisition of Pharmasset and advance Pharmasset’s product pipeline as planned; Gilead’s ability to successfully develop its HCV franchise; Gilead’s ability to develop an all oral antiviral regimen for HCV; and Gilead’s ability to achieve its anticipated full year 2011 financial results. Gilead directs readers to its Quarterly Report on Form 10-Q for the third quarter ended September 30, 2011 and subsequent current reports on Form 8-K. Gilead claims the protection of the Safe Harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. All forward-looking statements are based on information currently available to Gilead, and Gilead assumes no obligation to update any such forward-looking statements.

This announcement is neither an offer to purchase nor a solicitation of an offer to sell shares of Pharmasset. At the time the offer is commenced, Gilead will file a Tender Offer Statement on Schedule TO with the U.S. Securities and Exchange Commission, and Pharmasset will file a Solicitation/Recommendation Statement on Schedule 14D-9 with respect to the offer. Pharmasset stockholders and other investors are urged to read the tender offer materials (including an Offer to Purchase, a related Letter of Transmittal and certain other offer documents) and the Solicitation/Recommendation Statement because they will contain important information which should be read carefully before any decision is made with respect to the tender offer. The Offer to Purchase, the related Letter of Transmittal and certain other offer documents, as well as the Solicitation/Recommendation Statement, will be made available to all stockholders of Pharmasset at no expense to them. The Tender Offer Statement and the Solicitation/Recommendation Statement will be made available for free at the Commission's web site at www.sec.gov.

Agenda

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Pharmasset Acquisition Highlights

Terms of the Agreement

GILEAD PHARMASSET

- Cash tender offer at $137 per share
- Transaction value of approximately $11 billion
- Tender offer expected to close within Q1 12
  - Subject to minimum tender requirement
  - Hart-Scott-Rodino (antitrust) clearance
  - Other customary conditions

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Strategic Rationale

- Accelerates Gilead's strategy to develop the first all-oral regimen for the treatment of HCV
  - PSI-7977 is the most potent, advanced nucleotide in clinical development
  - Phase 3 clinical studies of PSI-7977 in combination with ribavirin open to enrollment
  - Targeted U.S. FDA approval in 2014
- Since HCV can be cured, it will be important to be first to market with an all-oral, well-tolerated regimen
- Opportunity for significant revenue growth and diversification in 2014 and beyond
  - Composition of matter patent protection for PSI-7977 into 2029
- Pharmasset is a strategic fit with Gilead's areas of operational excellence

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Fit with Gilead's Areas of Operational Excellence

- Established expertise and commitment to liver disease
- Preclinical, clinical development and regulatory expertise
  - Developed and commercialized 5 HIV and 2 hepatitis products
  - Viread regulatory approvals in approximately 140 countries
  - Established team: Quad NDA filing in 6 weeks after last patient, last visit
- Expertise in process research and development, and established worldwide API and product manufacturing network
  - Developed 1 fixed-dose combination and 3 single-tablet regimens in HIV
  - Manufacture tenofovir DF at >110 metric tons per year
- Established commercial operations in 23 countries worldwide, with expanding presence in Asia

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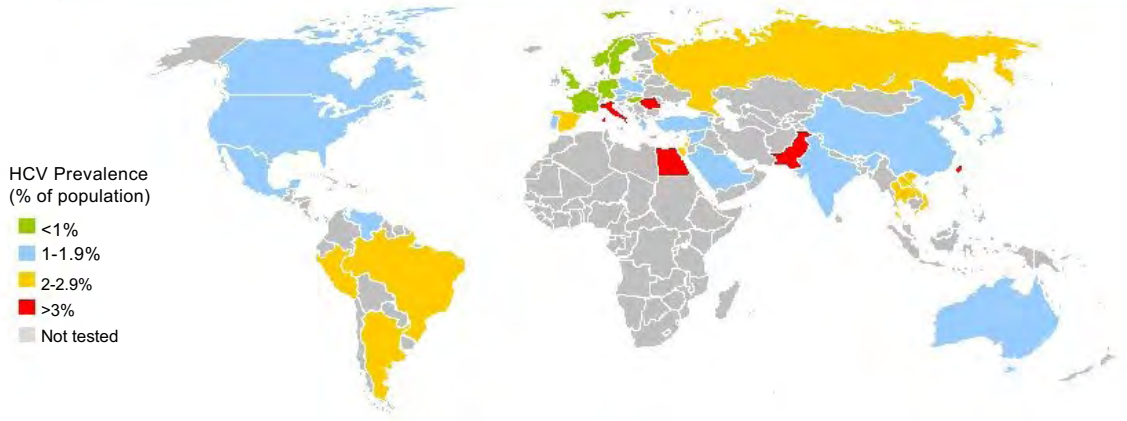
HCV Landscape

Global Prevalence of HCV is Estimated to be 160 Million Individuals (1)



HCV Prevalence in Core and Emerging Markets (M)

Region	US[2]	EU-Core 5[2]	Japan[2]	Europe Other[3]	Asia[3]	Latin America[3]
All GT	**2.9**	**3.7**	**0.6**	**6.7**	**70.8**	**5.4**
GT1 (%)	**73%**	**63%**	**70%**	**65%**	**39%**	**68%**

Sources: 1) Lavanchy, et al. 2011. 2) Gilead Forecast (2011 prevalence estimate). 3) Cornberg, Sievert, and Kershenobich, *et al* 2011. Country populations from 2009 World Bank estimates

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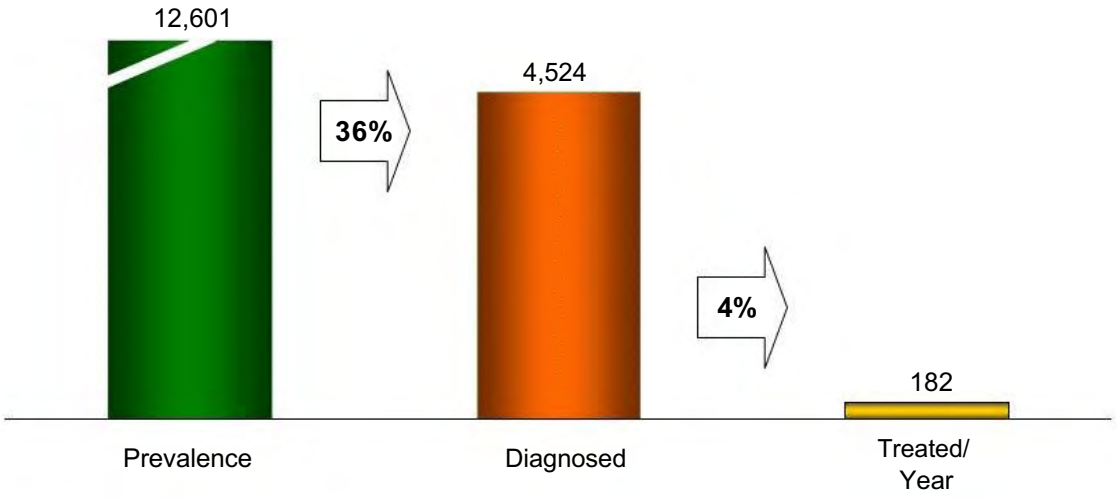
HCV: A Significant Unmet Medical Need

Over 12 Million Infected Individuals in Major Markets (1) with Fewer than 200,000 Treated per Year

Patients in thousands



1. Major markets include US, EU-5, Japan, Australia, Austria, Brazil, Denmark, Finland, Greece, Ireland, Norway, Poland, Portugal, Sweden, Switzerland, Turkey, Canada

Sources:

Prevalence – KantarHealth Core-5 EU epidemiology analysis (2010), NHANES (1999-2006), Armstrong (2004), Hepatology, 40(4:S1):176a, Chak (2011), Liver Intl., 8, 1090-1101, Cornberg (2011), Liver Intl., 31 (s2), 31-60, Kershenobich (2011), Liver Intl., 31 (s2), 18-29

Diagnosed – KantarHealth Core-5 EU epidemiology analysis (2010), Armstrong (2004) Hepatology, 40(4:S1):176a, Culver (2000), Transfusion 40:1176

Treated – IMS MIDAS (2004 – 2009), Synovate chart audits (2007), Roche and Schering Plough annual reports (2009)

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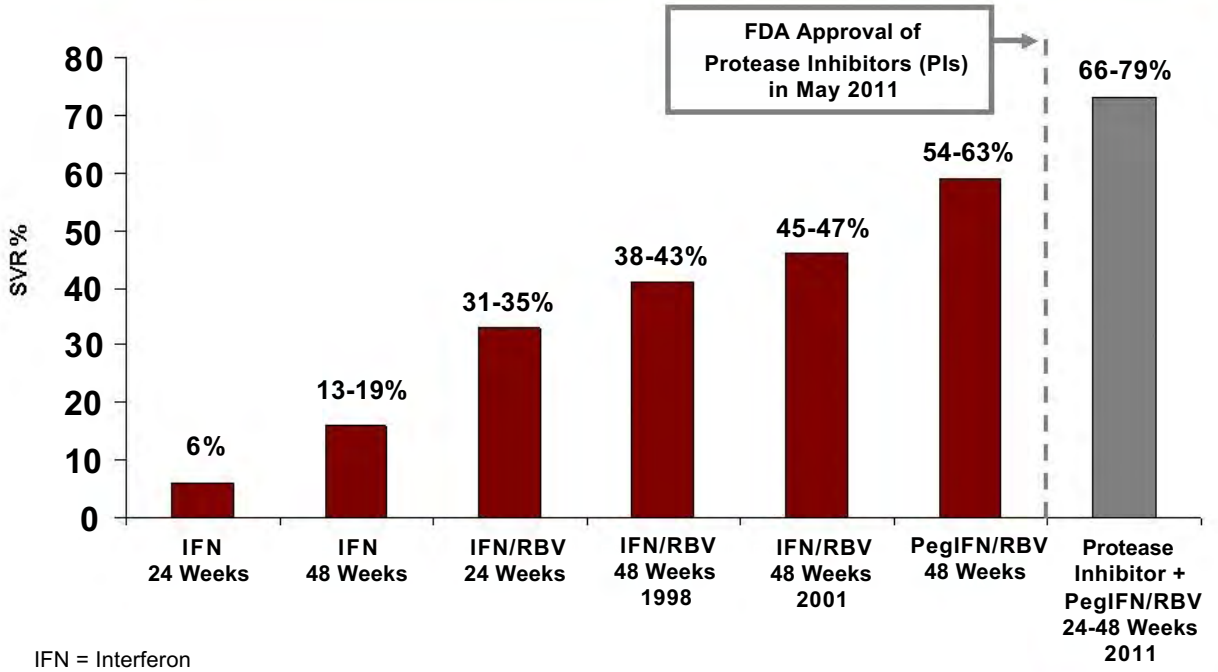
HCV Treatment Evolution



IFN = Interferon

RBV = Ribavirin

PegIFN = Pegylated Interferon

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Slide 11

Challenges of Current PI-based Treatment Remains

- Additional safety issues and exacerbation of side effects (rash and anemia)
  - Discontinuation rates significantly increased on PIs
- Lower response rates in sub-populations (previous IFN/RBV non-responders, cirrhotics)
- Burdensome for patients and practitioners
  - PIs dosed 2-3 times per day, plus ribavirin and a self-administered injection
  - Time intensive adverse event management, complexity of response guided therapy

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Ultimate Goal in HCV Therapy

- Once a day
- Pan-genotype
- No clinical resistance
- No response guided therapy
- Short duration
- Safe with manageable side effects
- High cure rates
- Suitable for all populations

- Easier for doctors and patients
- Leads to increased diagnosis and treatment
- Potential to cure many more patients
- Lowers cost to healthcare system due to prevention of end-stage liver disease

Ideal HCV Therapy Most Likely Achieved through a Combination of Two or More Drugs

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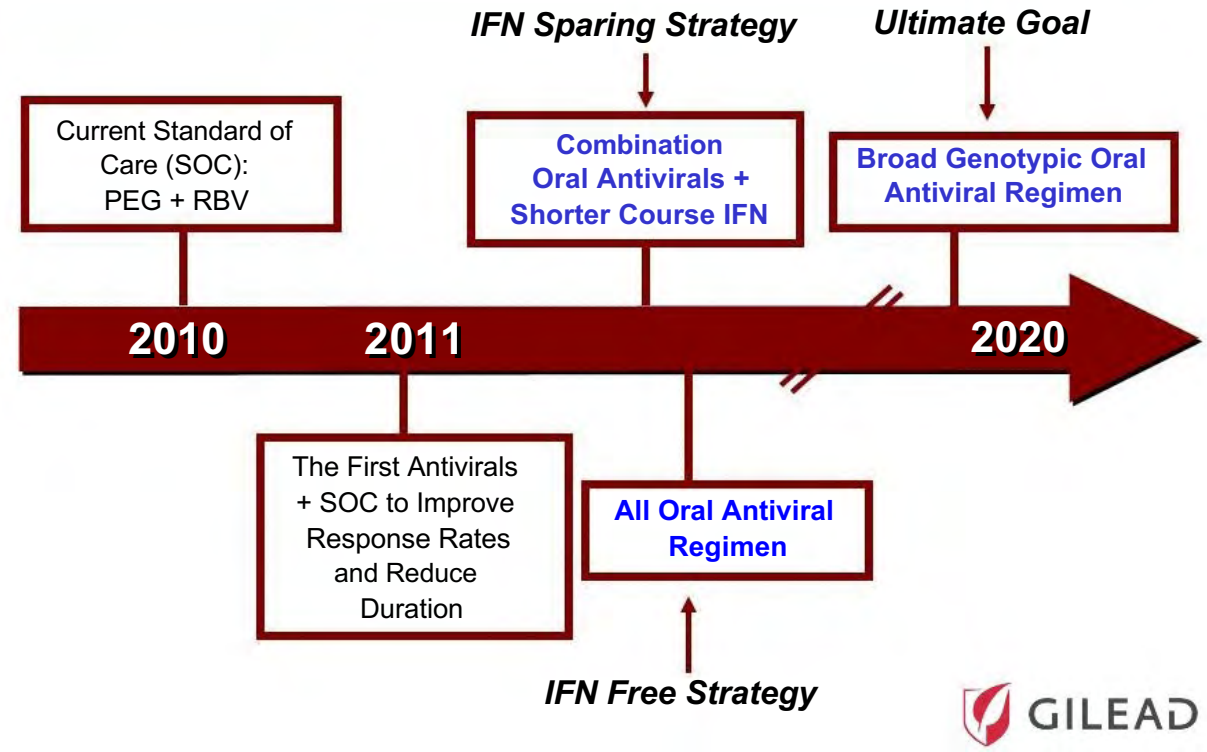
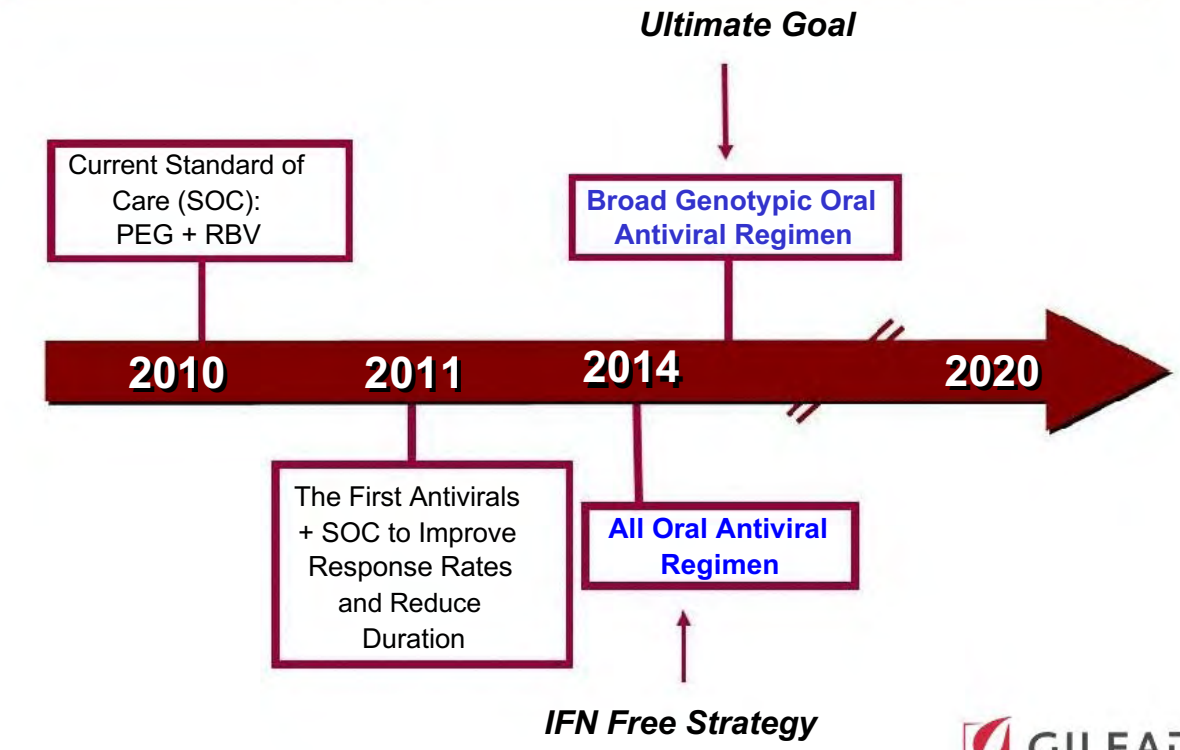
The Evolution of HCV Therapy: 2010



Slide 14

The Competitive Nature and Speed of Development Have Significantly Accelerated the Timelines



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Overview of Pharmasset HCV Portfolio

Pharmasset's HCV Nucleotide Portfolio

PSI-7977

- 3.6 log HCV RNA↓ with 400 mg QD over 3 days
- Phase 3 in combination with ribavirin open to enrollment
- Highest on treatment and SVR rates to date
- Unpartnered with worldwide rights

PSI-938

- 3.6 log HCV RNA↓ with 300 mg QD over 3 days
- Phase 2
- 14 day data, with ongoing 12 week studies
- Unpartnered with worldwide rights

RG 7128

- 0.6 log HCV RNA↓ with 1gm BID
- Phase 2b
- Partnered with Roche

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PSI-7977: Pharmasset's Lead Pyrimidine Nucleotide Analogue

- **Excellent safety profile**
  - 250 patients at 8 weeks or more
  - 1,500 patients by May 2014
- **High rates of cure in genotype 2/3**
  - 100% (10/10) with ribavirin
  - 60% (6/10) without ribavirin
- **Studies in genotype 1 ongoing**
  - Expecting Phase 2 SVR12 data early 2012
- **Multiple expanding data sets from studies in different patient populations**

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PSI-7977: Genotype 2/3 Phase 2 Results

(ELECTRON)

Time (Weeks)	PSI-7977 RBV 12 weeks PEG	PSI-7977 RBV NO PEG	PSI-7977 NO PEG NO RBV
	n/n (%) < LOD	n/n (%) < LOD	n/n (%) < LOD
2	8/11 (82%)	8/10 (80%)	**8/10 (80%)**
4	11/11 (100%)	10/10 (100%)	**10/10 (100%)**
12	11/11 (100%)	10/10 (100%)	**10/10 (100%)**
SVR4	11/11 (100%)	10/10 (100%)	**6/10 (60%)**
SVR12	11/11 (100%)	10/10 (100%)	**n/a**

n/a – not yet available

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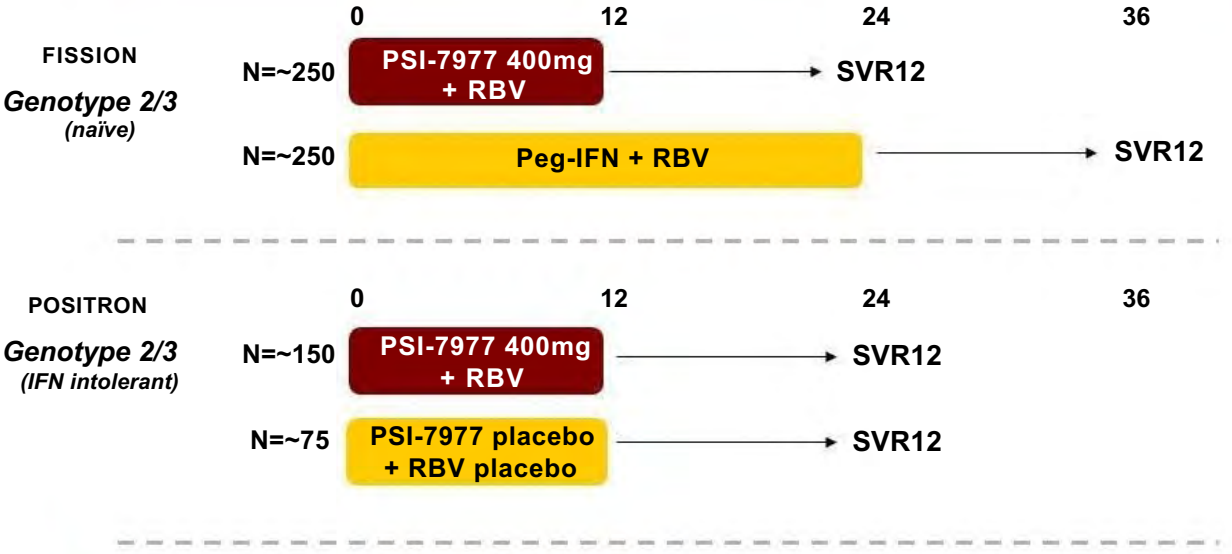
Pharmasset's Phase 3 Program
(Announced November 1, 2011)



- A third Phase 3 study to be initiated in genotype 1 patients in 1H 12
- Targeted U.S. FDA approval in 2014

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Key Remaining Questions in the Treatment of HCV

- Will one regimen work for all genotypes or will different regimens be required for different genotypes?
- How many molecules or mechanisms do you need?
- Can ribavirin be replaced?
- What is the minimum duration of therapy?
- Can HCV be cured with once-daily therapy?

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Gilead's Combined HCV Opportunity

Pharmasset and Gilead Combined HCV Efforts Position Us to Answer These Questions

- High barrier to resistance/pan-genotypic compounds will be an important component for any all-oral regimen
  - Pharmasset's PSI-7977 is the most advanced, pan-genotypic compound with a high barrier to resistance
  - Ongoing efforts at Gilead to identify other pan-genotypic compounds
- Complementary portfolio accelerates potential for oral regimens
  - Includesdirect acting antiviralswith four different mechanismsin Phase 2/3 clinical development
  - Potential to pursue different combinations to then answer the question of duration of treatment and necessity of ribavirin
- Complementary portfolios cover a number of opportunities for once-daily regimens
  - Potential for co-formulation

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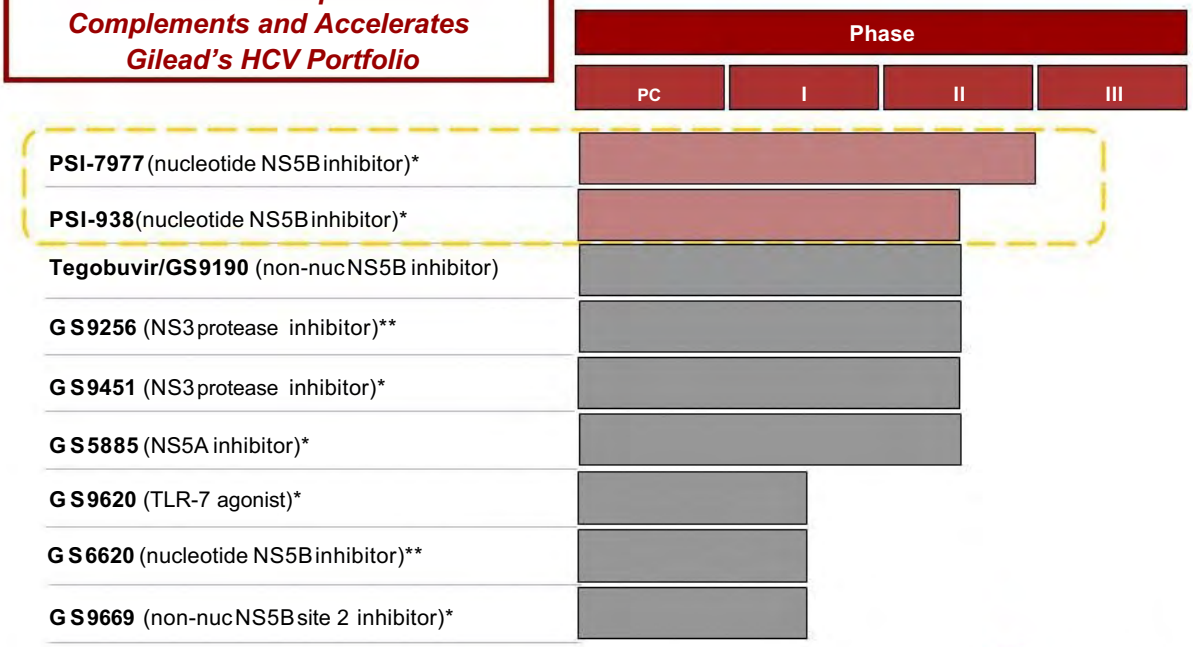
Combined HCV Clinical Portfolio

Pharmasset Acquisition Complements and Accelerates Gilead's HCV Portfolio



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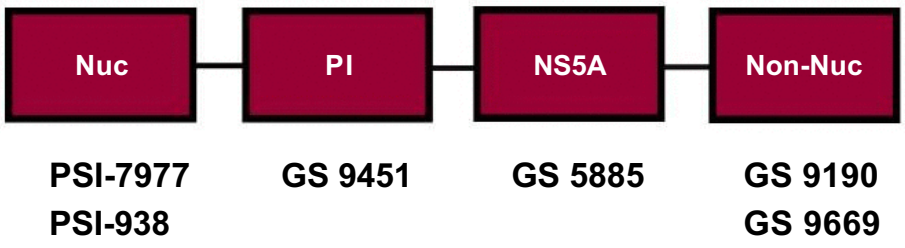
* Once-daily dosing
**No further clinical trials planned

All-Gilead Portfolio Increases the Chance of Developing Oral Therapies across Genotypes



Nuc	PI	NS5A	Non-Nuc
PSI-7977 PSI-938	GS 9451	GS 5885	GS 9190 GS 9669

Combination Therapies with High Potency May Further Shorten Duration and Eliminate Ribavirin

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2012 Key HCV Milestones

- Initiate and integrate Pharmasset's Phase 3 programs
  - GT 2/3 programs: no change
  - GT 1: Phase 2 data will determine strategy
- Initiate clinical trial with PSI-7977 to define minimum treatment duration in GT 2/3 patients
- Initiate multiple enabling drug-drug interaction studies with Gilead and Pharmasset assets
- Explore combinations that exclude ribavirin
- Initiate programs in pre-transplant and HIV co-infected populations
- SVR data from Gilead's all-oral Phase 2 Study 120 at EASL

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In Summary

- Accelerates Gilead's strategy to develop the first all-oral regimen for the treatment of HCV
- Since HCV can be cured, it will be important to be first to market with an all-oral, well-tolerated regimen
- Pharmasset is a strategic fit with Gilead's areas of operational excellence
- Opportunity to change revenue trajectory starting in 2014

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Gilead's Business Prospects

- Strong confidence in our core business
  - LTM HIV revenues of ~$6.4B in a total ~$13.0B market
  - LTM ~$1B in revenues coming from products outside HIV
- Anticipate major HIV product launches in 2012
  - New revenue sources through partnerships to follow
- More Phase 2/3 programs across therapeutic areas than ever before
  - HIV, liver disease, oncology/inflammation/fibrosis, respiratory and cardiovascular

Note: LTM = last twelve months

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Financial Impact of Pharmasset Acquisition

- Cash flows from core business will allow us to finance transaction
- Expect to use existing cash and $6.2 billion in incremental debt
- Committed to retaining investment grade credit rating
  - Debt/EBITDA ratio to return to ≤ 1.5x at closing + 1 year
- Transaction expected to be dilutive initially and significantly accretive beyond 2015
  - Increased interest expense associated with transaction debt
  - Share repurchases to offset dilution as debt is repaid

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Transaction Summary

- Unique opportunity to dramatically change HCV disease burden worldwide
- Potential to extend leadership in liver disease to HCV
- Opportunity to parallel the commercial success in HIV
- Redefined potential for revenue growth in 2014 and beyond

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Advancing Therapeutics.
Improving Lives.

Gilead to Acquire Pharmasset

November 21, 2011

Exhibit F

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant *(for all designated States except US)*: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

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(74) Agents: **MALEN, Peter L.** et al.; Viksnins Harris & Padys PLLP, 7900 International Drive, Suite 670, Bloomington, Minnesota 55123 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2013/040492 A2

(54) **Title**: METHODS FOR TREATING HCV

(57) **Abstract**: This invention relates to combinations of therapeutic molecules useful for treating hepatitis C virus infection. The present invention relates to methods, uses, dosing regimens, and compositions.

METHODS FOR TREATING HCV

PRIORITY OF INVENTION

This application claims priority to United States Provisional Application Number 61/535,885, filed 16 September 2011; and to United States Provisional Application Number 61/561,753, filed 18 November 2011. The entire content of each of these provisional applications is hereby incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to combinations of therapeutic molecules useful for treating hepatitis C virus infection. The present invention relates to methods, uses, dosing regimens, and compositions.

BACKGROUND OF THE INVENTION

Hepatitis is a disease occurring throughout the world. Hepatitis is generally of viral nature, although, if considered a state of chronic inflammation of the liver, there are other known, non-infectious causes. Viral hepatitis is by far the most common form of hepatitis. The U.S. Centers for Disease Control has estimated that at least 1.8% of the U.S. population has serologic evidence of HCV infection, in the majority of cases associated with chronic active infection. HCV is a positive-stranded RNA virus belonging to the Flaviviridae family and has closest relationship to the pestiviruses that include hog cholera virus and bovine viral diarrhea virus.

The HCV genome is a single-stranded, positive-sense RNA of about 9,600 bp coding for a polyprotein of 3009-3030 amino acids, which is cleaved co- and post-translationally by cellular and two viral proteinases into mature viral proteins (core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). The structural proteins, E1 and E2, are believed to be embedded into a viral lipid envelope and form stable heterodimers. The structural core protein is believed to interact with the viral RNA genome to form the nucleocapsid. The nonstructural proteins designated NS2 to NS5 include proteins with enzymatic functions involved in virus replication and protein processing including a polymerase, protease, and helicase. HCV replicates through the production of a complementary negative-strand RNA template.

HCV is a genetically diverse virus. Within a single infected patient, many variant viruses can be identified, leading to the description 'viral swarm', or viral quasispecies. Within the global human population, HCV is also genetically diverse, with at least 6 major 'genotypes' identified (Genotypes 1-6), and numerous subtypes (i.e., HCV Genotype 1a and 1b). HCV genotypes are defined by genomic phylogenetic analysis, and diagnosed (in a given patient) by HCV RNA sequence-based diagnostic assays.

The main route of infection with HCV is blood exposure. The magnitude of the HCV infection as a health problem is illustrated by the prevalence among high-risk groups. For example, in some surveys, 60% to 90% of hemophiliacs and more than 80% of intravenous

drug abusers in western countries had chronic HCV infection. For intravenous drug abusers, the prevalence varies from about 28% to 80% depending on the population studied. The proportion of new HCV infections associated with blood or blood product transfusion has been markedly reduced due to pharmaceutical advances and widespread use of sensitive serologic and RNA detection assays used to screen blood donors, however, a large cohort of aging, chronically infected persons is already established.

One available treatment for HCV infection is pegylated interferon-α (PEG-IFN α1a or PEG-IFN α1b), which is, under current treatment guidelines, administered weekly by subcutaneous injection for 24 to 48 weeks, dependent upon the HCV viral genotype being treated. Although greater than 50% of patients with Genotype 1 HCV infection may be expected to have suppression of HCV viremia at the completion of 48 weeks therapy, a significant proportion of these patients will have viral relapse. Accordingly, a Sustained Virologic Response (SVR, defined as HCV RNA negativity 24 weeks post treatment cessation, and considered tantamount to 'cure') is only achieved in 30-40% of Genotype 1 HCV infections treated with PEG-IFN alone. In addition, treatment with PEG-IFN + RBV is not well tolerated, with an adverse event profile that includes flu-like symptoms, thrombocytopenia, anemia, and serious psychiatric side effects. While treatment with the current standard of care is suboptimal, many patients are precluded from ever starting therapy due to comorbidities common in HCV-infected populations, including psychiatric disorders, advanced liver disease, and substance abuse.

Ribavirin is a nucleoside analog antiviral drug. Ribavirin is typically taken orally (by mouth) twice a day. The exact mechanism for ribavirin is unknown. However, it is believed that when ribavirin enters a cell it is phosphorylated; it then acts as an inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH). IMPDH inhibitors such as ribavirin reduce the intracellular synthesis and storage of guanine, a nucleotide "building block" necessary for DNA and RNA production, thus inhibiting viral replication. IMPDH inhibitors also interfere with the reproduction of rapidly proliferating cells and cells with a high rate of protein turnover. Treatment with ribavirin monotherapy has little effect on HCV RNA levels, but is associated with a decline in serum alanine transferase (ALT). This observation suggests that ribavirin may not be acting as an antiviral agent, but rather as a modulator of immune system function. Ribavirin is only approved for use, for HCV infection, in combination with IFN.

Treatment with the combination of PEG-IFN plus ribavirin improves SVR rates over those observed with PEG-IFN alone, in large part due to reduction in the frequency of viral relapse at the cessation of therapy. Large clinical trial SVR rates for PEG-IFN/ribavirin treated patients with HCV Genotype 1 infection have ranged from 40-55%. At the present time, PEG-IFN/ribavirin therapy is considered the 'standard-of-care' treatment for chronic HCV infection. The standard of care is, however, expected to change rapidly in the near future with approval of direct acting antiviral agents which will, initially, be used in combination with PEG-IFN/ribavirin.

Unfortunately, different genotypes of HCV respond differently to PEG-IFN/ribavirin therapy; for example, HCV genotype 1 is more resistant to therapy than types 2 and 3. Additionally, many current treatments for HCV produce unwanted side effects. Thus, there is currently a need for new anti-viral therapies. In particular there is a need for new antiviral therapies that produce fewer unwanted side-effects, that are more effective against a range of HCV genotypes, or that have less complicated dosing schedules, i.e. that require administration of agents fewer times during a day.

SUMMARY OF THE INVENTION

The present invention provides compositions and therapeutic methods that are useful for treating viral infections (e.g. HCV). Certain compositions and methods of the invention produce fewer unwanted side-effects, are more effective against a range of HCV genotypes, reduce the potential for viral rebound due to resistance selection and have shortened less complicated dosing schedules than currently available therapies.

Accordingly, in one embodiment the invention provides a composition comprising two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof.

In another embodiment the invention provides a method of treating an HCV infection in a human, comprising administering two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof to the human.

In another embodiment the invention provides a method for ameliorating one or more symptoms of an HCV infection in a human, comprising administering two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof to the human.

In another embodiment the invention provides a method for reducing viral load in a human with HCV, comprising administering two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof to the human.

In another embodiment the invention provides a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents in a human, comprising administering two or more compounds selected from Compound 1, Compound 2,

Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof to the human.

In another embodiment the invention provides the use of two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof in medical therapy.

In another embodiment the invention provides the use of two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof for the prophylactic or therapeutic treatment of a viral (e.g. HCV) infection.

In another embodiment the invention provides the use of a composition of the invention for the prophylactic or therapeutic treatment of a viral (e.g. HCV) infection.

In another embodiment the invention provides the use of two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof to prepare a medicament for treating a viral (e.g. HCV) infection in a human.

In another embodiment the invention provides the use of a composition of the invention to prepare a medicament for treating a viral (e.g. HCV) infection in a human.

In another embodiment the invention provides the use of two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof to prepare a medicament for ameliorating one or more symptoms of a viral (e.g. HCV) infection in a human.

In another embodiment the invention provides the use of a composition of the invention to prepare a medicament for ameliorating one or more symptoms of a viral (HCV) infection in a human.

In another embodiment the invention provides the use of two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof to prepare a medicament for reducing viral load in a human.

In another embodiment the invention provides the use of a composition of the invention to prepare a medicament for reducing viral load in a human.

In another embodiment the invention provides the use of two or more compounds selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and pharmaceutically acceptable salts thereof to prepare a medicament for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents in a human.

In another embodiment the invention provides the use of a composition of the invention to prepare a medicament for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents in a human.

The compositions and methods of the invention may provide "synergy" and "synergistic effects", i.e. the effect achieved when the active ingredients (including two or more Combination Compounds) are used together is greater than the sum of the effects that results from using the compounds separately.

The compositions and methods of the invention are beneficial because they provide treatments for a wide range of HCV genotypes and because they cause fewer or less serious side effects than current HCV therapies (e.g. treatments that include the administration of interferon). Additionally, certain combinations of compounds (e.g. Compounds 10 and 5, Compounds 10 and 6, and Compounds 10, 5, and 6) may provide a Sustained Virological Response (SVR) that is a significantly higher than that achieved by current therapies (e.g. HCV therapies). For example, some combinations of compounds may provide an SVR that is at least about 70% or at least about 80%.

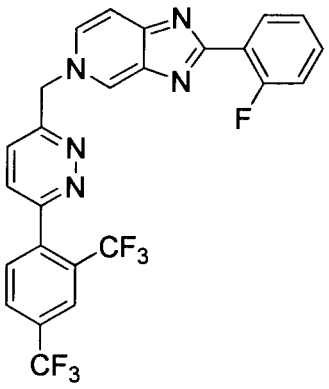
DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings. The fact that a particular term or phrase is not specifically defined should not be correlated to indefiniteness or lacking clarity, but rather terms herein are used within their ordinary meaning. When trade names are used herein, applicants intend to independently include the trade name product and the active pharmaceutical ingredient(s) of the trade name product.

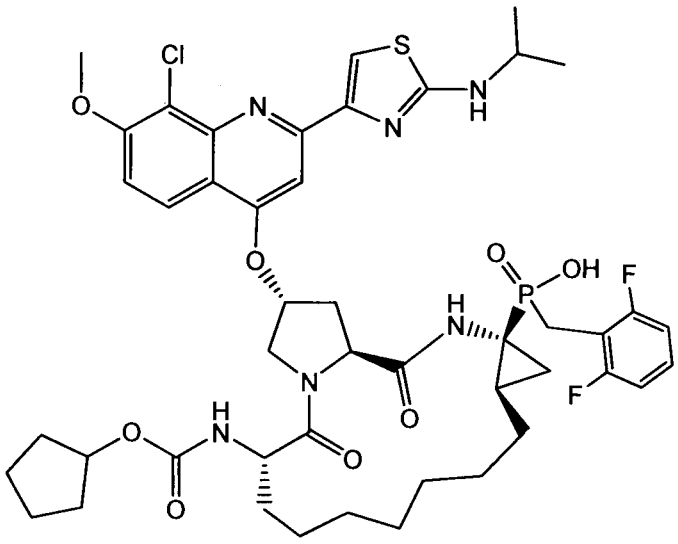
As used herein the term “Combination Compounds” refers to Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

As used herein, Compound 1 is:



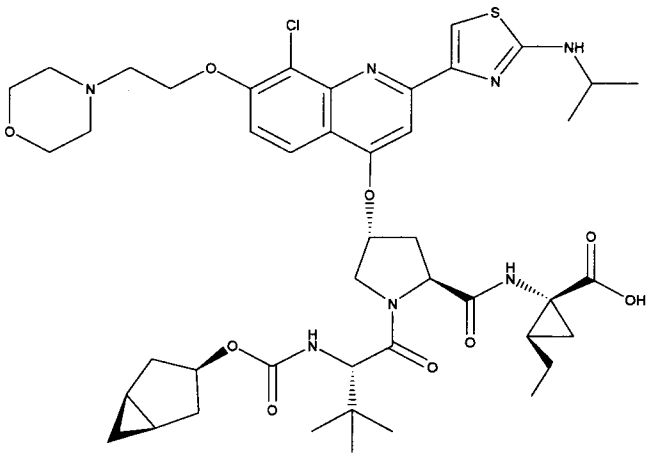
Compound 1 may also be referred to as 5-((6-(2,4-bis(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)-2-(2-fluorophenyl)-5*H*-imidazo[4,5-*c*]pyridine or 5H-imidazo[4,5-c]pyridine, 5-[[6-[2,4-bis(trifluoromethyl)phenyl]pyridazin-3-yl]methyl]-2-(2-fluorophenyl).

As used herein, Compound 2 is:

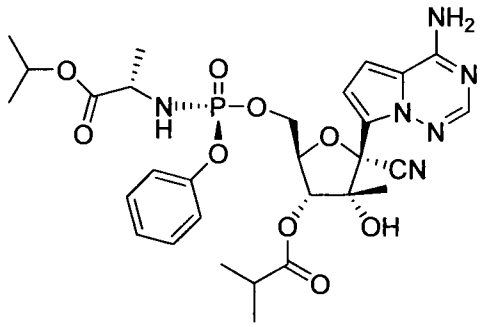


Compound 2 may also be referred to as (2*R*,6*S*,13a*R*,14a*S*,16a*S*)-2-(8-chloro-2-(2-(isopropylamino)thiazol-4-yl)-7-methoxyquinolin-4-yloxy)-6-(cyclopentyloxycarbonylamino)-5,16-dioxooctadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin-14a-yl(2,6-difluorobenzyl)phosphinic acid.

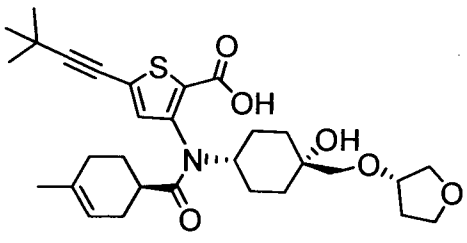
As used herein, Compound 3 is:



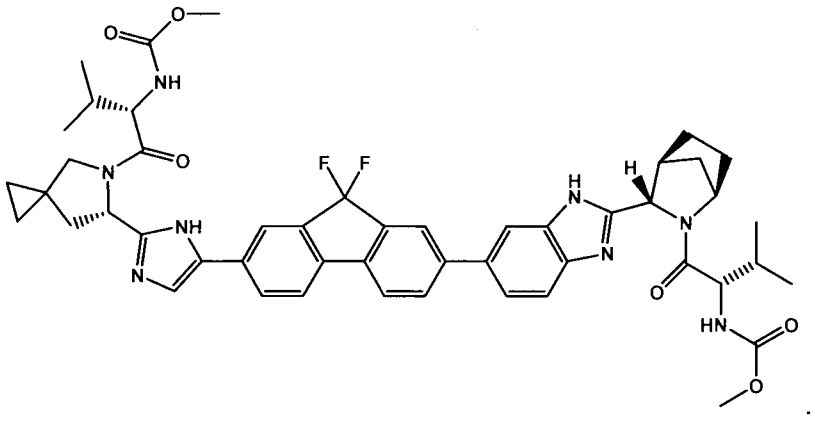
As used herein, Compound 4 is:



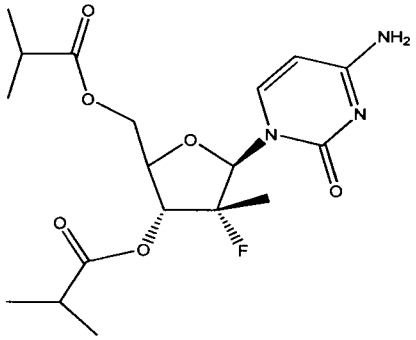
As used herein, Compound 5 is:



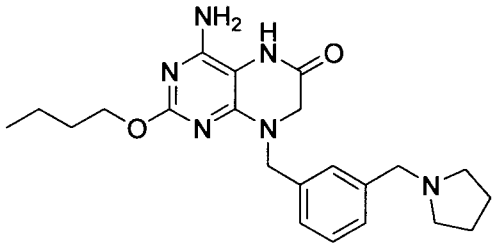
As used herein, Compound 6 is:



As used herein, Compound 7 is:

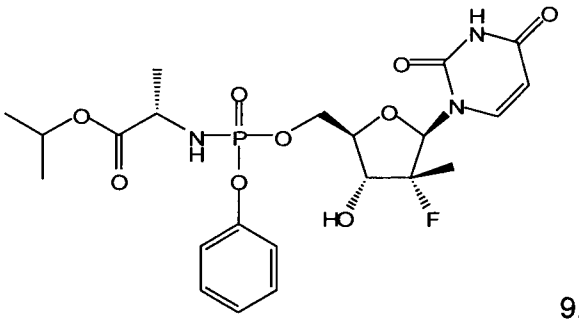


As used herein, Compound 8 is:



8.

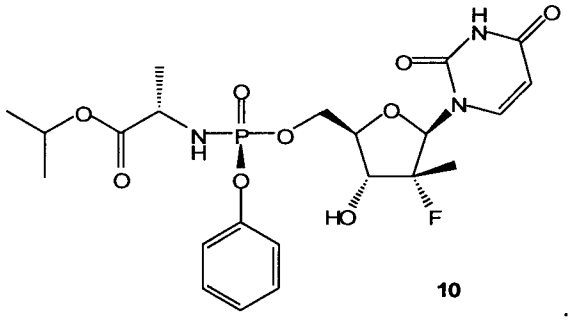
As used herein Compound 9 (diastereomer at P) is:



9.

With regard to Compound 9, reference is made to US 7,964,580 and US 2010/0298257, (both of which are incorporated by reference) with regard to manufacture and purification of Compound 9.

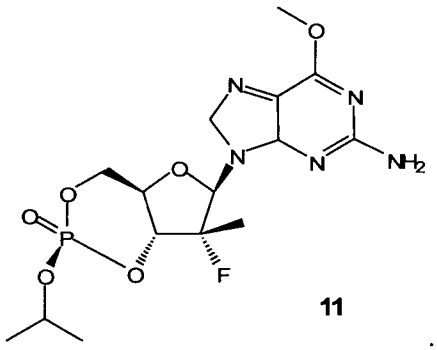
As used herein, Compound 10 (S-isomer of Compound 9) is:



10

With regard to Compound 10, reference is made to US 7,964,580 and US 2010/0298257, (both of which are incorporated by reference) with regard to manufacture and purification of Compound 10.

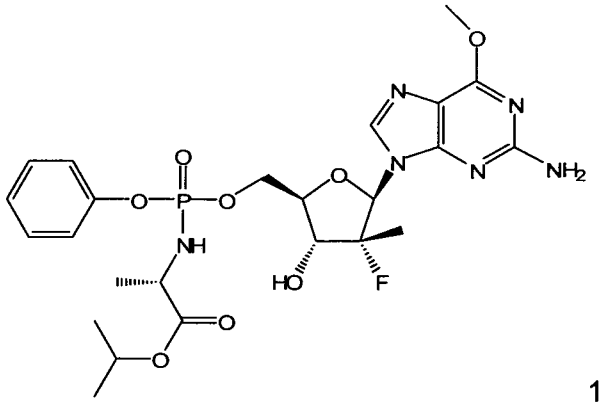
As used herein, Compound 11 is:



11

With regard to Compound 11, reference is made to US 2010/0081628 (which is hereby incorporated by reference) with regard to manufacture and purification of Compound 11.

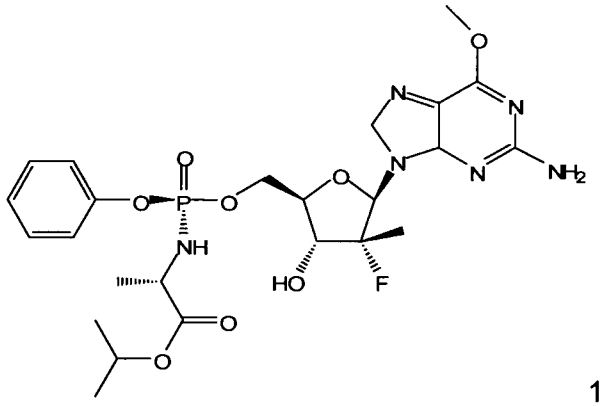
As used herein, Compound 12 (diastereomer at P) is:



12.

With regard to Compound 12, reference is made to US 20110015146 (which is hereby incorporated by reference) with regard to manufacture and purification of Compound 12.

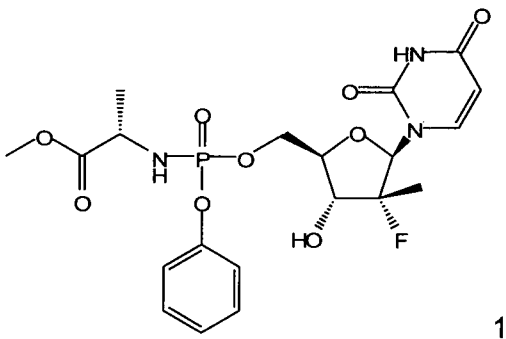
As used herein, Compound 13 (S-diastereomer of Compound 12 at P) is:



13.

With regard to Compound 13, reference is made to US 20110015146 (which is hereby incorporated by reference) with regard to manufacture and purification of Compound 13.

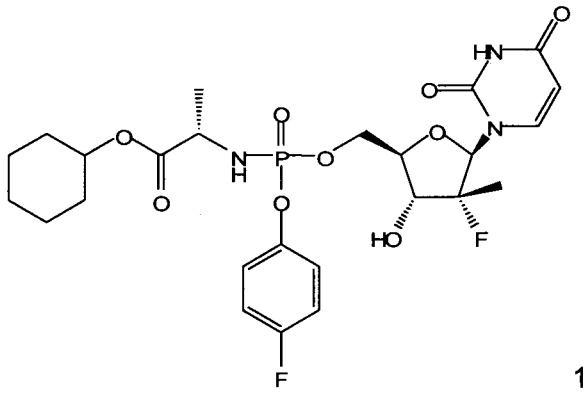
As used herein, Compound 14 is:



14.

With regard to Compound 14, reference is made to US 7,964,580 (which is hereby incorporated by reference) with regard to manufacture and purification of Compound 14.

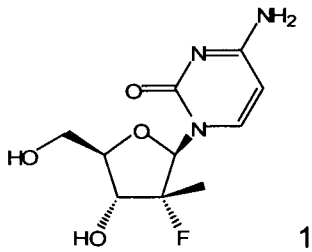
As used herein, Compound 15 is:



15.

With regard to Compound 15, reference is made to US 7,964,580 (which is hereby incorporated by reference) with regard to manufacture and purification of Compound 15.

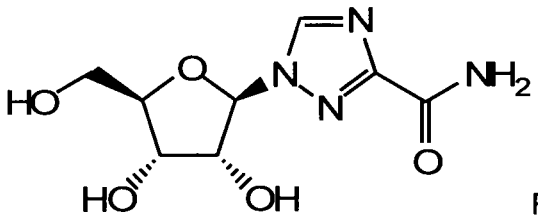
As used herein, Compound 16 is:



16.

With regard to Compound 16, reference is made to US 7,429,572 (which is hereby incorporated by reference) with regard to manufacture and purification of Compound 16.

With regard to ribavirin, reference is made to EP 0 093 401 B1, herein incorporated by reference with regard to a process for manufacture as well as to nomenclature concerning ribavirin. As used herein, ribavirin refers to:



Ribavirin.

Ribavirin is also referred to as 1-β-D-ribofuranosyl-1H-1,2,4-Triazole-3-carboxamide, 1-β-D-ribofuranosyl-1,2,4-triazol-3-carboxyamide; 1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide; COPEGUS (Roche); DRG-0028; HSDB 6513; ICN 1229; MegaRibavirin (e.g. in formulations of 100 mg of ribavirin/mL); NSC 163039; RAVANEX (BioPartners); REBETOL (Schering-Plough; Aesca; Bayer Schering Pharma; Essex; Pfizer; Trading Pharma; Zuellig Pharma); Ribamide; RIBAMIDIL (Biopharma, Russia); RIBASPHERE (Three Rivers Pharmaceuticals); Ribavarin; Ribavirina; Tribavirin; VILONA (Valeant Pharmaceuticals; ICN

Pharmaceuticals); VIRAMID (ICN Pharmaceuticals ; Alfa Wassermann); VIRAZOLE (Valeant Pharmaceuticals); and VIRIZADOLE (Uci-farma, Sao Bernardo do Campo, Sao Paulo, Brazil). In addition, as used herein ribavirin includes analogs of ribavirin, including taribavirin (VIRAMIDINE, ICN 3142).

The term "interferon" includes 1) interferons, *e.g.*, pegylated rIFN-alpha 2b (PEG-Intron, Merck & Co., Inc.), pegylated rIFN-alpha 2a (PEGASYS, Hoffmann-La Roche Inc.), rIFN-alpha 2b (INTRON® A, Merck & Co., Inc.), rIFN-alpha 2a (Roferon®-A, Hoffmann-La Roche Inc.), interferon alpha (MULTIFERON® Viranative AB Corporation, OPC-18, Alfaferone, Alfanative, subalin), interferon alfacon-1 (Valeant), interferon alpha-n1 (Wellferon™, Glaxo Wellcome), interferon alpha-n3 (ALFERON®-Hemispherx Biopharma, Inc.), interferon-beta-1a (AVONEX® Biogen Idec, DL-8234 Daiichi Pharmaceutical Co. Ltd), interferon-omega (omega DUROS®, Alza Corporation, Intarcia Therapeutics, Inc.; Biomed 510, Intarcia Therapeutics, Inc.), albinterferon alpha-2b (ALBUFERON®, Human Genome Sciences, INC.), IFN alpha-2b XL, BLX-883 (LOCTERON®, Biolex Therapeutics, INC.), DA-3021, glycosylated interferon alpha-2b (AVI-005), PEG-INFERGEN®, Amgen, Inc., Pegylated interferon lambda-1(type III) (PEGylated IL-29), and BELEROFON®, Nautilus Biotech.

The term "combination therapy" means compositions or methods or uses or the like that incorporate two or more of the Combination Compounds. Combination therapy may also incorporate other active ingredients in addition to the two or more of the Combination Compounds including, but not limited to: ribavirin, an interferon, an alpha-glucosidase 1 inhibitor, a hepatoprotectant, a Toll-like receptor (TLR)-7 agonist, a cyclophilin inhibitor, an HCV viral entry inhibitor, an HCV maturation inhibitor, and an HCV IRES inhibitor.

The term "active ingredient" means a component of a combination therapy that a exerts or is capable of exerting a pharmaceutical effect including any of the Combination Compounds, ribavirin, an interferon, an alpha-glucosidase 1 inhibitor, a hepatoprotectant, a TLR-7 agonist, a cyclophilin inhibitor, an HCV viral entry inhibitor, an HCV maturation inhibitor, and an HCV IRES inhibitor.

The term "treating" and grammatical equivalents thereof, when used in the context of treating a disease, means slowing or stopping the progression of a disease, or ameliorating at least one symptom of a disease, more preferably ameliorating more than one symptom of a disease. For example, an HCV patient may experience an improvement in one or all of the following symptoms that can be associated with HCV infection: increase in alanine aminotransferase (ALT) levels, fever, headache, muscle aches, jaundice, fatigue, loss of appetite, nausea, vomiting and diarrhea. Treatment of a hepatitis C virus infection can include reducing the HCV viral load in an HCV infected human being.

Certain of the compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or

enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by the formulae shown herein, as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes the individual isomers of the compounds represented by the formula shown herein as mixtures with isomers thereof in which one or more chiral centers are inverted. Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York, herein incorporated by reference in its entirety.

Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory.

A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Combinations

The present invention encompasses combinations of two or more of the Combination Compounds. Table I showing possible two-way (Combinations 1-21), three-way (Combinations 22-56), four-way (Combinations 57-92) and five-way (Combinations 93-113) combinations of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 of the invention is provided below. Compound 4, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 are nucleoside inhibitors of HCV NS5b polymerase and combinations of Combination Compounds will most often include only one of Compound 4, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 (See Column 6 of Table I).

TABLE I

		Compound 1	Compound 2	Compound 3	Compound 4 Or Compound 9 Or Compound 10 Or Compound 11 Or Compound 12 Or Compound 13 Or Compound 14 Or Compound 15 Or Compound 16	Compound 5	Compound 6	Compound 7
Combination	1	X	X					
Combination	2	X		X				
Combination	3	X			X			
Combination	4	X				X		
Combination	5	X					X	
Combination	6	X						X
Combination	7		X	X				
Combination	8		X		X			
Combination	9		X			X		
Combination	10		X				X	
Combination	11		X					X
Combination	12			X	X			
Combination	13			X		X		
Combination	14			X			X	
Combination	15			X				X
Combination	16				X	X		
Combination	17				X		X	
Combination	18				X			X
Combination	19					X	X	
Combination	20					X		X
Combination	21						X	X
Combination	22	X	X	X				
Combination	23	X	X		X			
Combination	24	X	X			X		
Combination	25	X	X				X	
Combination	26	X	X					X
Combination	27	X		X	X			
Combination	28	X		X		X		
Combination	29	X		X			X	
Combination	30	X		X				X
Combination	31	X			X	X		
Combination	32	X			X		X	
Combination	33	X			X			X
Combination	34	X				X	X	
Combination	35	X				X		X
Combination	36	X					X	X
Combination	37		X	X	X			
Combination	38		X	X		X		
Combination	39		X	X			X	
Combination	40		X	X				X
Combination	41		X		X	X		

Combination	42		X		X		X	
Combination	43		X		X			X
Combination	44		X			X	X	
Combination	45		X			X		X
Combination	46		X				X	X
Combination	47			X	X	X		
Combination	48			X	X		X	
Combination	49			X	X			X
Combination	50			X		X	X	
Combination	51			X		X		X
Combination	52			X			X	X
Combination	53				X	X	X	
Combination	54				X	X		X
Combination	55				X		X	X
Combination	56					X	X	X
Combination	57	X	X	X	X			
Combination	58	X	X	X		X		
Combination	59	X	X	X			X	
Combination	60	X	X	X				X
Combination	61	X	X		X	X		
Combination	62	X	X		X		X	
Combination	63	X	X		X			X
Combination	64	X	X			X	X	
Combination	65	X	X			X		X
Combination	66	X	X				X	X
Combination	67	X		X	X	X		
Combination	68	X		X	X		X	
Combination	69	X		X	X			X
Combination	70	X		X		X	X	
Combination	71	X		X		X		X
Combination	72	X		X			X	X
Combination	73	X			X	X	X	
Combination	74	X			X	X		X
Combination	75	X			X		X	X
Combination	76	X				X	X	X
Combination	77		X	X	X	X		
Combination	78		X	X	X		X	
Combination	79		X	X	X			X
Combination	80		X	X		X	X	
Combination	81		X	X		X		X
Combination	82		X	X			X	X
Combination	83		X		X	X	X	
Combination	84		X		X	X		X
Combination	85		X		X		X	X
Combination	86		X			X	X	X
Combination	87			X	X	X	X	
Combination	88			X	X	X		X
Combination	89			X	X		X	X
Combination	90			X		X	X	X
Combination	91				X	X	X	X
Combination	92							
Combination	93	X	X	X	X	X		
Combination	94	X	X	X	X		X	

Combination	95	X	X	X	X			X
Combination	96	X	X	X		X	X	
Combination	97	X	X	X		X		X
Combination	98	X	X	X			X	X
Combination	99	X	X		X	X	X	
Combination	100	X	X		X	X		X
Combination	101	X	X		X		X	X
Combination	102	X	X			X	X	X
Combination	103	X		X	X	X	X	
Combination	104	X		X	X	X		X
Combination	105	X		X	X		X	X
Combination	106	X		X		X	X	X
Combination	107	X			X	X	X	X
Combination	108		X	X	X	X	X	
Combination	109		X	X	X	X		X
Combination	110		X	X	X		X	X
Combination	111		X	X		X	X	X
Combination	112		X		X	X	X	X
Combination	113			X	X	X	X	X

Compositions

One aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 1 and further comprising a second compound selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. In one specific embodiment of the invention, the second compound may be Compound 2, Compound 3, Compound 4, Compound 5 or Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 2 and further comprising a second compound selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. In one specific embodiment of the invention, the second compound may be Compound 4. In one specific embodiment of the invention, the second compound may be Compound 3. In one specific embodiment of the invention, the second compound may be Compound 5.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 3 and further comprising a second compound selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. In one specific embodiment of the invention, the second compound may be Compound 1. In one specific embodiment of the invention, the second compound may be Compound 4. In one

specific embodiment of the invention, the second compound may be Compound 5. In one specific embodiment of the invention, the second compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising a first compound selected from the group consisting of Compound 4 and further comprising a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. In one specific embodiment of the invention, the second compound may be Compound 1 or Compound 2 or Compound 3 or Compound 6. In one specific embodiment of the invention, the second compound may be Compound 1. In one specific embodiment of the invention, the second compound may be Compound 2. In one specific embodiment of the invention, the second compound may be Compound 3. In one specific embodiment of the invention, the second compound may be Compound 5. In one specific embodiment of the invention, the second compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 5 and further comprising a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. In one specific embodiment of the invention, the second compound may be Compound 1. In one specific embodiment of the invention, the second compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 6 and further comprising a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. In one specific embodiment of the invention, the second compound may be Compound 1. In one specific embodiment of the invention, the second compound may be Compound 2. In one specific embodiment of the invention, the second compound may be Compound 3. In one specific embodiment of the invention, the second compound may be Compound 4.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 7 and further comprising a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising a first compound selected from the group consisting of Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and further comprising a second compound selected from the

group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 1 and further comprising a second compound and a third compound each selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, or Compound 4, or Compound 5 or Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 3. The second compound may be Compound 2 and the third compound may be Compound 5. The second compound may be Compound 3 and the third compound may be Compound 5.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 2 and further comprising a second compound and a third compound each selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 5. The second compound may be Compound 3 and the third compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 3 and further comprising a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second

compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 5.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising a first compound selected from the group consisting of Compound 4 and further comprising a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6. The second compound may be Compound 1 and the third compound may be Compound 5. The second compound may be Compound 2 and the third compound may be Compound 5.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 5 and further comprising a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 6 and further comprising a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 4. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 5. The second compound may be Compound 2 and the third compound may be Compound 5. The second compound may be Compound 3 and the third compound may be Compound 5.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 7 and further comprising a second

compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising a first compound selected from the group consisting of Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and further comprising a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 1 and further comprising a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, Compound 4, Compound 5, or Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2, the third compound may be Compound 4, and the fourth compound may be Compound 6. The second compound may be Compound 3, the third compound may be Compound 4, and the fourth compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 2 and further comprising a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 3 and further comprising a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7,

Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 4, the third compound may be Compound 5, and the fourth compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising a first compound selected from the group consisting of Compound 4 and further comprising a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1, Compound 2, Compound 3, or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 5 and further comprising a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 6 and further comprising a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3, or Compound 4. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 7 and further comprising a second

compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising a first compound selected from the group consisting of Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and further comprising a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 1 and further comprising a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, Compound 4, Compound 5 or Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 2 and further comprising a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 3 and further comprising a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6. The second compound may be Compound 1 and the third compound may be

Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising a first compound selected from the group consisting of Compound 4 and further comprising a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 5 and further comprising a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.
The second compound may be Compound 1.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 6 and further comprising a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3, and Compound 4. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising Compound 7 and further comprising a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5,

Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes a composition, e.g. a pharmaceutical composition, the composition comprising a first compound selected from the group consisting of Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and further comprising a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Salts

The Combination Compounds and other active ingredients can be in the form of a salt. Typically, but not absolutely, the salts of the Combination Compounds and other active ingredients are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the Combination Compounds and/or other active ingredients. Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as chloride, bromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates.

Pharmaceutical Formulations

The Combination Compounds and/or other active ingredients can be formulated with conventional carriers or excipients, which can be selected in accord with ordinary practice. Tablets typically contain excipients, glidants, fillers, binders and the like. Aqueous formulations can be prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986), herein incorporated by reference in its entirety. Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for an active ingredient to be administered alone it may be preferable to present one or more active ingredients as pharmaceutical formulations. The formulations of the invention, both for veterinary and for human use, comprise at least one active ingredient, together with one or more acceptable carriers and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the administration routes set forth below. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally can be found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.), herein incorporated by reference in its entirety. Such methods include the step of bringing into association an active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations can be prepared by uniformly and intimately bringing into association one or more active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of an active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. An active ingredient may also be administered as a bolus, electuary or paste.

A tablet can made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine an active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally can be formulated so as to provide slow or controlled release of an active ingredient.

For administration to the eye or other external tissues e.g., mouth and skin, the formulations can be preferably applied as a topical ointment or cream containing an active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, an active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, an active ingredient may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including

PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of an active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of Combination Compounds and/or other active ingredients may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60 (ICI Americas Inc.), Span 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Pharmaceutical formulations according to the present invention comprise one or more active together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing active ingredients may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing an active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium

or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where an active ingredient(s) is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein an active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending an active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth herein, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide an active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-

occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 µg of an active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein an active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for an active ingredient. An active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising an active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising an active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising an active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 μm (including particle sizes in a range between 0.1 and 500 μm in increments such as 0.5 μm, 1 μm, 30 μm, 35 μm, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of an active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of infections as described herein.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to an active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations can be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations can be those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of Combination Compounds and/or other active ingredients may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Combination Compounds and other active ingredients can also be formulated to provide controlled release of an active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of an active ingredient. Accordingly, the invention also provides compositions comprising two or more of the Combination Compounds formulated for sustained or controlled release.

Dosages

The effective dose of an active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active disease or condition, the method of delivery, and the pharmaceutical formulation, and can be determined by the clinician using conventional dose escalation studies.

By way of example, compositions of the invention (e.g. tablets) can be formulated to provide effective doses. For example, with respect to Compound 1, or a pharmaceutically acceptable salt thereof, the composition may comprise from 1.0 mg to 100 mg, from 5 mg to 40 mg, from 30 mg to 50 mg, or 20 mg or 40 mg and can be adapted to be administered one or more times daily to a human being in need thereof in combination with any one or more of Compound 2, Compound 3, Compound 6, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. With respect to Compound 2 or a pharmaceutically acceptable salt thereof, the composition may comprise from 25 mg to 800 mg, from 50 mg to 400 mg, or from 60 mg to 300 mg or from 70 mg to 200 mg or may be 150 mg and can be adapted to be administered one or more times daily to a human being in need thereof in combination with any one or more of Compound 1, Compound 3, Compound 6, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. With respect to Compound 3, or a pharmaceutically acceptable salt thereof, the composition may comprise from 10 mg to 1000 mg, or 50 to 400 mg, or 100mg to 400mg or 200 mg to 400 mg and can be adapted to be administered one or more times daily to a human being in need thereof in combination with any one or more of Compound 1, Compound 2, Compound 6, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. With respect to Compound 4, or a pharmaceutically acceptable salt thereof, the composition may comprise from 25mg to 400mg or from 25mg to 200mg can be adapted to be administered one or more times daily to a human being in need thereof in combination with any one or more of Compound 1, Compound 2, Compound 3, Compound 6, Compound 5 and Compound 7. With respect to Compound 5, or a pharmaceutically acceptable salt thereof, the composition may comprise from 50mg to 1000mg or 100mg to 750mg can be adapted to be administered one or more times daily to a human being in need thereof in combination with any one or more of Compound 1, Compound 2, Compound 3, Compound 6, Compound 4, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. With respect to Compound 6, or a pharmaceutically acceptable salt thereof, the composition may comprise from 1mg to 500mg or from 3 mg to 300 mg or from 3 mg to 200mg or from 3 mg to 100 mg or from 10 mg to 90 mg or from 30 mg to 90 mg can be adapted to be

administered one or more times daily to a human being in need thereof in combination with any one or more of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. With respect to Compound 7, or a pharmaceutically acceptable salt thereof, the composition may comprise from 100 micrograms up to 3000mg, from 25mg up to 2000mg, or from 50mg up to 1000mg and can be adapted to be administered one or more times daily (e.g. four times daily) to a human being in need thereof in combination with any one or more of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. With respect to Compounds 9 and 10, or pharmaceutically acceptable salts thereof, the composition may comprise 10 mg to 1000mg per day (according to US 2010/0298257). With respect to Compound 11, or pharmaceutically acceptable salts thereof, the composition may comprise 1mg to 1000mg per day (according to US 2010/0081628). Dosages for Compounds 1-7 that are co-administered may need to be adjusted to account for potential drug-drug interactions. For example, although it does not appear that Compound 1 affects drug metabolizing systems, Compound 2 appears to have the effect of increasing the exposure of Compound 1 approximately 2-3X. Therefore, a dose reduction (e.g. 2x-3x) of Compound 1 would be anticipated when Compound 1 is combined with Compound 2. In combination with Compound 16, Compound 2 appears to have the effect of increasing the exposure of Compound 6 approximately 5x, so dose reduction (e.g. 3x-5x) of Compound 16 would be anticipated when Compound 16 is dosed with Compound 2. Therefore, a 10 mg dose of Compound 6 when coadministered with Compound 2 approximate to a 30 mg dose.

The two or more Combination Compounds may be administered in conjunction with Ribavirin in amounts of about 800mg, 1000mg or 1200mg per day in single or multiple dosages (e.g. about 400mg, 500mg or 600mg twice daily).

Use of Combinations of the Invention

In practice of this aspect of the invention, Combination Compounds may be used in the dosages set forth above.

One aspect of the present invention includes Compound 1 for use in a method of treating HCV infections, wherein compound 1 is used in combination with a second compound selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, Compound 4, Compound 5 or Compound 6.

Another aspect of the present invention includes Compound 2 for use in a method of treating HCV infections, wherein compound 2 is used in combination with a second compound

selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4.

Another aspect of the present invention includes Compound 3 for use in a method of treating HCV infections, wherein compound 3 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6.

Another aspect of the present invention includes Compound 4 for use in a method of treating HCV infections, wherein Compound 4 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1 or Compound 2 or Compound 3 or Compound 6.

Another aspect of the present invention includes Compound 5 for use in a method of treating HCV infections, wherein Compound 5 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes Compound 6 for use in a method of treating HCV infections, wherein Compound 6 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 4.

Another aspect of the present invention includes Compound 7 for use in a method of treating HCV infections, wherein Compound 7 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes Compound 9 for use in a method of treating HCV infections, wherein Compound 9 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6, and Compound 7.

Another aspect of the present invention includes Compound 10 for use in a method of treating HCV infections, wherein Compound 10 is used in combination with a second

compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6, and Compound 7.

Another aspect of the present invention includes Compound 11 for use in a method of treating HCV infections, wherein Compound 11 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6, and Compound 7.

Another aspect of the present invention includes Compound 12 for use in a method of treating HCV infections, wherein Compound 12 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6, and Compound 7.

Another aspect of the present invention includes Compound 13 for use in a method of treating HCV infections, wherein Compound 13 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6, and Compound 7.

Another aspect of the present invention includes Compound 14 for use in a method of treating HCV infections, wherein Compound 14 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6, and Compound 7.

Another aspect of the present invention includes Compound 15 for use in a method of treating HCV infections, wherein Compound 15 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6, and Compound 7.

Another aspect of the present invention includes Compound 16 for use in a method of treating HCV infections, wherein Compound 16 is used in combination with a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6, and Compound 7.

Another aspect of the present invention includes Compound 1 for use in a method of treating HCV infections, wherein compound 1 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, or Compound 4, or Compound 5 or Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 2 for use in a method of treating HCV infections, wherein compound 2 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 3 for use in a method of treating HCV infections, wherein compound 3 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 4 for use in a method of treating HCV infections, wherein Compound 4 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 5 for use in a method of treating HCV infections, wherein Compound 5 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes Compound 6 for use in a method of treating HCV infections, wherein Compound 6 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10,

Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 4. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4.

Another aspect of the present invention includes Compound 7 for use in a method of treating HCV infections, wherein Compound 7 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes Compound 9 for use in a method of treating HCV infections, wherein Compound 9 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes Compound 10 for use in a method of treating HCV infections, wherein Compound 10 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes Compound 11 for use in a method of treating HCV infections, wherein Compound 11 is used in combination with a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes Compound 1 for use in a method of treating HCV infections, wherein compound 1 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, Compound 4, Compound 5, or Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 2 for use in a method of treating HCV infections, wherein compound 2 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 3 for use in a method of treating HCV infections, wherein compound 3 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 4 for use in a method of treating HCV infections, wherein Compound 4 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1, Compound 2, Compound 3, or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 5 for use in a method of treating HCV infections, wherein Compound 5 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes Compound 6 for use in a method of treating HCV infections, wherein Compound 6 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7,

Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3, or Compound 4. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4.

Another aspect of the present invention includes Compound 7 for use in a method of treating HCV infections, wherein Compound 7 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes Compound 9 for use in a method of treating HCV infections, wherein Compound 9 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes Compound 10 for use in a method of treating HCV infections, wherein Compound 10 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes Compound 11 for use in a method of treating HCV infections, wherein Compound 11 is used in combination with a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes Compound 1 for use in a method of treating HCV infections, wherein compound 1 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, Compound 4, Compound 5 or Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 2 for use in a method of treating HCV infections, wherein compound 2 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 3 for use in a method of treating HCV infections, wherein compound 3 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 4 for use in a method of treating HCV infections, wherein Compound 4 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6.

Another aspect of the present invention includes Compound 5 for use in a method of treating HCV infections, wherein Compound 5 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes Compound 6 for use in a method of treating HCV infections, wherein Compound 6 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group

consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3, or Compound 4. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4.

Another aspect of the present invention includes Compound 7 for use in a method of treating HCV infections, wherein Compound 7 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes Compound 9 for use in a method of treating HCV infections, wherein Compound 9 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes Compound 10 for use in a method of treating HCV infections, wherein Compound 10 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes Compound 11 for use in a method of treating HCV infections, wherein Compound 11 is used in combination with a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

One aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 1 and further comprising administering a second compound selected from the group consisting of comprising Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10,

Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, Compound 4, Compound 5 or Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 2 and further comprising administering a second compound selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 3 and further comprising administering a second compound selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 4 and further comprising administering a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1 or Compound 2 or Compound 3 or Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 5 and further comprising administering a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 6 and further comprising administering a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 4.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 7 and further comprising administering a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 9 and further comprising administering a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 10 and further comprising administering a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 11 and further comprising administering a second compound selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 1 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, or Compound 4, or Compound 5 or Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 2 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 3 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 4. The second

compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 4 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 5 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 6 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 4. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be

Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 7 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 9 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 10 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 11 and further comprising administering a second compound and a third compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 1 and further comprising administering a second compound, a third compound and a fourth compound each selected from the group consisting

of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, Compound 4, Compound 5, or Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 2 and further comprising administering a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 3 and further comprising administering a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 4 and further comprising administering a second

compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1, Compound 2, Compound 3, or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 5 and further comprising administering a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 6 and further comprising administering a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3, or Compound 4. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 7 and further comprising administering a second compound, a third compound and a fourth compound each selected from the group consisting

of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 9 and further comprising administering a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 10 and further comprising administering a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 11 and further comprising administering a second compound, a third compound and a fourth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 1 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 3, Compound 4, Compound 5 or Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3

and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 2 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 3 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 4. The second compound may be Compound 1 and the third compound may be Compound 6. The second compound may be Compound 4 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 4 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7. The second compound may be Compound 1, Compound 2, Compound 3 or Compound 6. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 1 and the third compound may be

Compound 6. The second compound may be Compound 2 and the third compound may be Compound 6. The second compound may be Compound 3 and the third compound may be Compound 6.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 5 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 6 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16. The second compound may be Compound 1, Compound 2, Compound 3, and Compound 4. The second compound may be Compound 1 and the third compound may be Compound 2. The second compound may be Compound 1 and the third compound may be Compound 3. The second compound may be Compound 4 and the third compound may be Compound 6. The second compound may be Compound 2 and the third compound may be Compound 4. The second compound may be Compound 3 and the third compound may be Compound 4.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 7 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 9 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 10 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Another aspect of the present invention includes a method for ameliorating one or more symptom of HCV infection in a human, a method for reducing viral load in a human diagnosed with HCV, a method of treating HCV in a human subject, and a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents, each method comprising administering Compound 11 and further comprising administering a second compound, a third compound, a fourth compound and a fifth compound each selected from the group consisting of Compound 1, Compound 2, Compound 3, Compound 5, Compound 6 and Compound 7.

Routes and Modes of Administration

Two or more of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 and any other components of a combination therapy can be adapted to be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) and the like. It will be appreciated that the preferred route may vary with, for example, the condition of the recipient.

A synergistic effect may be attained when the active ingredients are: (1) co-formulated (e.g. in a unitary dosage form) and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained

when the compounds are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

Co-administration of a Combination Compound with one or more Combination Compounds generally refers to simultaneous or sequential administration of one or more Combination Compounds, such that therapeutically effective amounts of two or more Combination Compounds are present in the body of the patient. In some cases, Combination Compounds (e.g. two, three or four Combinations Compounds) will be co-formulated to allow administration at the same time. In some cases, co-formulated Combination Compounds may be co-administered with one or more additional Combination Compounds.

Co-administration also includes administration of unit dosages of the Combination Compounds before or after administration of unit dosages of one or more other active ingredients, for example, administration of two or more Combination Compounds within seconds, minutes, or hours of the administration of one or more other active ingredients. For example, a unit dose of a Combination Compound can be administered first, followed within seconds or minutes by administration of a unit dose of a second Combination Compound, followed within seconds or minutes by administration of a unit dose of one or more other active ingredients. Alternatively, a unit dose of one or more other active ingredients can be administered first, followed within seconds or minutes by administration of a unit dose of a Combination Compound, followed within seconds or minutes by administration of a unit dose of a second Combination Compound. In some cases, it may be desirable to administer a unit dose of a Combination Compound first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a second Combination Compound, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active ingredients. In other cases, it may be desirable to administer a unit dose of one or more other active ingredients first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a Combination Compound, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a second Combination Compound. Where three or more Combinations Compounds are administered with one or more additional active ingredients, the Combination Compounds may be administered one after another within seconds, minutes, or hours (e.g. 1-12 hours) of each other and the one or more additional active ingredients may be administered before, during or after the administration of the Combination Compounds. Where Combination Compounds are co-formulated, they can be administered simultaneously, or before or after the administration of one or more additional active ingredients.

Unless otherwise specified, the combination therapy may be administered as separate dosage forms with each active ingredient, administered together or separately, sequentially or concurrently, and close in time or remote in time to each other.

The course of treatment can extend, for example, from about 12 weeks to about 48 weeks, or longer, for example, from about 12 weeks to about 24 weeks.

The present invention includes a combination of therapeutically effective components to ameliorate at least one symptom of HCV infection in a human being including, but not limited to, nausea, vomiting, loss of appetite, fatigue, jaundice, vomiting, diarrhea, dehydration, abdominal pain, cirrhosis of the liver. In addition, in some HCV infected individuals the use of combination therapy is effective to reduce the viral load of HCV viral particles present in the body of the infected person by a statistically significant amount. Viral load can be measured, for example, by measuring plasma HCV RNA levels using, for example, the COBAS TaqMan HCV assay (Roche Molecular Systems). Typically, an HCV infected person who is treated with the Combination Compounds in accordance with the present invention experiences an improvement in one or all of the symptoms associated with the HCV infection.

Combinations of Two or more of the Combination Compounds with Ribavirin but not Interferon

As discussed above, some current HCV treatments include the administration of interferon, but this treatment typically produces unwanted side effects. Therefore it would be desirable to find effective HCV treatments that do not require the administration interferon.

One aspect of the present invention provides for compositions, methods, uses and the like for the treatment of HCV comprising administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, without administering one or more interferons. This aspect of the invention may be particularly useful because it allows for the effective treatment of HCV without the side effects associated with the administration of one or more interferon.

In one embodiment of the present invention, the combined amount of ribavirin and Combination Compounds or pharmaceutically acceptable salts thereof, optionally with one or more additional agents, is effective to treat HCV infection.

Another aspect of the present invention includes a method for ameliorating one or more symptoms of HCV infection in a human comprising: administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, without concurrent administration of one or more interferon. In this regard, the present invention does not foreclose the potential for dosing one or more interferon. Rather, the present invention may be used in conjunction with another therapy that, in fact, includes one or more interferon. An aspect of the present invention includes efficacious treatment of HCV with ribavirin without the need for one or more interferon.

Another aspect of the present invention includes a method for reducing viral load in a human diagnosed with HCV comprising: administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, but not one or more interferon.

Another aspect of the present invention includes a method for treating HCV in a human subject consisting essentially of administration of ribavirin in conjunction with two or more of the Combination Compounds or pharmaceutically acceptable salts thereof.

Another aspect of the present invention includes a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents comprising: administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, without concurrent administration of one or more interferon.

Similarly, another aspect of the present invention includes a composition, e.g. a pharmaceutical composition for ameliorating one or more symptom of HCV infection in a human comprising two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, without one or more interferon. Another aspect of the present invention includes a composition for reducing viral load in a human diagnosed with HCV comprising two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, but not one or more interferon. Another aspect of the present invention includes a composition for treating HCV in a human subject consisting essentially of ribavirin in conjunction with two or more of the Combination Compounds or pharmaceutically acceptable salts thereof. Another aspect of the present invention includes a composition for ribavirin-based HCV therapy comprising two or more of the Combination Compounds or pharmaceutically acceptable salts thereof, with the proviso that said composition does not include one or more interferon. Another aspect of the present invention includes a composition for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents comprising two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, without one or more interferon.

Similarly, another aspect of the present invention includes use of: two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, without one or more interferon, in the manufacture of a medicament for ameliorating one or more symptoms of HCV infection in a human; as well as use of: two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, but not one or more interferon, in the manufacture of medicament for reducing viral load in a human diagnosed with HCV; as well as use of ribavirin in conjunction with two or more of the Combination Compounds or pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating HCV in a human subject, wherein said use does not include use of one or more interferon; as well as use of two or more of the Combination Compounds or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for ribavirin-based HCV therapy, wherein

said use avoids administration of one or more interferon; as well as use of two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, without one or more interferon in the manufacture of a medicament for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents.

Another aspect of the present invention includes a combination comprising ribavirin and two or more of the Combination Compounds or pharmaceutically acceptable salts thereof, which combination is substantially free of one or more interferon. In one embodiment, the combination may occur as separate dosage forms with each active ingredient, administered together or separate, sequentially or concurrently, and close in time or remote in time to each other.

Another aspect of the present invention includes a kit comprising: ribavirin, two or more of the Combination Compounds and instruction regarding a treatment regimen to treat, reduce viral load, or delay onset or progression of HCV wherein the treatment regimen includes administration of the two or more of the Combination Compounds and ribavirin without administration of one or more interferon. In one embodiment, such a kit may also include packaging, such as a blister pack. Alternatively, such a kit may provide for individual prescription and dosing of each component as separately packaged pharmaceutics, but when combined with the instruction regarding a treatment regimen to treat, reduce viral load, or delay onset or progression of HCV, such is intended to be within the scope of the present invention.

Another aspect of the present invention includes a pharmaceutical composition comprising: ribavirin; two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and one or more pharmaceutically acceptable carriers. In one embodiment, the pharmaceutical composition may be a unitary dosage form.

Unless otherwise specified, the combination therapy with Ribavirin may be administered as separate dosage forms with each active ingredient administered (including the Combination Compounds), may be administered together (e.g., in the form of a unit dosage, such as a tablet) or separately, sequentially or concurrently, and close in time or remote in time to each other. If administered separately, each compound may be administered with the other(s) at the same time, or either before or after such administration of the other(s). The active ingredients can be administered daily. In one embodiment, a daily dosage of the active ingredients is administered in separate sub-doses, such as one, two, three or four times per day. Advantageously, the daily dosage of Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin may be administered once per day.

Although the present invention includes compositions, methods, uses and the like for the treatment of HCV comprising administering two or more Combination Compounds or a pharmaceutically acceptable salt thereof; and ribavirin, but not one or more interferon, the present invention does not foreclose the potential for dosing one or more interferon to the

human. Rather, the present invention may be used in conjunction with another therapy for another indication that, in fact, includes one or more interferon.

Combinations of Two or more of the Combination Compounds with Ribavirin and Interferon

Another aspect of the present invention provides for compositions, methods, uses and the like comprising administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof and ribavirin, and one or more interferon for treatment of HCV. The administration of more interferon may be in temporal relation to the administration of the Combination Compounds and ribavirin.

Another aspect of the present invention includes a method for ameliorating one or more symptoms of HCV infection in a human comprising administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof, ribavirin, and one or more interferons. Another aspect of the present invention includes a method for reducing viral load in a human diagnosed with HCV comprising: administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof along with ribavirin and one or more interferons.

Another aspect of the present invention includes a method of ribavirin-based HCV therapy comprising administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof along with ribavirin, and one or more interferons.

Another aspect of the present invention includes a method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents comprising: administering two or more of the Combination Compounds or pharmaceutically acceptable salts thereof along with ribavirin and one or more interferons.

Another aspect of the present invention includes use of two or more of the Combination Compounds or pharmaceutically acceptable salts thereof ribavirin, and one or more interferons, in the manufacture of a medicament for ameliorating one or more symptoms of HCV infection in a human. Another aspect of the present invention includes use of two or more of the Combination Compounds or pharmaceutically acceptable salts thereof along with ribavirin and one or more interferons, in the manufacture of medicament for reducing viral load in a human diagnosed with HCV. Another aspect of the present invention includes use of ribavirin in conjunction with two or more of the Combination Compounds or pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating HCV in a human subject, wherein said use includes use of one or more interferons. Another aspect of the present invention includes use of two or more of the Combination Compounds or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for ribavirin-based HCV therapy, wherein said use includes administration of one or more interferon. Another aspect of the present invention includes use of two or more of the Combination Compounds or pharmaceutically acceptable salts thereof, ribavirin, and one or more interferons in the manufacture of a

medicament for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents.

Another aspect of the present invention includes a combination comprising ribavirin and two or more of the Combination Compounds or pharmaceutically acceptable salts thereof, which combination includes one or more interferons.

Another aspect of the present invention includes a kit comprising: ribavirin, two or more of the Combination Compounds and one or more interferon; and instructions regarding a treatment regimen to treat, reduce viral load, or delay onset or progression of HCV wherein the treatment regimen includes administration of the two or more of the Combination Compounds and ribavirin and administration of one or more interferon. In one embodiment, such a kit may also include packaging, such as a blister pack. Alternatively, such a kit may provide for individual prescription and dosing of each component as separately packaged pharmaceutics, but when combined with the instruction regarding a treatment regimen to treat, reduce viral load, or delay onset or progression of HCV, such is intended to be within the scope of the present invention.

Another aspect of the present invention includes a pharmaceutical composition comprising: two or more of the Combination Compounds or pharmaceutically acceptable salts thereof, ribavirin, and one or more interferon; and one or more pharmaceutically acceptable carriers. In one embodiment, the pharmaceutical composition may be a unitary dosage form.

Unless otherwise specified, the combination therapy with Ribavirin and one or more interferons may be administered as separate dosage forms with the one or more interferons administered to the patient and each of the remaining active ingredients to be employed in the combination therapy (including the Combination Compounds) are administered together (e.g., in the form of a unit dosage, such as a tablet) or separately, sequentially or concurrently, and close in time or remote in time to each other. If administered separately, each active ingredient may be administered with the other(s) at the same time, or either before or after such administration of the other(s). The active ingredients can be administered daily. In one embodiment, a daily dosage is administered in separate sub-doses, such as one, two, three or four times per day.

Combination Therapy, Including Additional Therapeutics

In another embodiment, non-limiting examples of suitable combinations include the combinations of two or more of Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, Compound 6, Compound 7, Compound 9, Compound 10, Compound 11, Compound 12, Compound 13, Compound 14, Compound 15 and Compound 16 with one or more additional active ingredients including HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists,

cyclophilin inhibitors, HCV IRES inhibitors, HCV entry inhibitors, HCV maturation inhibitors, HCV assembly inhibitors, HCV infectivity inhibitors and pharmacokinetic enhancers, as well as other drugs for treating HCV. More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of:

(i) HCV NS3 protease inhibitors, e.g., boceprevir (SCH-503034, SCH-7), telaprevir (VX-950), TMC-435 (IUPAC N-[(2R,3aR,10Z,11aS,12aR,14aR)-2-[2-(4-Isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-5-methyl-4,14-dioxo-1,2,3,3a,4,5,6,7,8,9,11a,12,12a,13,14,14a-hexadecahydrocyclopenta[c]cyclopropa[g][1,6]diazacyclotetradecin-12a-ylcarbonyl]cyclopropanesulfonamide], ABT-450, ACH-1625, ACH-2684, BI-201335, BI-1230, MK-5172, MK-7009, SCH-900518, VBY-376, VX-500, GS-9256, GS-9451, BMS-605339, PHX-1766, AS-101, YH-5258, YH-5530, YH-5531, and ITMN-191 (R-7227);

(ii) alpha-glucosidase 1 inhibitors, e.g., celgosivir (MX-3253), UT-231B, Miglitol;

(iii) hepatoprotectants, e.g., emericasan (IDN-6556), ME-3738, silibilin, and MitoQ;

(iv) nucleoside or nucleotide inhibitors of HCV NS5B polymerase, e.g., ., R1626, R7128 (R4048), IDX184, IDX-102, PSI-661, PSI-938, PSI-7851, PSI-7977, BCX-4678, valopicitabine (NM-283), MK-0608 and TMC649128;

(v) non-nucleoside inhibitors of HCV NS5B polymerase, e.g., filibuvir (PF-868554), ABT-333, ABT-072, BI-207127, VCH-759, VCH-916, JTK-652, MK-3281, VBY-708, VCH-222, A848837, ANA-598, GL60667, GL59728, A-63890, A-48773, A-48547, BC-2329, VCH-796 (nesbuvir), GSK625433, BILN-1941, and XTL-2125;

(vi) HCV NS5A inhibitors, e.g., ACH-2928, AZD-2836 (A-831), AZD-7295 (A-689), BMS-766, BMS-790052, BMS-824393, and PPI-461;

(vii) TLR-7 agonists, e.g., imiquimod, 852A, ANA-773, ANA-975, AZD-8848 (DSP-3025), PF-04878691, and SM-360320and Compound 8;

(viii) cyclophilin inhibitors, e.g., DEBIO-025, SCY-635, and NIM811;

(ix) HCV IRES inhibitors, e.g., MCI-067;

(x) pharmacokinetic enhancers, e.g. roxythromycin, BAS-100, SPI-452, PF-4194477, TMC-41629;

(xi) HCV entry inhibitors

(xii) HCV assembly inhibitors;

(xiii) HCV maturation inhibitors;

(xiv) HCV infectivity inhibitors; and

(xv) other drugs for treating HCV, e.g., thymosin alpha 1 (Zadaxin), nitazoxanide (Alinea, NTZ), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon

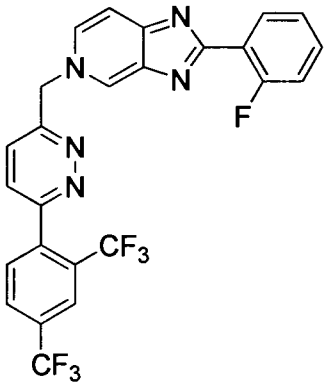
(CPG-10101), KRN-7000, civacir, GI-5005, XTL-6865, BIT225, PTX-111, ITX2865, TT-033i, ANA 971, NOV-205, tarvacin, EHC-18, VGX-410C, EMZ-702, AVI 4065, BMS-650032, BMS-791325, Bavituximab, MDX-1106 (ONO-4538), Oglufanide, FK-788, and VX-497 (merimepodib)..

SYNTHETIC EXAMPLES

Synthetic protocols for the preparation of Compounds 1, 2, 3, 6, 7, and 8 are known in the literature. Additionally, a synthetic protocol for preparing each of the Combination Compounds is provided in the Examples below.

Compound **1** can be prepared using synthetic methods and intermediates like those described in US 7,754,720. Compound **1** can also be prepared as described in the following Example.

Example 1: 5-({6-[2,4-bis(trifluoromethyl)phenyl]pyridazin-3-yl}methyl)-2-(2-fluorophenyl)-5H-imidazo[4,5-c]pyridine **1**.



1

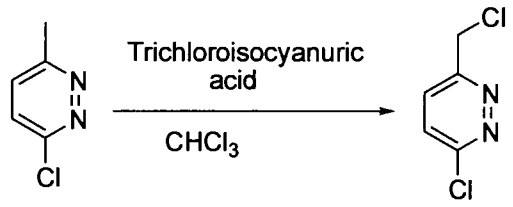
Compound	MW	Amount	Moles	Equivalents
104	453.79	95mg	0.209	1
DME	500µL			
2N aq. Na_2CO_3		313µL	0.626	3
105	257.93	80.9mg	0.313	1.5
$Pd(PPh_3)_4$	1155	12mg	0.0104	0.05

Compound **103** was dissolved in dimethoxyethane (DME). To this solution was added 2,4-bis(trifluromethyl)phenylboronic acid **105** and a 2N aq. Na_2CO_3 solution. To the resulting biphasic mixture was added $Pd(PPh_3)_4$ and the reaction was then heated at 80°C for 72 hrs. The reaction was cooled to room temperature and filtered through Celite and the Celite washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified on 6g SiO_2 using $MeOH/CH_2Cl_2$ to elute compound. The compound thus obtained was contaminated with $PPh_3(O)$. The product was repurified on a 1 mm Chromatotron plate with 0 to 5% $MeOH/CH_2Cl_2$ in 1% steps. The pure fractions were combined and concentrated *in vacuo*, then dried on high vacuum for 12 hrs. 11.8 mg of the free base of compound 1 was obtained with no

PPh_3 contamination. ^1H NMR (300MHz,CD_3OD) δ 6.20 (s, 2), 7.32 (m, 3), 7.52 (m, 1), 7.78 (d, 1), 7.89 (d, 1), 7.95 (s, 2), 8.15 (m, 3), 8.35 (d, 1), 9.12 (s, 1); LC/MS M+H = 518.

The intermediate compound **104** was prepared as follows.

a. Preparation of Compound **102**.

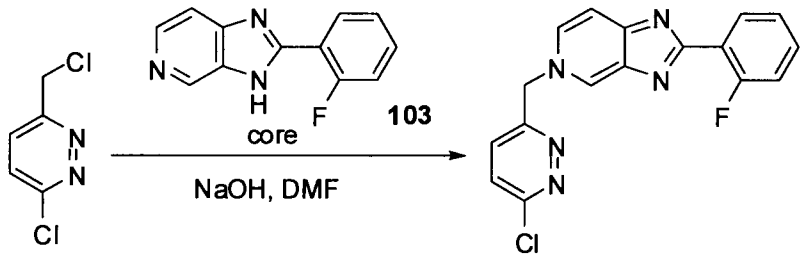


101 **102**

Compound	MW	Amount	mmoles	Equivalents
101	128.56	5 g	38.9	1
TCCA	232.41	3.62 g	15.6	0.4
$CHCl_3$		130 mL		

To a solution of the commercially available starting material **101** in $CHCl_3$, trichloroisocyanuric acid (TCCA) was added at 60°C. Then the solution was stirred for 1.5 hrs, cooled, and filtered with HiFlo-Celite. The filtrate was concentrated and dried with vacuum. The yield was 5.037 g of compound **102**.

b. Preparation of Compound **104**.



102 **104**

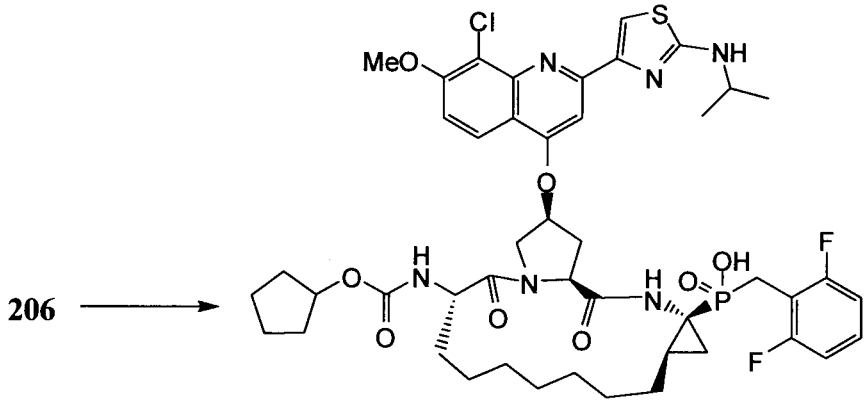
Compound	MW	Amount	mmoles	Equivalents
102	163	5.073 g	31.12	1
103	213.2	6.635 g	31.12	1
NaOH (10%)	40	1.245 g	31.12	1
DMF		320 mL		

To a solution of compound **103** in DMF (dimethylformamide), NaOH was added. Compound **102** was dissolved in DMF (20 mL) and added to the solution slowly. The reaction

was stirred for 3 hrs, was diluted with water and extracted with EtOAc. The organic layer was dried with Na_2SO_4. The solvent was removed and the product recrystallized with dichloromethane. The yield was 5.7 g of compound **103**.

Compound **2** can be prepared using synthetic methods and intermediates like those described in USSN 12/202319 (US 20100051763 A1). Compound **2** can also be prepared as described in the following Example.

Example 2: Preparation of Compound **2**.

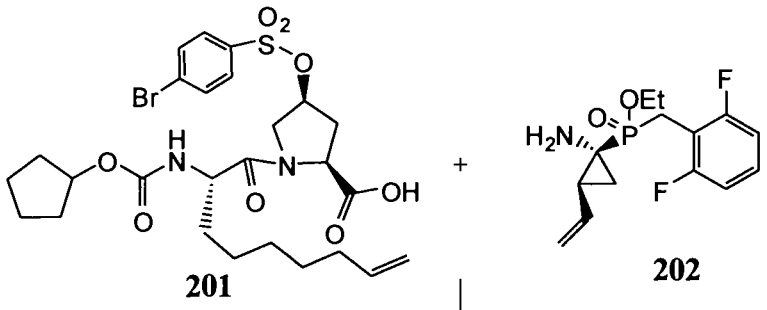


2

Phosphinate ester **206** (23.7 g, 24.05 mmol) was dissolved in CH_3CN (240 mL) and cooled to 0°C. Iodotrimethylsilane (17.4 mL, 122.3 mmol) was added at a fast drop-wise pace followed by, after 10 min, 2,6-lutidine (17.0 mL, 146.4 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 1 h then cooled back down to 0°C and 2,6-lutidine (11.1 mL, 95.6 mmol) followed by MeOH (24 mL) were added. The solution was concentrated *in vacuo* and the crude residue was purified by HPLC to afford 12.68 g of Compound **2** in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 9.3 Hz, 1H), 8.28 (s, 1H), 7.85 (s, 1H), 7.64 (d, J = 9.6 Hz, 1H), 7.35-7.22 (m, 1H), 7.02-6.89 (m, 2H), 5.85 (bs, 1H), 4.82-4.71 (m, 2H), 4.33 (bs, 1H), 4.28-3.99 (m, 3H), 4.16 (s, 3H), 3.57-3.28 (m, 2H), 2.90-2.78m, 1H), 2.63-2.50 (m, 1H), 2.08-1.91 (m, 1H), 1.91-170 (m, 2H), 1.70-1.13 (m, 22H), 1.37 (d, J = 6.9 Hz, 6H); 31P NMR (121.4 MHz, CD_3OD) δ 42.4; LCMS (M+1): 957.35. g.

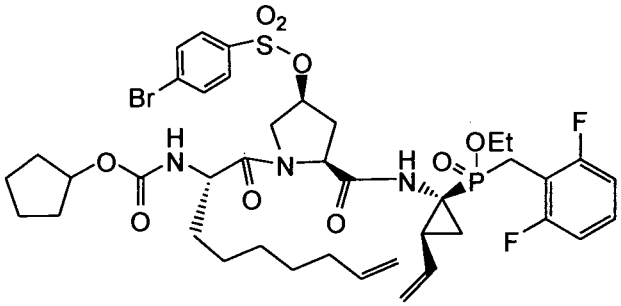
Intermediate compound **206** was prepared as follows.

a. Preparation of Compound **203**.



201

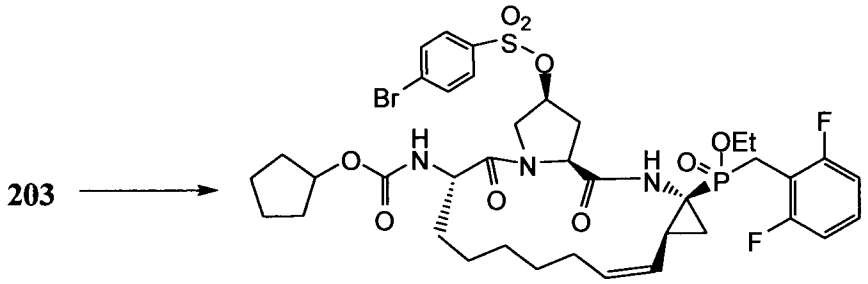
202



203

Compound **201** (17.42 g, 28.30 mmol) was dissolved in THF (136 mL) and cooled to 0°C. To the solution was added N-methylmorpholine (4.7 mL, 42.7 mmol). After 10 min at 0°C, *i*-butylchloroformate (4.05 mL, 30.96 mmol) was added dropwise. After an additional 1 h, (1-amino-2-vinyl-cyclopropyl)-(2,6-difluoro-benzyl)-phosphinic acid ethyl ester **202** (8.94 g, 29.70 mmol) was slowly added as a solution in THF (20 mL). The suspension was warmed to room temperature and after 2 h it was partitioned between H_2O (400 mL) and ethylacetate (200 mL). The aqueous layer was extracted with ethylacetate (200 mL x 2) and the combined organic layers were washed with HCl (1N, 225 mL) and H2O (200 mL). The acid wash and aqueous wash were combined and back-extracted with ethylacetate (175 mL x 2, 100 mL x 2). The combined organic layers were washed with brine (400 mL), dried over Na2SO4, and concentrated *in vacuo* providing 25.06 g of diene **203** in 98.5% crude yield. LCMS (M + 1): 898.06.

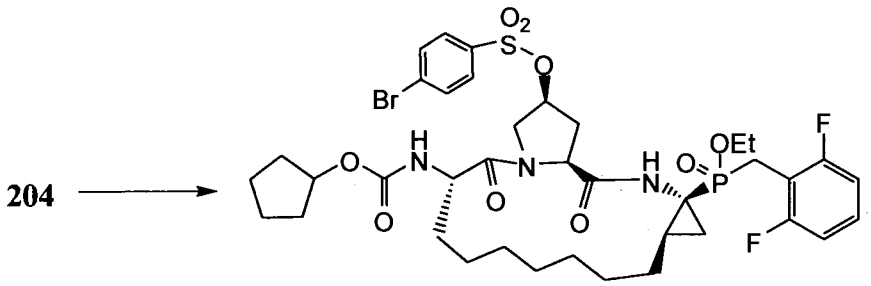
b. Preparation of Compound **204**.



204

Compound **203** (12.91 g, 14.36 mmol) was dissolved in CH_2Cl_2 (1440 mL) and the solution was degassed for 30 minutes. The solution was heated to 40°C and Grubb's G1 catalyst (2.95 g, 3.59 mmol) was added. The reaction was refluxed for 17 h whereupon tris-hydroxymethylphosphine (22.3 g, 18.0 mmol), TEA (50 mL, 35.9 mmol), and H_2O (400 mL) were added and the reaction mixture was heated to reflux for an additional 16 hours. The reaction mixture was cooled to room temperature and the two layers were separated. The organic layer was washed with H_2O (400 mL) and brine (300 mL), dried over MgSO4, and concentrated. The crude residue was purified by silica-gel chromatography to afford 8.30 g of macrocyclic olefin **204** in 66% yield. LCMS (M + 1): 870.09.

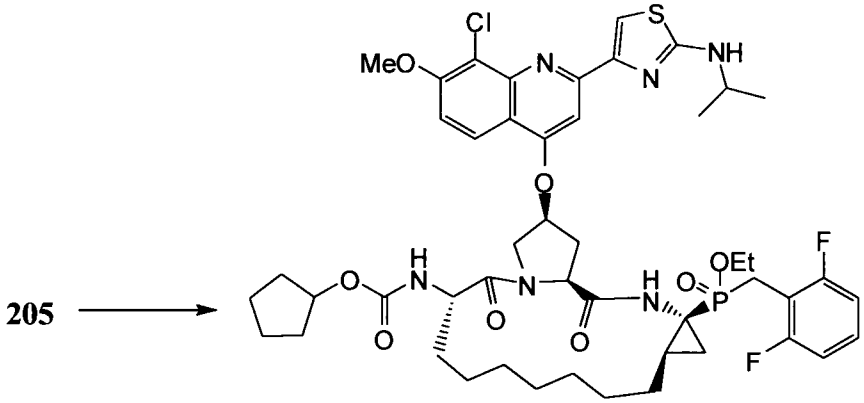
c. Preparation of Compound **205**.



205

The macrocyclic olefin **204** (7.34 g, 8.42 mmol) was dissolved in ethylacetate (105 mL) and rhodium on alumina (5% wt, 2.945 g, 0.40 wt %) was added. The system was evacuated and flushed with H_2 (1 atm, 3x). To the system, after 3 h, was added more rhodium on alumina (5% wt, 842 mg, 0.10 wt %) and evacuated and flushed with H_2 (1 atm, 3x). After an additional 1 h the suspension was filtered and concentrated *in vacuo* providing 6.49 g of reduced macrocycle **205** in 88% crude yield. LCMS (M + 1): 872.04.

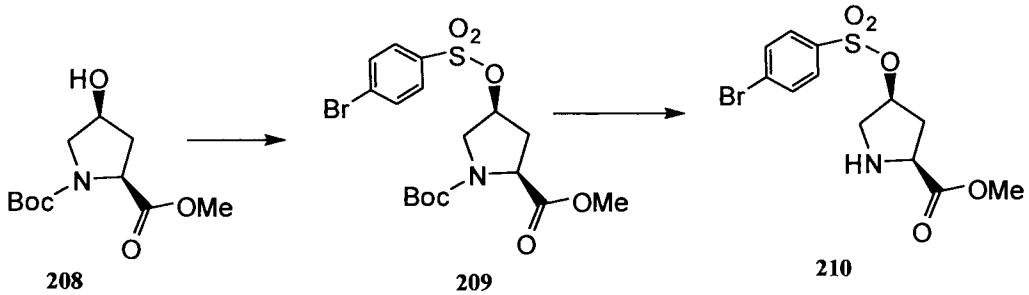
d. Preparation of Compound **206**.

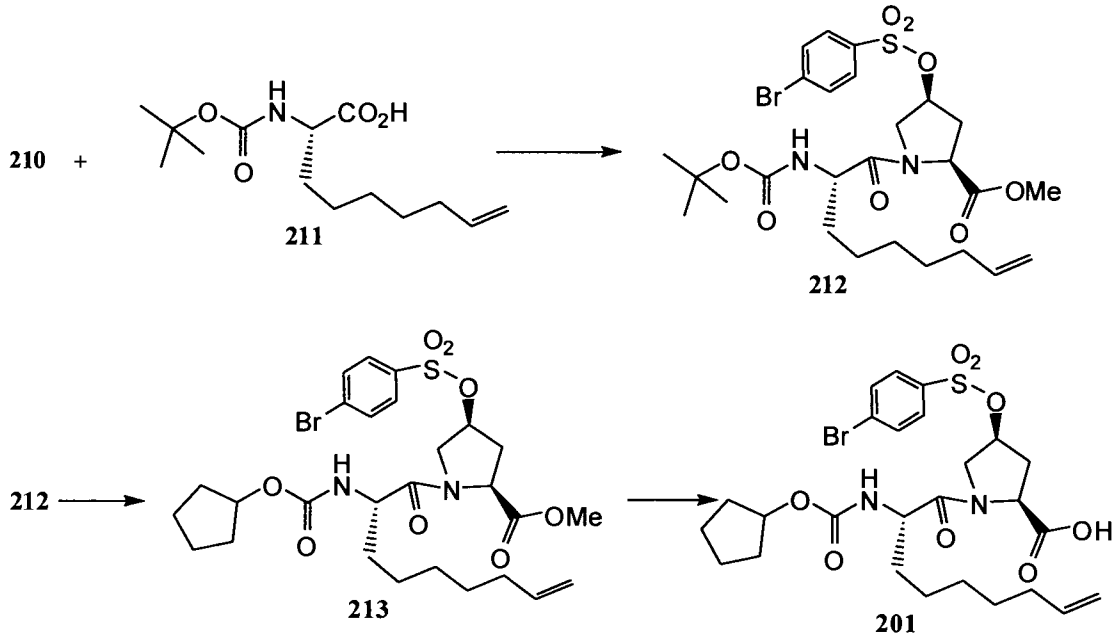


206

The brosylate macrocycle **205** (6.49 g, 7.67 mmol) was dissolved in N-methylpyrrolidinone (25.0 mL) and 8-chloro-2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-ol **207** (2.564 g, 7.33 mmol) followed by Cs_2CO_3 (4.40 g, 13.50 mmol) were added. The mixture was heated to 65°C for 6 h then diluted with ethylacetate (200 mL) and washed with LiCl (5%, 250 mL). The aqueous layer was extracted with ethylacetate (100 mL x 2) and the combined organic layers were washed with brine (150 mL), dried over $Na_2SO_4/MgSO_4$, and concentrated *in vacuo*. The crude residue was purified via silica-gel chromatography (ethylacetate-methanol) affording 4.39 g of aminothiazole **206** in 58% yield. LCMS (M + 1): 985.28.

Intermediate Compound **201** can be prepared as follows.





e. Preparation of compound **209**.

Compound **208** (7.00 g, 28.55 mmol) and DABCO (5.13 g,45.94 mmol) were dissolved in toluene (30 mL). A toluene (11 mL) solution of brosylchloride (10.22 g, 40.01 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was diluted with EtOAc (210 mL) and 0.5N HCl (200 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (200 mL), dried with Na_2S0_4, filtered, and concentrated. The crude product was purified by combi-flash to give 12.23 g of compound **209** in 92% yield.

f. Preparation of compounds **210** and **212**.

Compound **209** (12.2 g, 26.3 mmol) was treated with 4 N HCl / 1,4-dioxane (60 mL) and stirred for 1 hour. The reaction mixture was concentrated and dried under vacuum for 20 minutes. The crude amine HCl salt of compound **210** was dissolved in DMF (150 mL) and acid **211** (14.2 g, 52.6 mmol) was added. HATU (20.0 g, 52.6 mmol) and NMM (13.5 g, 131.5 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction was diluted with EtOAc (300 mL), washed with 1 N HCl (200 mL), saturated $NaHCO_3$, brine, dried with Na_2SO_4, and concentrated. The crude product was purified by combi-flash to give 15.1 g of compound **212** in 93% yield.

g. Preparation of compound **213**.

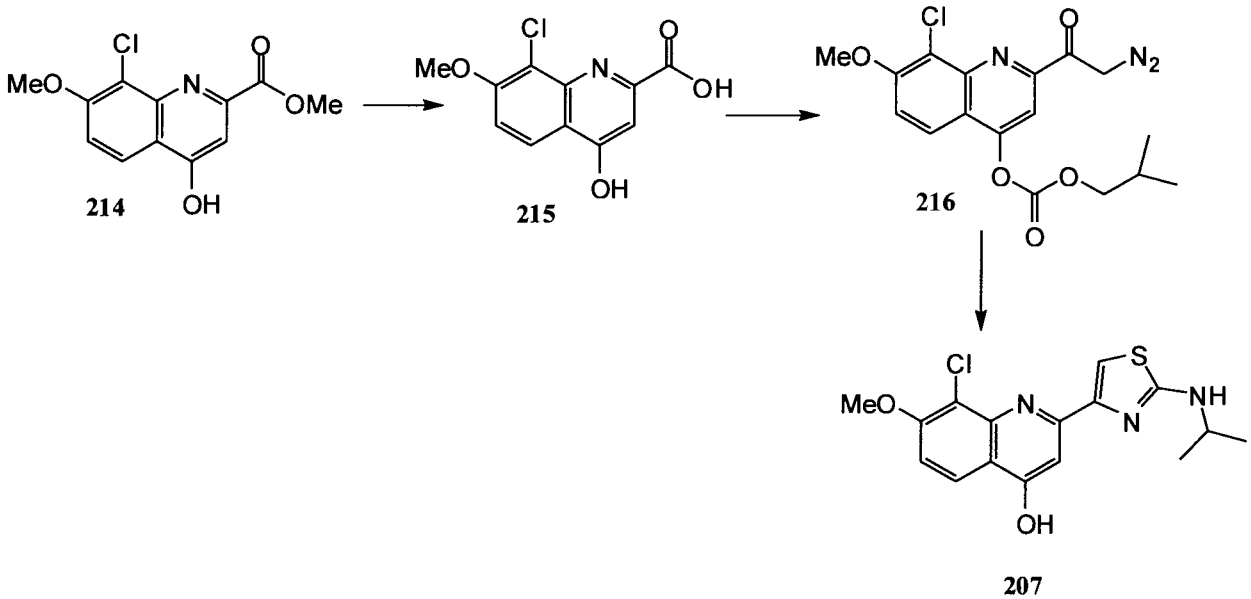
To a solution of **212** (12.8 g, 20.7 mmol) in CH_2Cl_2 (50 mL) was added 4 N HCl in 1,4-dioxane (50 mL, 200 mmol). The reaction mixture was stirred at room temperature for 2 hours, concentrated, dried under vacuum for 20 minutes, and then dissolved in CH_3CN (50 mL).

Saturated $NaHCO_3$ in H_20 (50 mL) was added and stirred for 5 minutes. Freshly prepared cyclopentylchloroformate in THF (50mL) was added. The reaction was complete within 1 h. The solvent was removed under reduced pressure and the residue was diluted with EtOAc. The mixture was brought to pH = 2 with 1 N HCl and the two layers were separated. The organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated to give crude compound **213** (3.18 g).

h. Preparation of compound **201**.

The crude ester **213** (3.18 g, 5.07 mmol) was dissolved in THF (25 mL), H_2O (25 mL), and then MeOH (6 mL) and LiOH (660 mg, 25.4 mmol) was added. The reaction mixture was stirred at room temperature for 1h and diluted with EtOAc. The reaction mixture was acidified to pH 2 with 1 N HCl and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x). The combined organic layers were washed with brine, dried with Na_2SO_4 concentrated and dried under vacuum to give 3.09 g of acid **201**.

Intermediate 8-chloro-2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-ol **207** can be prepared as follows.



i. Preparation of 8-chloro-4-hydroxy-7-methoxyquinoline-2-carboxylic acid **215**.

To a solution of methyl 8-chloro-4-hydroxy-7-methoxyquinoline-2-carboxylate **214** (36.5g, 0.145 mol) in a mixture of 1:1 of MeOH: THF (160 mL total) was added a solution of LiOH (30.5 g, 0.725 mol) in H_20 (80 mL). The mixture was stirred at room temperature for an hour when LCMS analysis showed complete conversion to the carboxylic acid. The reaction was worked up by removal of the volatiles and adjusting the pH of the solution to 6 using

aqueous 6N HCl. The resulted gummy residue was filtered and dried on the lyophilizer for 2 days to provide 34.4 g (99.6 %) of compound **215** as a white solid. EI MS *(m/z)* 253.9 [M+H].

j. Preparation of 2-(2-diazo-l-oxo)-8-chloro-7-methoxyquinolin-4-yl isobutyl carbonate **216**.

To a solution of 8-chloro-4-hydroxy-7-methoxyquinoline-2-carboxylic acid **215** (10.2 g, 0.04 mol) in THF (400 mL) was added triethyl amine (12.3 mL, 0.088 mol) and *i*-Butylchloroformate (11.6 mL, 0.088 mol) at 0°C under an argon atmosphere. The mixture was stirred at 0°C for 1 hour when LCMS analysis demonstrated completion of the reaction to provide the desired mixed anhydride. EI MS *(m/z)* 454.0 [M+H]. To the reaction mixture of the anhydride was added a 1M solution of diazomethane (121 mL, 0.121 mol) in diethyl ether via a plastic funnel at 0°C. This mixture was allowed to stir while warming up to room temperature for additional 2 hours. Analysis of the mixture by LCMS demonstrated completion of the reaction. The septum was removed and the reaction was stirred for additional 20 minutes before removal of the solvent. The residue was dried further under high vacuum to provide compound **216**, which was carried on to the next step. EI MS *(m/z)* 377.9 [M+H].

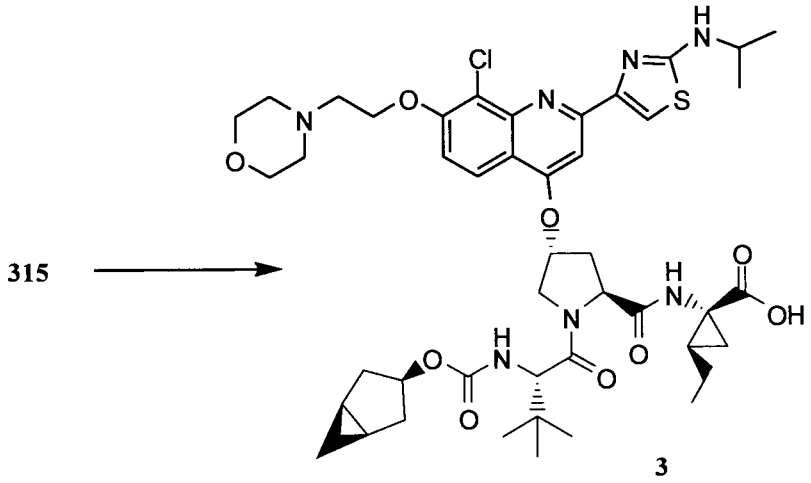
k. Preparation of 8-chloro-2-(2-(isopropylamino)thiazol-4-yl)-7-methoxyquinoiin-4-ol **207**.

To a cooled solution of 2-(2-diazo-l-oxo)-8-chloro-7-methoxyquinolin-4-yl isobutyl carbonate **216** (15.2 g, 0.040 mol) at 0°C in THF (268 mL) was added 48% HBr (23 mL, 0.201 mol) slowly over 15 minutes. The solution was stirred at 0°C for an additional 40 minutes when LCMS analysis demonstrated complete reaction. The reaction was worked up by addition of aqueous 1N NaOH (180 mL) at 0° C to adjust the pH of the aqueous layer to 9. The layers were separated and the aqueous layer was washed with EtOAc (2 x 200 mL). Combined organic extracts were washed with brine and dried over MgS04. The solvent was removed *in vacuo* to provide 17.7 g of a yellow solid. EI MS *(m/z)* 4^{31}.9 [M+H].

The solution of the bromoketone obtained from the previous reaction was suspended in i-propanol (270 mL) and isopropylisourea (9.4 g, 0.080 mol). The reaction mixture was heated at 72 °C for 32 hours. LCMS analysis of the reaction demonstrated complete conversion to the desired product. The reaction was allowed to cool to room temperature to allow for the product to precipitate out of the solution. The reaction was further cooled to 0°C for 12 hours before filtration. The filtrate was washed with ether and dried on lyopholizer to provide 8.03 g of compound **207** as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J*= 9 Hz, 1H), 7.74 (s, 1H), 7.44 (d, *J*= 10Hz), 1H), 7.07 (s, 1H), 4.05 (s, 3H), 3.92 (pentet, *J*=6 Hz, 1H), 1.25 (d, *J*= 7 Hz, 6H): EI MS *(m/z)* 350.0 [M+H].

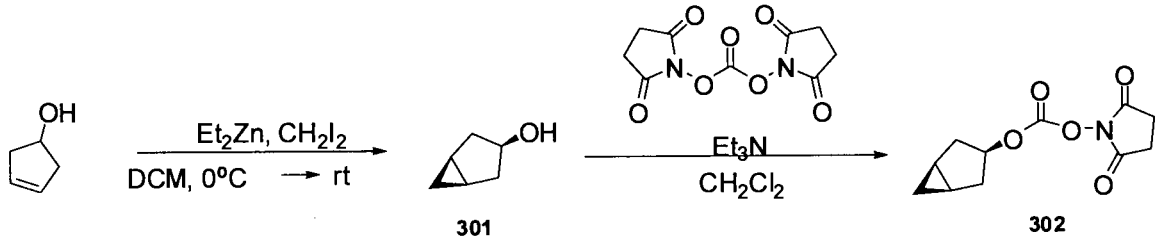
Compound **3** can be prepared using synthetic methods and intermediates like those described in USSN 12/215,605 (US 20090257978 A1). Compound **3** can also be prepared as described in the following Example.

Example 3: Preparation of Compound **3**



Compound **315** (12 g, 13 mmol) was dissolved in THF (200 ml), LiOH (11g, 260 mmol) in H_2O (200 ml) was added, followed by MeOH (200 ml). The mixture was kept stirring at room temperature for 20 hours. Upon completion of the reaction, 4 N HCl in H_2O was added to adjust pH to 7 at 0 °C. The mixture was extracted with EtOAc (2 x 400 ml). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give compound **3** as a yellow solid (11 g, 93%). LC/MS = 911.52(M^++1). ^{1}H NMR (300MHz, CD_3OD) δ 7.95 (d, 1H), 7.90 (s, 1H), 7.48 (s, 1H), 7.31 (d, 1H), 5.42 (s, 1H), 4.37 (dd, 1H), 4.20 (m, 2H), 3.83-3.56 (m, 7H), 3.50 (m, 2H), 3.39 (m, 2H), 2.45 (m, 1H), 2.27(m, 1H), 1.62 (m, 2H), 1.50 (m, 1H), 1.33 (m, 2H), 1.18 (m, 1H), 1.05 (m, 8H), 0.90 (m, 3H), 0.76 (m, 11H), 0.14-0.04 (m, 2H)

The intermediate compound **315** was prepared as follows.



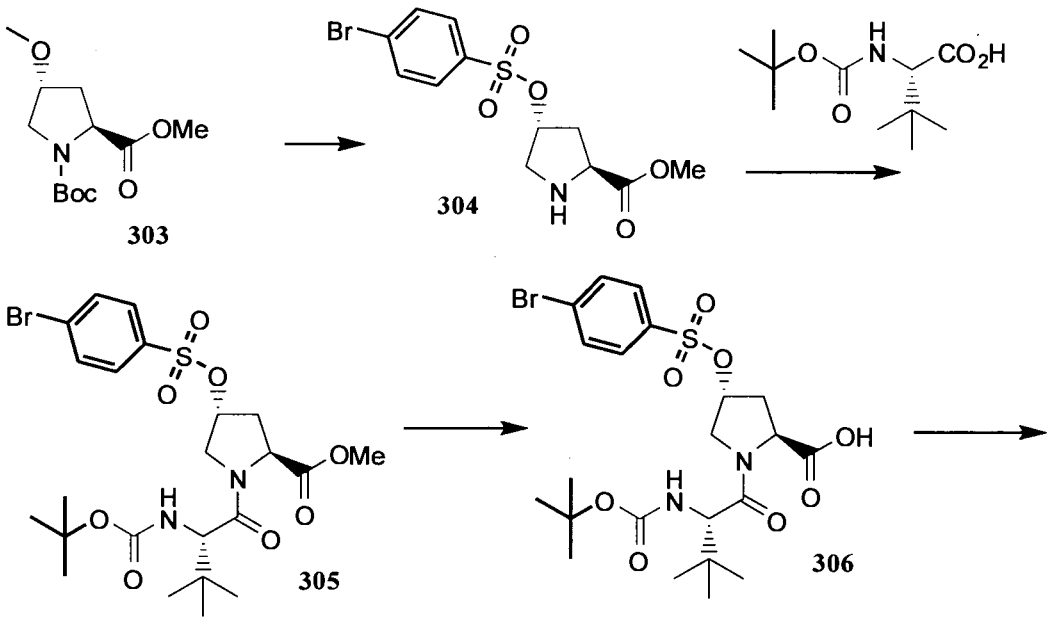
a. Preparation of compound **301**.

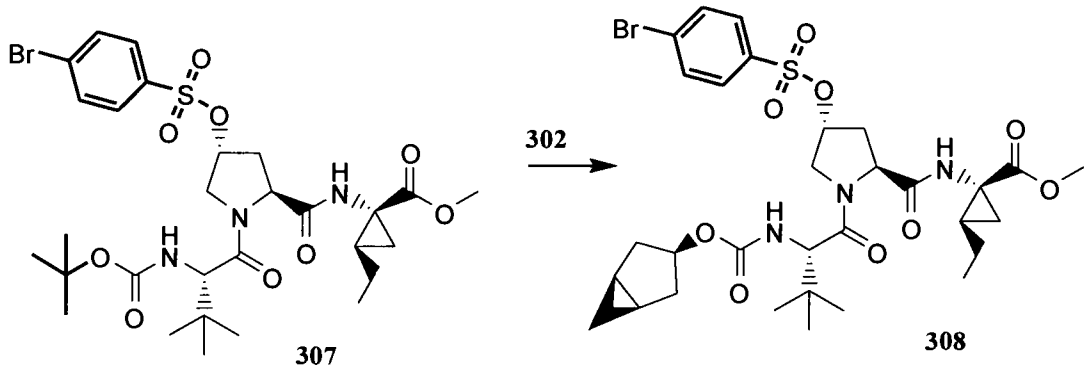
To a dry, argon purged three-neck round bottom flask (1000 mL) were added anhydrous dichloromethane (100 mL) and Et_2Zn (28 mL, 273 mmol) at 0 °C. (CAUTION: Source of argon can not be from needle. Use appropriate glass adapter only. A second bubbler can also be

attached to the flask to prevent excessive pressure build up.) Cyclopenten-3-ol (10.0 mL, 119 mmol) was then added dropwise (large quantity of ethane gas was produced) to the flask and the reaction mixture was allowed to stir until the evolution of gas had ceased. Diiodomethane (22 mL, 242 mmol) was then added dropwise over a period of 30 minutes. The reaction was allowed to warm to room temperature and continued to stir overnight under a positive flow of argon, at which point TLC analysis had indicated complete disappearance of the starting alcohol. The reaction was then diluted with CH_2Cl_2 and quenched with 2M HCl (white precipitate should be completely dissolved). The biphasic mixture was poured into a separatory funnel and the organic layer was collected. The solvent was removed under reduced pressure until 100 mL of material containing compound **301** remained.

b. Preparation of compound **302**.

Anhydrous dichloromethane (525 mL) was added to the flask followed by the dropwise addition of triethylamine (34 mL, 245 mmol). The reaction continued to stir at room temperature under a positive flow of nitrogen at which point, disuccinimidylcarbonate (40.7 g, 159 mmol) was added to the flask portion wise. The reaction was allowed to stir until TLC analysis indicated complete disappearance of the starting material (2-3 days). Upon completion, the reaction mixture was quenched with 1M HCl (200 mL x 2) and washed with H_20 (200 mL x 2). The desired material was extracted using CH_2Cl_2 and the combined organic layers were dried using anhydrous $MgSO_4$ and passed through a silica plug. The solvent was removed under reduced pressure and the crude material was purified using flash chromatography (R_f = 0.33, 1:1 Hex/EtOAc) to provide compound **302** (22 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5. 24 (t, 1H), 3.82 (s, 4H), 2.24 (m, 2H), 2.03 (d, 2H), 1.38 (m, 2H), 0.48 (m, 1H), 0.40 (m, 1H).





c. Preparation of compound **304**.

N-*t*-Boc-cis-4-Hydroxy-L-Proline methyl ester **303** (100.0 g, 407.7 mmol) and DABCO (1.5eq, 68.6g, 611.6 mmol) were dissolved in anhydrous toluene (200 mL) in a 2 L three necked round bottom flask with a mechanical stirrer and an addition funnel. After cooling the solution to 0 °C under N_2, A solution of 4-Bromo-benzenesulfonyl chloride (1.3eq, 135.6g, 530.0 mmol) in 300 mL of toluene was added through addition funnel over 60 minutes. The reaction mixture was stirred and warmed to room temperature overnight (16 hours). The mixture was slowly poured into 2L 1M Na_2CO_3 (aq.), and the product was extracted with EtOAc (2L). After the organic phase was washed by 0.5 N HCl (2L), H_2O (1L), and brine (1L), it was dried ($MgSO_4$), concentrated to give 195.45 g of a yellow oily brosylate product.

To a solution of the above brosylate (407.7 mmol) in dichloromethane (300 mL) was slowly added 4.0 M HCl in dioxane (500 mL, 5eq) and the resulting solution was allowed to stir at room temperature for 2 hours. After ether (500mL) was added to the reaction mixture, the mixture was stirred for 15 minutes and the white precipitate was collected by filtration. The solid was washed with ether and hexane and then dried under vacuum overnight to obtain 153.0 g of the HCl amine salt of compound **304**, 381.8 mmol, in 94% yield for two steps.

d. Preparation of compound **305**.

To a solution of Boc-*tert*-butyl-glycine (97.0g, 420.0 mmol) in DMF (200mL) and methylene chloride (200mL) were added HATU (217.76g, 572.7 mmol) and Hunig's base (126 mL, 1145.4 mmol) at room temperature. After the mixture was stirred for 20 minutes at room temperature, a solution of the previous HCl salt (153.0 g, 381.8 mmol) and Hunig's base (126 mL, 1145.4 mmol) in DMF (200mL) and dichloromethane (200mL) was added to the above acid mixture in one portion. The reaction mixture was stirred at room temperature for 3h, with monitoring by LCMS. The reaction mixture was concentrated to remove dichloromethane under reduced pressure and the white solid that formed was filtered off. The remaining DMF solution was diluted with ethyl acetate (1L), washed successively with 3% LiCl (aq) (3x650mL), sat'd NH_4Cl (2x500mL), 0.5N HCl (aq) (2x600mL), brine (500mL), sat'd $NaHCO_3$ (3x500mL),

and brine (500mL). The resulting organic fraction was dried ($MgSO_4$) and concentrated to afford compound **305** (111g).

e. Preparation of compound **306**.

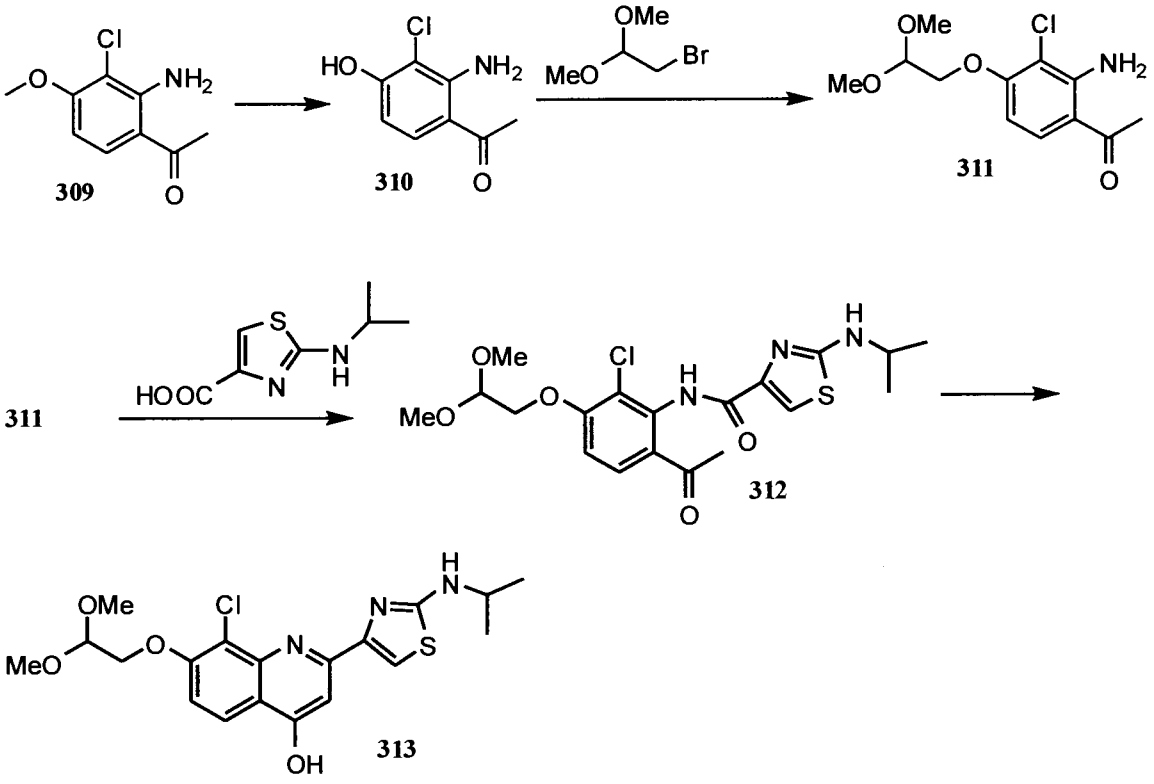
To a solution of the methyl ester **305** (120 g, 207.8 mmol) in THF (300 mL), MeOH (75 mL) was added a solution of LiOH (26.18 g, 623.4 mmol) in H_2O (150 mL). The solution was allowed to stir at room temperature for 4 hours. The mixture was cooled in an ice-bath while acidifying with 3N HCl to pH about 5.5, stirred for 10minutes, and the resulting white solids were collected by filtration. The solids were washed with more water, ether and hexane. The solids were dried under vacuum at 40°C overnight to give 95.78g (82%) of the acid **306**.

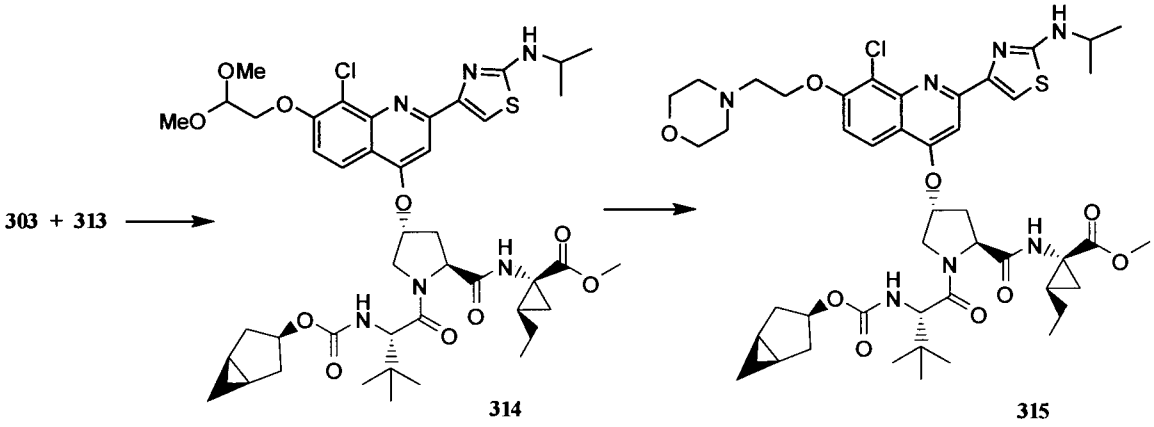
f. Preparation of compound **307**.

To a solution of the carboxylic acid **306** (81.4 g, 144.27 mmol) in DMF (200mL) and dichloromethane (200mL) was added HATU (82.3g, 216.4 mmol) and Hunig's base (47.5 mL, 432.8 mmol) at room temperature. After the mixture was stirred for 20 minutes at room temperature, a solution of amine (158.7 mmol) and Hunig's base (47.5 mL, 1145.4 mmol) in DMF (200mL) and dichloromethane (200mL) was added to the above acid mixture in one portion. The reaction mixture was stirred at room temperature for 3 hours and monitored by LCMS. After the mixture was concentrated under reduced pressure to remove dichloromethane, the white solids that formed were filtered off. The remaining DMF solution was diluted with ethyl acetate (600mL) and successively washed with 3% LiCl (aq) (2x550mL), sat'd NH_4Cl (500mL), 1N HCl (aq) (500mL), sat'd $NaHCO_3$ (500mL), and brine (300mL). The resulting organic fraction was dried (Na_2SO_4) and concentrated to afford compound **307** (111g).

g. Preparation of compound **308**.

Compound **307** was dissolved in 4N HCl in dioxane (300 mL) at room temperature and stirred for 2 hours. It was then concentrated under vacuum, and co-evaporated with dichloromethane (2 x 200mL) to dryness. The residue was dissolved in EtOAc (600mL) and sat'd aq. $NaHCO_3$ (1L). It was stirred vigorously. After 10 minutes, carbonic acid bicyclo[3.1.0]hex-3-yl ester 2,5-dioxo-pyrrolidin-1-yl ester **302** (41.4 g, 173.1 mmol) was added in one portion. After the resulting mixture was stirred for another 30 minutes, the organic layer was collected and washed with brine (500mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography on silica gel with ethyl acetate/hexane to afford 94.44 g (92%) of compound **308**.





h. Preparation of compound **310**.

1-(2-Amino-3-chloro-4-hydroxy-phenyl)-ethanone **309** (70.7 g, 354 mmol) was stirred in 48% aq. HBr (500 mL) at 110 °C for 72 hours. After the mixture was cooled to 0 °C with stirring, the solids were filtered and washed with water. The resulting solids were triturated with a saturated $NaHCO_3$ solution (~350 mL), filtered, washed with water, and dried under vacuum to give ~ 40 g (61%) of crude **310** as a dark brown solid. LC/MS = 186 (M^++1).

i. Preparation of compound **311**.

1-(2-Amino-3-chloro-4-hydroxy-phenyl)-ethanone **310** (40 g, 215 mmol) was dissolved in DMF (360 ml). Cesium carbonate (140 g, 430 mmol) was added, followed by

bromoacetaldehyde dimethyl acetal (54.5 g, 323 mmol). The mixture was then vigorously stirred at 65 °C for 24 hours. Upon cooling to room temperature, EtOAc (1 L) and H_2O (1 L) were added to the mixture. The organic layer was extracted with EtOAc (1 x 400 ml). The combined organic layer was washed with aqueous 3% LiCl solution (2 x 1L), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give compound **311** as a white solid (39 g, 67%).

j. Preparation of compound **312**.

To a mixture of 1-[2-Amino-3-chloro-4-(2,2-dimethoxy-ethoxy)-phenyl]-ethanone **311** (13 g, 47.5 mmol) and isopropylaminothiazole-4-carboxylic acid hydrobromide (12.64 g, 47.5 mmol) in pyridine (150 ml) was slowly added phosphorus oxychloride (9.47 g, 61.8 mmol) at -40 °C. The mixture was then stirred at 0 °C for 4 hours. Upon completion of the reaction, H_2O (30 ml) was added dropwise to the mixture. The mixture was then stirred at 0 °C for another 15 minutes. The mixture was concentrated *in vacuo*. The residue was diluted with EtOAc, washed with a sat. $NaHCO_3$ aqueous solution. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, hexanes were added slowly to the solution, and a yellow solid started to crash out. More hexanes were added until not much product was left in the mother liquid to provide compound **312** (18 g, 85%).

k. Preparation of compound **313**.

2-Isopropylamino-thiazole-4-carboxylic acid [6-acetyl-2-chloro-3-(2,2-dimethoxy-ethoxy)-phenyl]-amide **312** (18 g, 40.7 mmol) was suspended in toluene (400 ml). NaH (2.4 g, 61 mmol) was added to the vigorously stirred mixture while monitoring H_2 evolution. The mixture became a clear solution during heating to reflux. The reaction was complete after refluxing for 3 hours. The mixture was cooled to room temperature. A solution of AcOH (69.2 mmol) in H_2O (3 vol) was added to the mixture. After vigorous agitation for 1 hour at 0 °C, the solids were collected by filtration, rinsed forward with H_2O. The wet cake was dried under high vacuum to a constant weight to provide compound **313** (15 g, 86%).

l. Preparation of compound **314**.

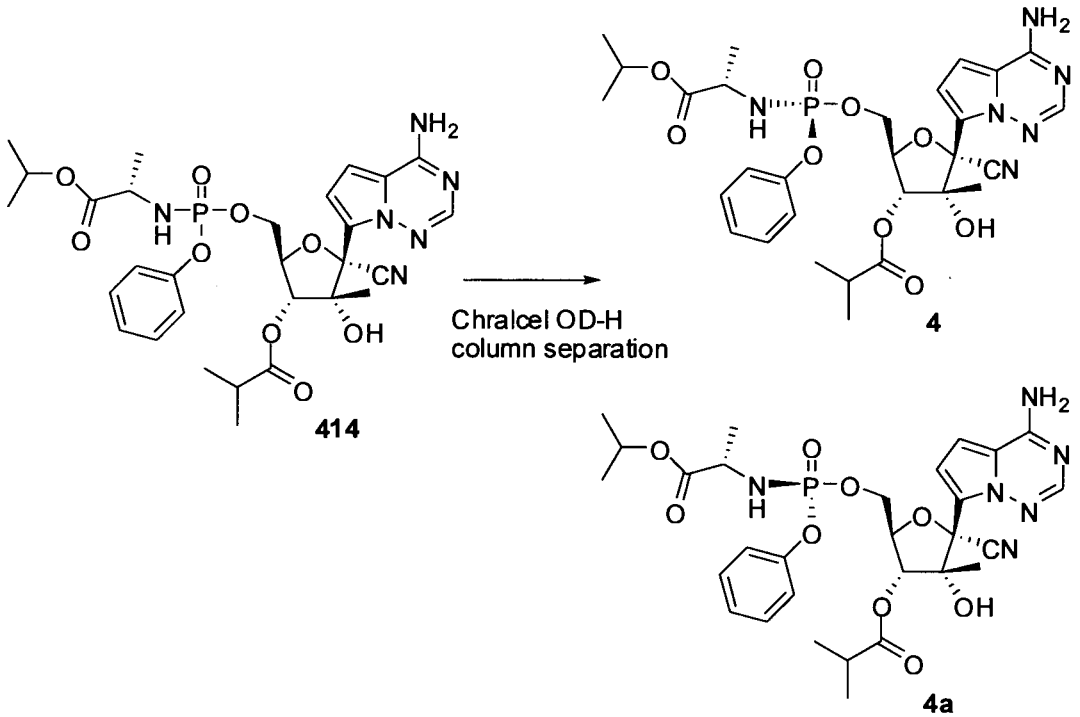
To a mixture of brosylate intermediate **303** (15 g, 35 mmol) and compound **313** (27.5 g, 38.5 mmol) in NMP (200 ml) was added cesium carbonate (25.1 g, 77 mmol). The mixture was stirred at 65 °C for 5 hours. The reaction was cooled to room temperature and EtOAc (600 ml) and an aqueous solution of 3% LiCl (600 ml) were added to the mixture. The organic layer was washed with aqueous 3% LiCl (1 x 600 ml), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the desired methyl ester as a yellow solid (23.6 g, 75%). LC/MS = 900.13(M^++1).

m. Preparation of compound **315**.

Methyl ester **314** (23.6 g, 26 mmol) was dissolved in glacial acetic acid (200 ml), 1.4 N HCl in H_2O (75 ml) was added to the solution. The mixture was stirred at 60 °C for 1 hour. Upon completion of the reaction, the mixture was concentrated to remove the solvents, coevaporated with toluene (x 2) to remove residual acetic acid. The residue was then dissolved in EtOAc (500 ml) and sat. $NaHCO_3$ aqueous solution (enough to neutralize the mixture) while monitoring CO_2 evolution. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was further dried under high vacuum for 1 h and used as is for the next step. The crude was dissolved in CH_2Cl_2 (360 ml), morpholine (3.4 g, 39 mmol) and sodium triacetoxyborohydride (7.2 g, 34 mmol) were added to the mixture at 0 °C. Then glacial acetic acid (0.47 g, 7.8 mmol) was added dropwise to the mixture. The reaction was complete in 10 minutes at 0 °C. Sat. $NaHCO_3$ aqueous solution was added to quench the reaction. After stirring for another 20 minutes, the organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the desired amine product **315** as a yellow solid (12 g, 50%). LC/MS = 924.63(M^++1).

Compound **4** can be prepared as described in the following Example.

Example 4: Preparation of Compound **4**.



Diastereomeric mixture **414** was dissolved in heptane and isopropanol (70%:30%, 230 mg in 4.5 mL of the mixed solvents) and subjected to chiral column separation under the following conditions:

Column: Chiralcel OD-H, 2 x 25 cm

Solvent system: 70% heptane and 30% isopropanol

Flow rate: 6 mL/min.

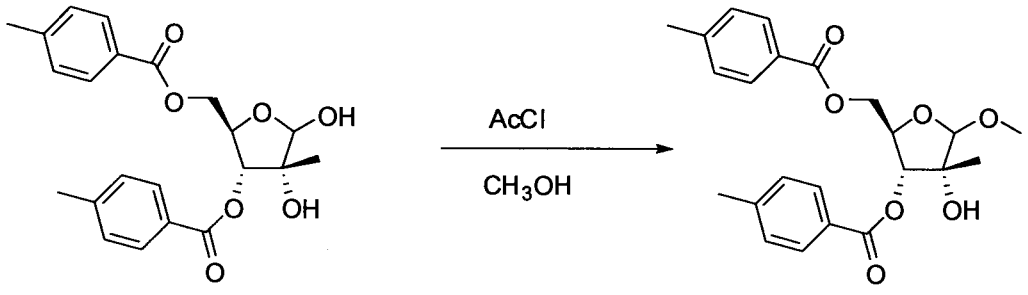
Loading volume per run: 2.5 mL

Compound 4 had a retention time of 20 minutes. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.1-7.3 (m, 5H), 6.83 (d, 1H), 6.71 (d, 1H), 6.09 (brs, 2H), 5.95 (s, 1H), 5.04 (m, 2H), 4.67 (q, 1H), 4.35-4.52 (m, 2H), 4.00 (m, 2H), 2.74 (m, 1H), 1.40 (d, 3H), 1.2-1.3 (12H), 0.98 (s, 3H). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 2.72 (s). Compound 4 was subsequently recrystallized from MTBE for x-ray quality crystals.

Compound **4a** had a retention time 50 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.1-7.3 (m, 5H), 6.83 (d, 1H), 6.73 (d, 1H), 6.02 (brs, 2H), 5.95 (s, 1H), 5.08 (d, 1H), 5.00 (m, 1H), 4.68 (q, 1H), 4.38-4.56 (m, 2H), 3.98 (m, 2H), 2.74 (m, 1H), 1.40 (d, 3H), 1.2-1.3 (12H), 0.99 (s, 3H). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 2.61 (s).

The intermediate diastereomeric mixture **414** was prepared as follows.

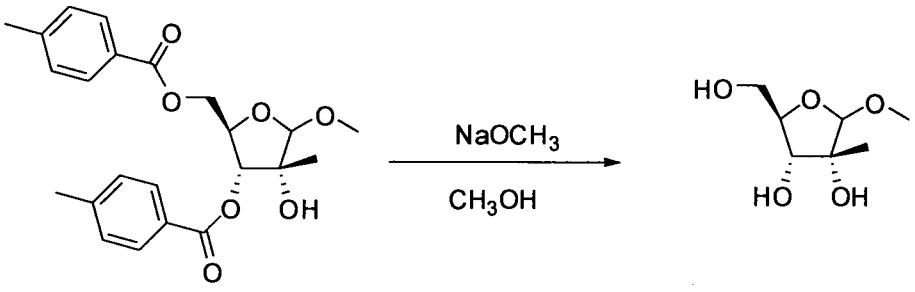
a. Preparation of Compound **402**.



401 **402**

To a solution of compound **401** (22.0 g, 54.9 mmol, prepared according to the procedures described in *J.O.C.*, 2004, 6257) in methanol (300 mL) was dropwise added acetyl chloride (22 mL) at 0 °C using a dropping funnel over a period of 30 minutes and then stirred at room temperature for 16 hours. The mixture was concentrated, re-dissolved in ethyl acetate (400 mL), washed with ice-cold 2 N NaOH, and concentrated to dryness, affording the crude methyl ether **402** as an oil. MS = 437.2 ($M + Na^+$).

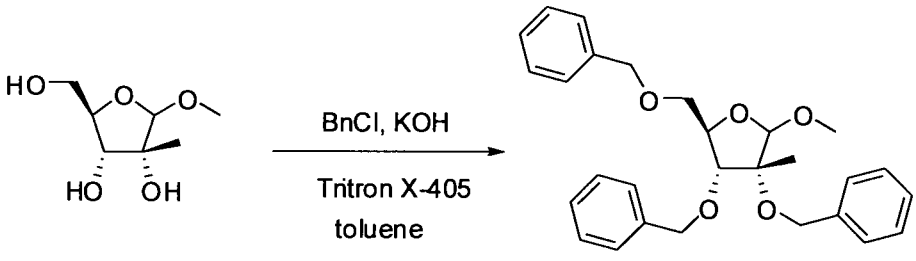
b. Preparation of Compound **403**.



402 **403**

To a solution of compound **402** in methanol (300 mL) was added 0.5 M sodium methoxide solution in methanol (20 mL, 10 mmol), and stirred for 16 hours at room temperature. The reaction was quenched with 4.0 N HCl solution in dioxane (2.5 mL, 10 mmol). The mixture was then concentrated, affording the crude compound **403**. MS = 201.0 ($M + Na^+$).

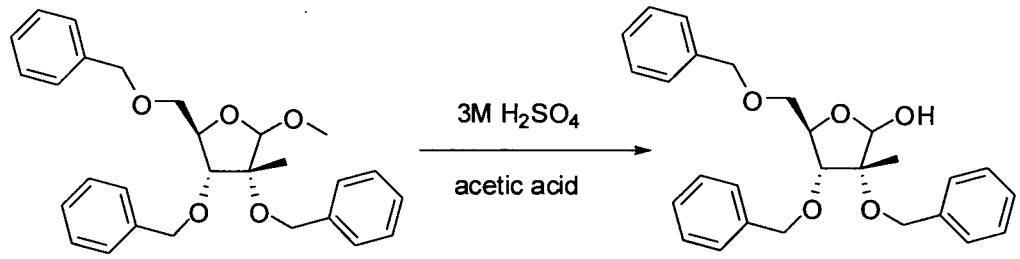
c. Preparation of Compound **404**.



403 **404**

A mixture of compound **403**, Tritron X-405 (70% in water, 6.0 g), 50% KOH (in water, 85 g) in toluene (500 mL) was heated to reflux with a Dean-Stark trap attached. After 1 hour collecting 25 mL of water, benzyl chloride (33 g, 260 mmol) was added and continued to reflux with stirring for 16 hours. The mixture was then cooled and partitioned between ethyl acetate (400 mL) and water (300mL). The organic layer was washed with water (300 mL), and concentrated. The residue was purified by silica gel column chromatography (20% EtOAc / hexanes), affording the methyl ether **404** as an oil (22.0 g, 89% in three steps). ^1H NMR (300 MHz, $CDCl_3$): δ 7.3 (m, 15H), 4.5 - 4.9 (m, 7H), 4.37 (m, 1H), 3.87 (d, 1H), 3.56 (m, 2H), 3.52 (s, 3H), 1.40 (s, 3H).

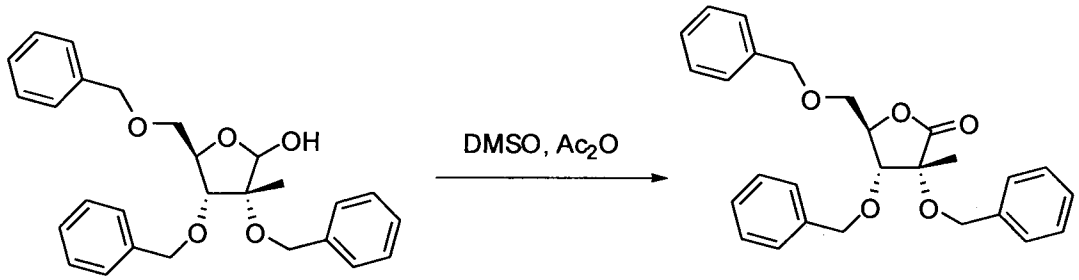
d. Preparation of Compound **405**.



404 **405**

To a solution of **404** (22.0 g, 49.0 mmol) in acetic acid (110 mL) was added 3 M sulfuric acid (prepared by mixing 4.8 g of concentrated sulfuric acid with 24 mL of water) and stirred at 70 °C for 8 hours. The mixture was concentrated to a volume of 20 mL, and partitioned between ethyl acetate and ice-cold 2N NaOH. The ethyl acetate layer was concentrated, and purified by silica gel column chromatography (~35% EtOAc / hexanes), affording compound **405** as an oil (17.0 g, 80%). MS = 457.2 ($M + Na^+$).

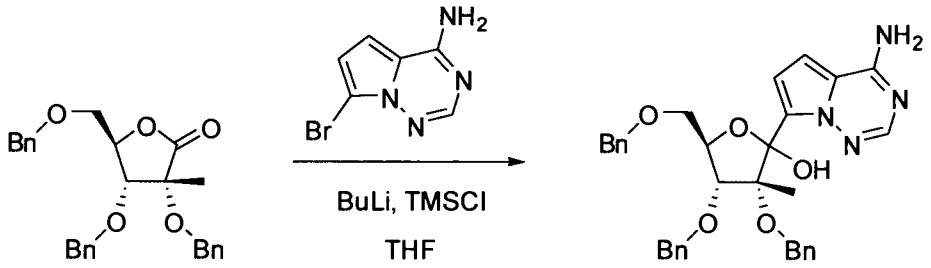
e. Preparation of Compound **406**.



405 **406**

To a solution of compound **405** (45 g, 104 mmol) in DMSO (135 mL) was dropwise added acetic anhydride (90 mL, 815 mmol) at room temperature under argon. The mixture was stirred for 16 hours at room temperature, and then poured into ice-water (1 L) while stirring. After ice was completely melted (30 minutes), ethyl acetate (500 mL) was added. The organic layer was separated. This extraction process was repeated three times (3x500 mL). The organic extracts were combined and concentrated. The residue was purified by silica gel column chromatography (20% EtOAc / hexanes), affording compound **406** as an oil (39 g, 88%). ^1H NMR (300 MHz, DMSO-d_6): δ 7.3 (m, 15H), 4.4 - 4.8 (m, 7H), 4.08 (d, J = 7.5 Hz, 1H), 3.75 (dd, J = 2,4, 11.4 Hz, 1H), 3.64 (dd, J = 5.4, 11.4 Hz, 1H), 1.51 (s, 3H).

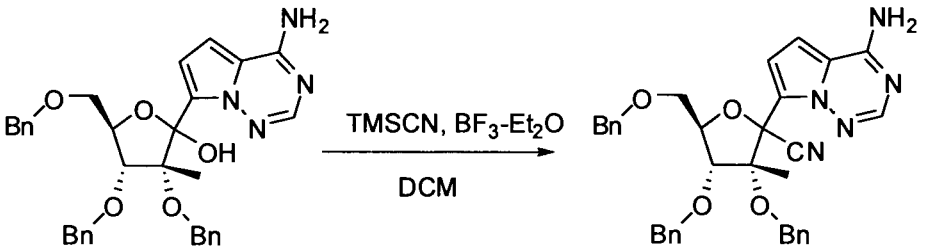
f. Preparation of Compound **407**.



406 **407**

To a dry, argon purged round bottom flask (100 mL) were added 7-bromo-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine (234 mg, 1.10 mmol) (prepared according to WO2007056170) and anhydrous THF (1.5 mL). TMSCl (276 µL, 2.2 mmol) was then added and the reaction mixture stirred for 2 hours. The flask was placed into a dry ice/acetone bath (-78 °C) and BuLi (2.5 mL, 4.0 mmol, 1.6M in hexanes) was added dropwise. After 1 hour, a solution of compound 406 (432.5 mg, 1.0 mmol) in THF was cooled to 0 °C and then added to the reaction flask dropwise. After 1 hour of stirring at -78 °C, the flask was warmed to 0 °C and sat. NH_4Cl (5 mL) was added to quench the reaction. The organics were extracted using EtOAc (3 x 10 mL) and the combined organic layers were dried using $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified using flash chromatography (hexanes / EtOAc). 560 mg (90 %) of compound **407** was isolated as a mixture of two anomers. LC/MS = 567.2 (M + H^+). ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (m, 1H), 7.27 (m, 15H), 7.01 (m, 1H), 6.51 (m, 1H), 4.66 (m, 8H), 4.40 (m, 2H), 3.79 (m, 3H), 1.62 (s, 2'-CH_3 from the one anomer), 1.18 (s, 2'-CH_3 from the other anomer).

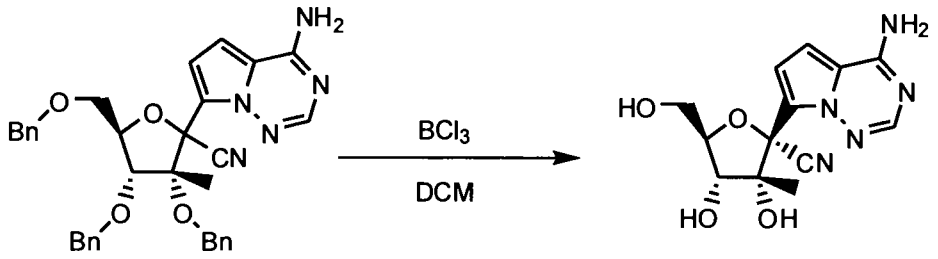
g. Preparation of Compound **408**.



407 **408**

To a solution of Compound **407** (1 g, 1.77 mmol) in CH_2Cl_2 (20 mL) at 0° C was added TMSCN (1.4 mL, 10.5 mmol) and BF_3-Et_2O (1 mL, 8.1 mmol). The reaction mixture was stirred at 0 °C for 0.5 hours, then at room temperature for additional 0.5 hour. The reaction was quenched with $NaHCO_3$ at 0 °C, and diluted with CH_3CO_2Et. The organic phase was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel, eluted with CH_3CO_2Et-hexanes (1:1 to 2:1), to give compound **408** (620 mg, 61%) as an isomeric mixture. MS = 576.1 (M + H^+).

h. Preparation of Compound **409**.

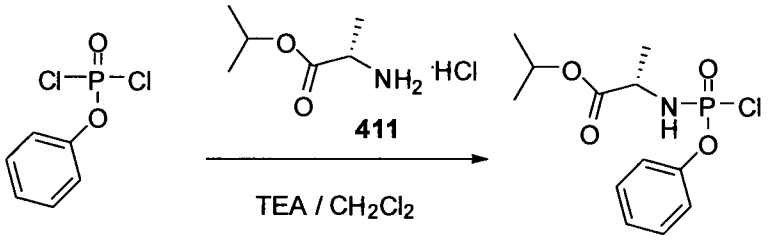


408 **409**

To a solution of compound **408** (150 mg, 0.26 mmol) in CH_2Cl_2 (4 mL) at -78 °C was added BCl_3 (2 mL, 1M in CH_2Cl_2). The reaction mixture was stirred at -78 °C for 1 hour. The reaction was quenched at -78 °C by dropwise addition of TEA (2 mL) and MeOH (5 mL). The mixture was allowed to warm up to room temperature, evaporated, and co-evaporated with MeOH several times. The residue was treated with $NaHCO_3$ (1 g in 10 mL H_2O), concentrated and purified by HPLC to give the desired product compound **409** (48 mg, 60%). ^1H NMR (300 MHz, D_2O): δ 7.74 (s 1H), 6.76 (d, J = 5 Hz, 1H), 6.73 (d, J = 5 Hz, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 3.8 (m, 2H), 0.84 (s, 3H). MS = 305.9 (M + H^+). The other alpha-anomer was also obtained (9 mg, 11%): ^1H NMR (300 MHz, D_2O): δ 7.70 (s 1H), 6.8 (d, J = 5 Hz, 1H), 6.7 (d, J =

5 Hz, 1H), 4.25 (d, J = 9 Hz, 1H), 4.07 (m, 1H), 3.85 (m, 1H), 3.7 (m, 1H), 1.6 (s, 3H). MS = 306.1 ($M + H^+$).

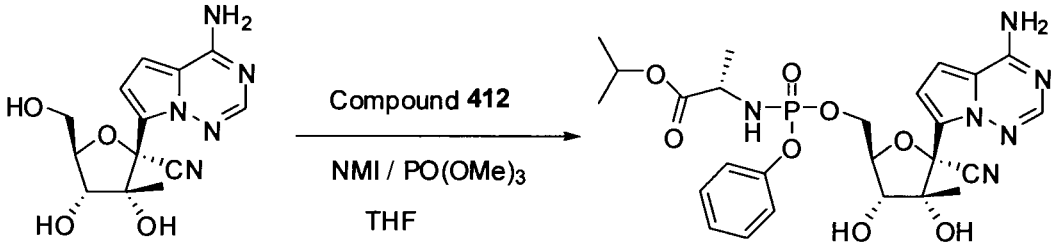
i. Preparation of Compound **412**.



410 **412**

Compound **410** (commercially available, 4.99 g, 23.8 mmol) was dissolved in dichloromethane (100 mL) and alanine isopropyl ester hydrochloride **411** (3.98 g, 23.8 mmol) was added. The resulting clear solution was cooled -78 °C for 30 min. Triethylamine (6.63 mL, 47.5 mmol) was added dropwise over 15 minutes. The mixture was then allowed to warm to room temperature. After 16 hours, the solvent was removed by argon stream. The residue was re-dissolved in MTBE (25 mL) and the insoluble was removed by filtration under argon. The filtrate was condensed by argon stream and the crude product **412** was used for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): 7.1-7.4 (m, 5H), 5.1 (m, 1H), 4.35 (m, 1H), 4.15 (m, 1H), 1.5 (d, 3H), 1.2 (m, 6H). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 7.8 and 8.4 (2s).

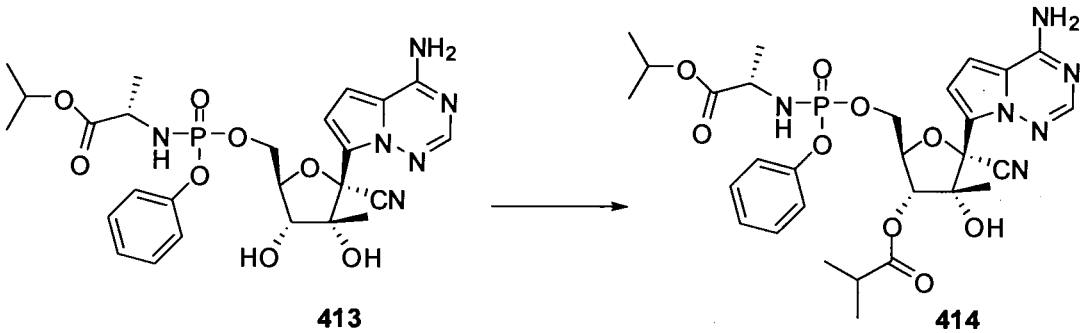
j. Preparation of Compound **413**.



409 **413**

To a solution of compound **409** (1.03 g, 3.37 mmol) in trimethyl phosphate (2.0 mL) and THF (20 mL) was added *N*-methyl imidazole (1.5 g, 18.3 mmol) at 0 °C. A solution of compound **412** (2.5 g, 8.18 mmol) in THF (3 mL) was dropwise added. The resulting mixture was allowed to warm to room temperature over 1.5 hours. The mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was concentrated and the residue was purified by silica gel chromatography (ethyl acetate to 10% ethanol / ethyl acetate), affording 1.15 g (59%) of compound **413** as 1:1 diastereomeric mixture at phosphorous. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.1-7.4 (m, 5H), 6.8 (2d, 1H), 6.7 (2d, 1H), 6.08 (brs, 2H), 5.03 (m, 1H), 4.6 (m, 1H), 4.4 (m, 2H), 3.9-4.1 (m, 3H), 1.31 (d, 3H), 1.2 (m, 6H), 0.83 (s, 3H). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 2.78 (s). MS = 575.1 ($M + H^+$).

k. Preparation of Compound **414**.



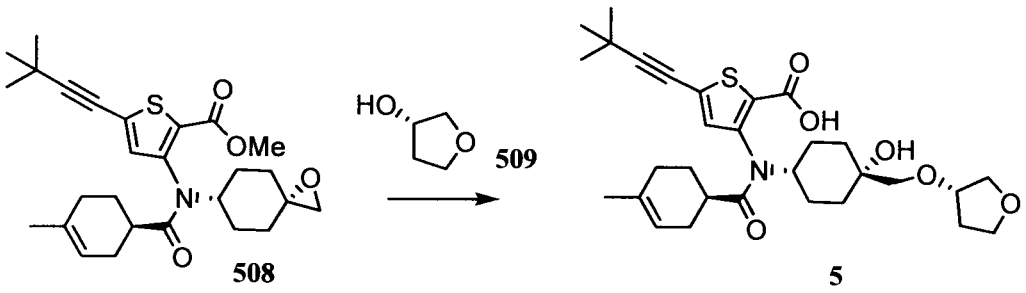
413 **414**

To a solution of compound **413** (175 mg, 0.305 mmol) in acetonitrile (2 mL) was added *N,N*-dimethylformamide dimethyl acetal (41 µL, 0.34 mmol, 1.1 eq.) and stirred at room temperature for 1 hour. The reaction was complete (by LCMS). The mixture was then concentrated to dryness. To the residue were added DCC (250 mg, 1.21 mmol, 4 eq.), acetonitrile (5 mL) and isobutyric acid (55 mg, 58 µL, 2 eq.). The mixture was stirred at room temperature for 48 hours. Water (0.2 mL) and trifluoroacetic acid (0.1 mL) were added at 0 °C and stirred at room temperature for 64 hours. Sodium bicarbonate (500 mg) was added at 0 °C. The mixture was stirred at room temperature for 0.5 hour and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (5% methanol /

dichloromethane), affording 144 mg (73%) of compound **414** as 1:1 diastereomeric mixture at phosphorus. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.1-7.4 (m, 5H), 6.83 (d, 1H), 6.71 (2d, 1H), 5.97 (brs, 2H), 5.94 (d, 1H), 5.07 (2d, 1H), 5.01 (m, 1H), 4.68 (m, 1H), 4.4 (m, 2H), 4.0 (m, 2H), 2.74 (m, 1H), 1.4 (2d, 3H), 1.2-1.3 (12H), 0.98 and 0.99 (2s, 3H). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 2.56 and 2.65 (2s). MS = 645.1 ($M + H^+$).

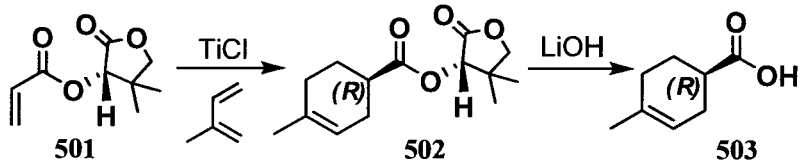
Compound **5** can be prepared as described in the following Example.

Example 5: Preparation of 5: 5-(3,3-dimethylbut-1-yn-1-yl)-3-[(*cis*-4-hydroxy-4-{[(3*S*)-tetrahydrofuran-3-yloxy]methyl}cyclohexyl){[(1*R*)-4-methylcyclohex-3-en-1-yl]carbonyl}amino]thiophene-2-carboxylic acid **5**.



5-(3,3-dimethyl-but-1-ynyl)-3-[((1R)-4-methyl-cyclohex-3-enecarbonyl)-(1-oxa-spiro[2.5]oct-6-yl)-amino]-thiophene-2-carboxylic acid methyl ester **508** (132 mg, 0.28 mmol) and (*S*)-tetrahydro-furan-3-ol **509** (247 mg, 2.8 mmol) in 1-methyl-pyrrolidin-2-one (3 mL) were treated with potassium *tert*-butoxide (251 mg, 2.24 mmol) , sealed at heated to 40 °C for 16 hours. After cooling the mixture was treated with 2 M HCl until pH 3, partitioned between ethyl acetate and water and separated. The organic layer was washed with 5% lithium chloride solution, water, brine, and dried over sodium sulfate. After filtration and concentration the residue was purified by HPLC with CH_3CN (0.1% TFA)/H_2O(0.1% TFA) to afford 107 mg (70% yield) of compound **5** as a white powder: MS (m/z): 544.0 [M+H]+; HPLC retention time 4.22 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

The intermediate compound **508** was prepared as follows.



a. Preparation of Compound **502**.

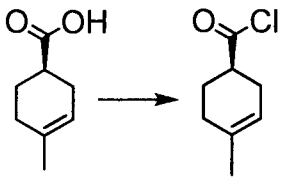
(S)-3-hydroxy-4,4-dimethyldihydrofuran-2(3H)-one (2.60 g, 20 mmol) and diisopropylethylamine (5.2 mL, 30 mmol) in dichloromethane (25 mL) was cooled to -10 °C and treated dropwise with acryloyl chloride (2.03 mL, 25 mmol) and stirred for 2 h. 1M HCl (20 mL) was added and the organic layer was washed with sodium bicarbonate and water. The organic layer was dried over sodium sulfate, filtered and concentrated. Flash chromatography (10-40% EtOAc, hexanes) afforded 2.09 g (57% yield) of the desired (S)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl acrylate **501** as a clear oil.

(S)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl acrylate **501** (2.05 g, 11.1 mmol) in dichloromethane (17.5 mL) and hexanes (2.5 mL) was cooled to -10 °C and treated with titanium tetrachloride (2.2 mL, 1 M in dichloromethane, 2.2 mmol). The yellow solution was stirred for 15 minutes and treated with isoprene (1.67 mL, 16.7 mmol) dropwise over 5 minutes. After stirring for 2 hours, an additional portion of isoprene (1.67 mL, 16.7 mmol) was added and the reaction mixture was stirred at -10 to 0 °C for 3.5 hours. The reaction mixture was quenched with ammonium chloride (sat. aq.). Water and ethyl acetate: hexanes (1:1) were added. The organic layer was separated and the aqueous layer was extracted again with ethyl acetate:hexanes (1:1). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (10-50% EtOAc:Hex, 80 g column) to afford 1.30 g (46% yield) of (R)-((S)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl) 4-methylcyclohex-3-enecarboxylate **502** as a clear oil.

b. Preparation of Compound **503**.

(R)-((S)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl) 4-methylcyclohex-3-enecarboxylate **502** (1.30 g, 5.15 mmol) in THF (10 mL), water (1 mL) and methanol (1 mL) was treated with lithium hydroxide monohydrate (2.16 g, 51.5 mmol) and warmed to 50 °C with stirring. After 1hour, the reaction mixture treated with 1M HCl. The mixture was extracted with hexanes:THF (10:1), dried over sodium sulfate, filtered and concentrated to 0.738 g (quantitative yield) of (R)-4-methylcyclohex-3-enecarboxylic acid **503** as a white powder.

c. Preparation of Compound **504**.

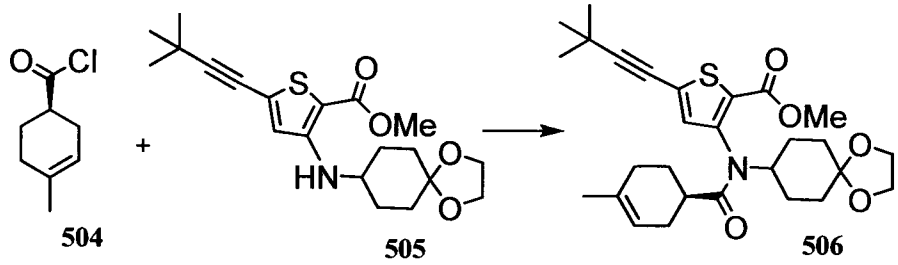


503 **504**

(R)-4-methylcyclohex-3-enecarboxylic acid **503** (371 mg, 2.65 mmol), azeotropically dried by evaporation from toluene, was treated with potassium phosphate tribasic (1.13 g, 7.94 mmol), suspended in dichloromethane (7.6 mL) and treated with dimethylformamide (4 drops).

The reaction mixture was cooled to 0 °C and treated dropwise with oxalyl chloride (0.75 mL, 7.9 mmol). The reaction mixture was allowed to warm to ambient temperature while stirring for 2 hours. After filtering the solids, the solution was concentrated, treated with hexanes and concentrated again to afford (R)-4-methylcyclohex-3-enecarbonyl chloride **504** as a light yellow oil which was used immediately in the next step.

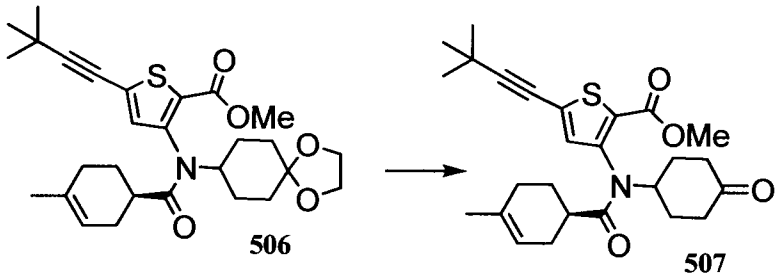
d. Preparation of Compound **506**.



504 505 506

(R)-4-methylcyclohex-3-enecarbonyl chloride **504** (2.65 mmol), 5-(3,3-dimethyl-but-1-ynyl)-3-(1,4-dioxa-spiro[4.5]dec-8-ylamino)-thiophene-2-carboxylic acid methyl ester **505** (250 mg, 0.66 mmol) and potassium phosphate tribasic (562 mg, 2.65 mmol) were suspended in dichloroethane (1.7 mL), sealed with a cap and heated to 90 °C. After 16 hours, the reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was separated and the aqueous extracted again with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Flash chromatography (10-40% EtOAc:Hexanes) afforded 220 mg (67% yield) of the desired 5-(3,3-dimethyl-but-1-ynyl)-3-[(1,4-dioxa-spiro[4.5]dec-8-yl)-((1*R*)-4-methyl-cyclohex-3-enecarbonyl)-amino]-thiophene-2-carboxylic acid methyl ester **506** as a beige foam.

e. Preparation of Compound **507**.

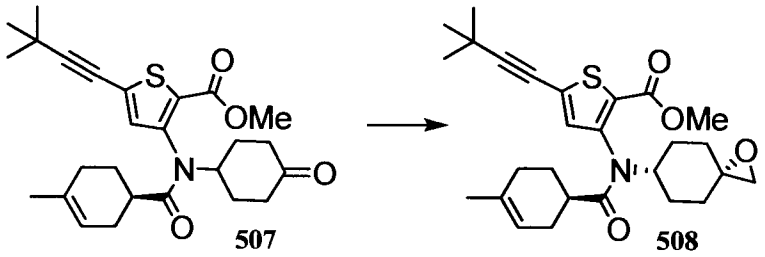


506 507

5-(3,3-Dimethyl-but-1-ynyl)-3-[(1,4-dioxa-spiro[4.5]dec-8-yl)-((1*R*)-4-methyl-cyclohex-3-enecarbonyl)-amino]-thiophene-2-carboxylic acid methyl ester **506** (219 mg, 0.438 mmol) was dissolved in THF (3.5 mL) and treated with 4M HCl (1.75 mL, 7.01 mmol). The reaction mixture was heated to 45 °C and stirred 2 h. Ethyl acetate was added and the organic layer was separated then washed with water, sodium bicarbonate (sat aq), water, and brine. The organic

layer was dried over sodium sulfate, filtered and concentrated to 0.190 g (95% yield) of the desired 5-(3,3-dimethyl-but-1-ynyl)-3-[((1*R*)-4-methyl-cyclohex-3-enecarbonyl)-(4-oxo-cyclohexyl)-amino]-thiophene-2-carboxylic acid methyl ester **507** as a white foam.

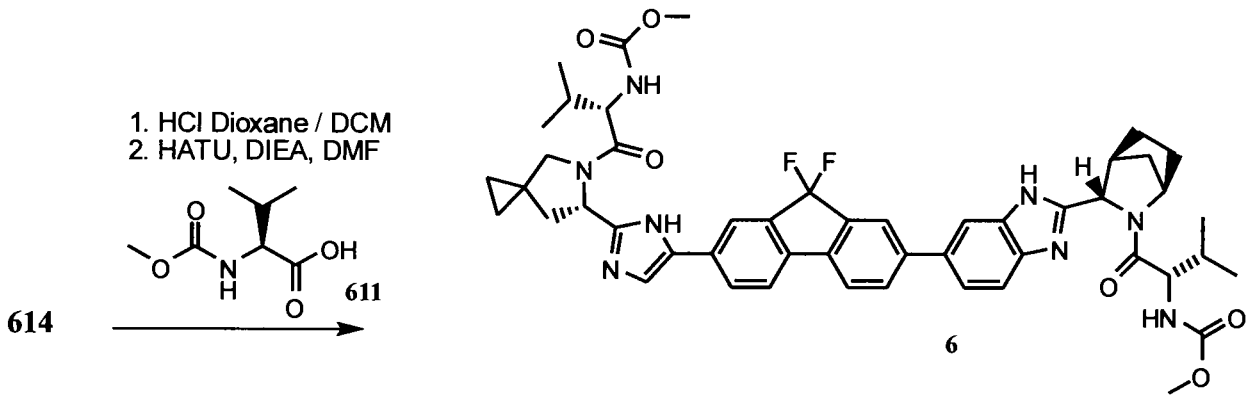
f. Preparation of Compound **508**.



Trimethylsulfoxonium chloride (79 mg, 0.62 mmol) in DMSO (1.5 mL) was treated with sodium hydride (21 mg, 60% oil dispersion, 0.53 mmol) and stirred at ambient temperature for 10 min. 5-(3,3-Dimethyl-but-1-ynyl)-3-[((1R)-4-methyl-cyclohex-3-enecarbonyl)-(4-oxo-cyclohexyl)-amino]-thiophene-2-carboxylic acid methyl ester **507** in THF (1 mL + 0.5 mL) was added dropwise and the reaction mixture was stirred for 45 min. The orange solution was treated with 5% citric acid until pH 3 and partitioned between water and ethyl acetate. The organic layer was separated and the aqueous was extracted again with ethyl acetate. The combined organics were washed with 5% LiCl, water and brine, and dried over sodium sulfate. After filtration and concentration, the residue was purified by flash chromatography (20-75% EtOAc:hexanes) to afford 0.134 g (70% yield) of 5-(3,3-dimethyl-but-1-ynyl)-3-[((1*R*)-4-methyl-cyclohex-3-enecarbonyl)-(1-oxa-spiro[2.5]oct-6-yl)-amino]-thiophene-2-carboxylic acid methyl ester **508** as a white powder.

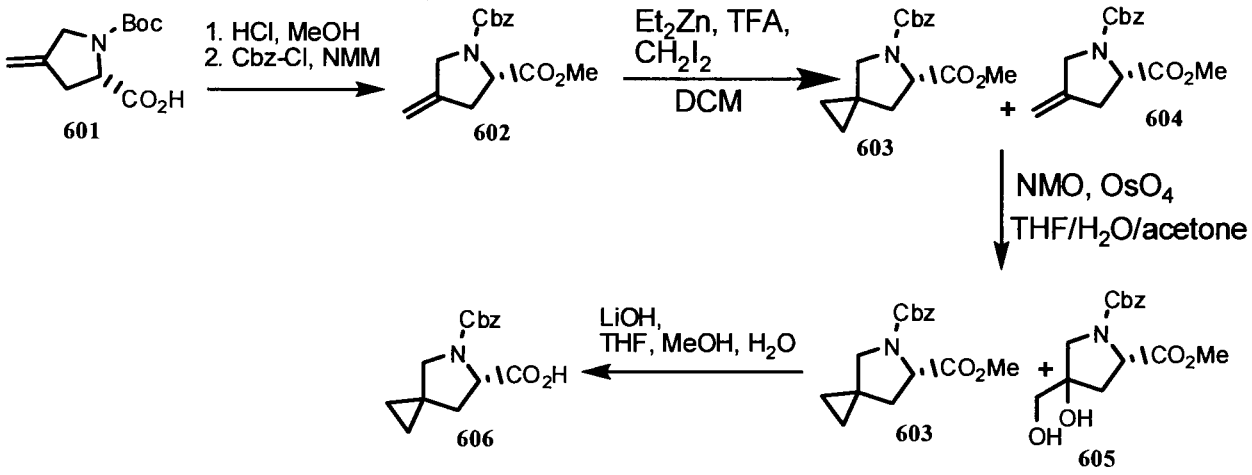
Compound 6, Can be prepared using synthetic methods and intermediates like those described in USSN 12/779,023 (US 20100310512 A1). Compound 6, Can also be prepared as described in the following Example.

Example 6: Preparation of (1-{3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester **6**.



3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester **614** (115 mg, 0.138 mmol) was dissolved in methylene chloride (2 mL) and HCl in dioxane (4M, 2 mL) was added and stirring at room temperature was continued. After 20 minutes, all volatiles were removed *in vacuo.* The crude material was used in the next step without further purification. The crude material was dissolved in DMF (1.5 mL) and DIEA (53.4 mg, 0.414 mmol) was added. A solution of 2- (*L*) Methoxycarbonylamino-3-methyl-butyric acid **611** (24.2 mg, 0.138 mmol), HATU (52.4 mg, 0.138 mmol) and DIEA (17.8 mg, 0.138 mmol) in DMF (1 mL) was added. The reaction was stirred at room temperature. After 20 minutes, the reaction was diluted with EtOAc and was washed with aqueous bicarbonate solution, aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was purified by RP-HPLC (eluent: water / MeCN w/ 0.1% TFA) to yield compound **6** (76 mg). LCMS-ESI$^+$: calc'd for $C_{49}H_{54}F_2N_8O_6$: 888.9 (M^+); Found: 890.0 ($M+H^+$). ^{1}H-NMR: 300 MHz, (dmso-d_6) δ: 8.20-7.99 (m, 8H), 7.73 (s, 2H), 7.37 – 7.27 (m, 2H), 5.25 (dd, J = 7.2 Hz, 1H), 4.78 (s, 1H) 4.54 (s, 1H), 4.16 (m, 1H), 4.02 (m, 1H), 3.87 (m,1H), 3.74 (m, 1H), 3.55 (s, 3H), 3.53 (s, 3H), 2.75 (m, 1H), 2.25 (m, 2H), 2.09 – 2.04 (m, 2H), 1.88 – 1.79 (m, 2H), 1.54 (m, 1H), 0.94 - 0.77 (m, 15H) 0.63 (m, 4H) ppm. ^{19}F-NMR: 282 MHz, (dmso-d_6) δ: -109.1 ppm [-74.8 ppm TFA].

The intermediate compound **614** was prepared as follows.



a. Preparation of compound 4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester **602**.

4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester **601** (10.0 g, 44 mmol) was dissolved in MeOH (75 mL) at room temperature and HCl (4M in dioxane, 75 mL) was added. Stirring at room temperature was continued for 4 hours. All volatiles were removed *in vacuo* and a beige solid was obtained. The crude material was suspended in methylene chloride (100 mL) and N-Methyl morpholine (13.3 g, 132 mmol) was added. The mixture was cooled to 0 °C and benzyl chloroformate (8.26 g, 48.4 mmol) was added while stirring. After 30 minutes, the reaction was warmed to room temperature and the solution was washed with water and aqueous HCl (1M). The solution was dried over sodium sulfate. Filtration and evaporation of solvents gave crude product, which was purified by silica gel chromatography (eluent: EtOAc / hexanes) to yield compound **602** (10.2 g). LCMS-ESI$^+$: calc'd for $C_{15}H_{17}NO_4$: 275.3 (M^+); Found: 276.4 ($M+H^+$).

b. Preparation of a mixture of Compounds **603** and **604**.

An oven-dried 3-neck round bottom flask was equipped with a nitrogen inlet adaptor and a 250 mL addition funnel. The third neck was sealed with a septum. The flask was charged with a stir bar, dichlorormethane (120 mL) and diethyl zinc (1.0 M in hexane, 118 mL, 118 mmol) then cooled to 0 °C in an ice bath. The addition funned was charged with dichloromethane (40 mL) and trifluoroacetic acid (9.1 mL, 118 mmol). After the diethyl zinc solution had cooled to 0 °C (about 25 minutes), the trifluoroacetic acid solution was added dropwise over 20 min to the stirred reaction mixture. After stirring for another 20 min at 0 °C, diiodomethane (9.5 mL, 118 mmol) was added slowly over 4 minutes. After another 20 min, 4-methylene-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester **602** (8.10 g, 29.4 mmol) was added in 30 mL dichloromethane by cannula. The flask containing 4-methylene-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester was then rinsed with another 10 mL dichloromethane and this solution was also transferred to the reaction mixture by cannula.

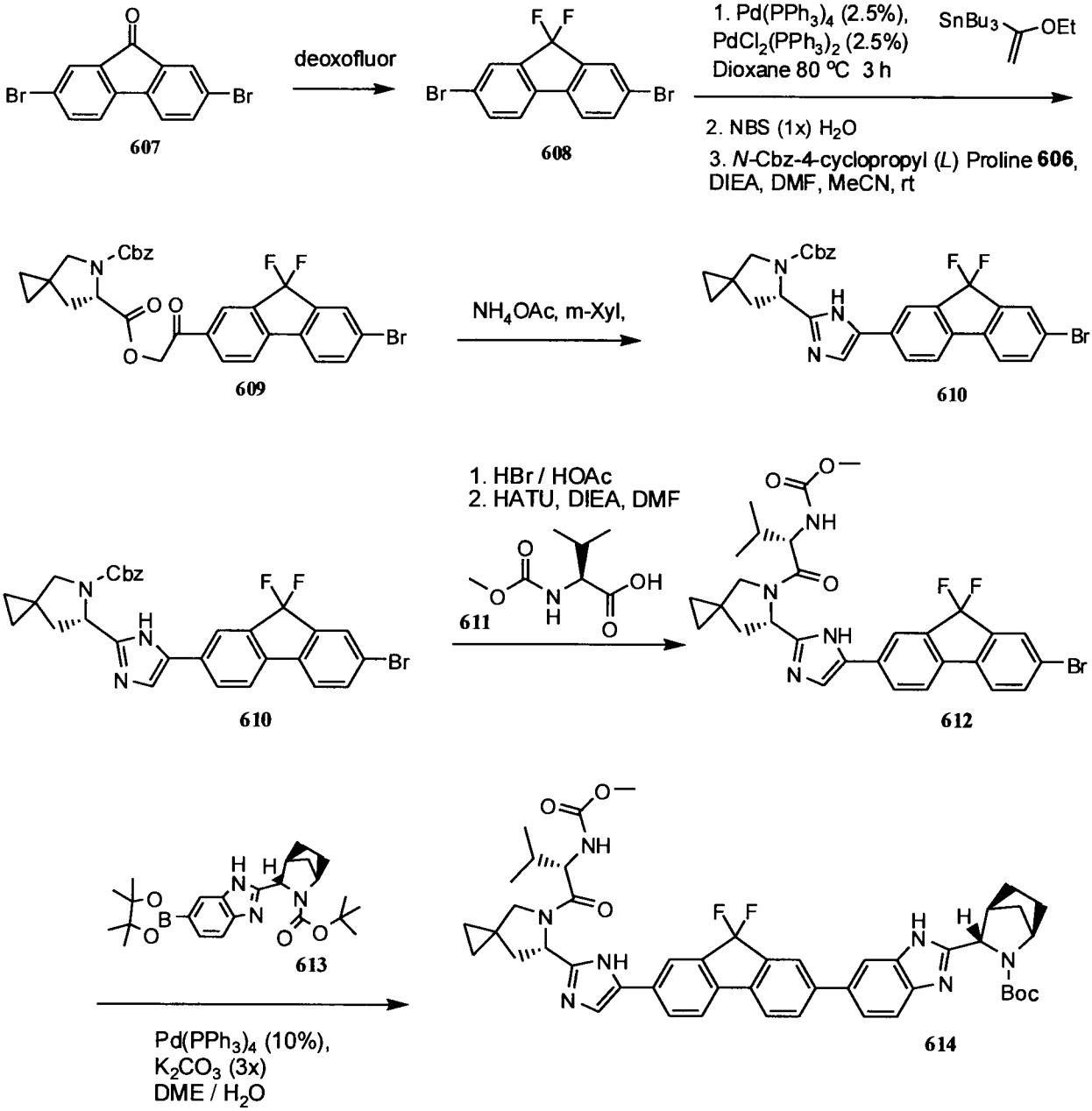
The reaction mixture was allowed to warm to RT and stirred for 110 h (about 5 days) after which the reagents were quenched with saturated aqueous ammonium chloride (~150 mL). The contents of the flask were slowly poured into a 2 L sep funnel containing saturated aqueous sodium bicarbonate (800 mL). The aqueous phase was extracted three times with 300 mL ethyl acetate. The combined organics were dried over magnesium sulfate and concentrated to provide a mixture of Compounds **603** and **604**.

c. Preparation of a Compound **603**.

The crude material from sub-part b was dissolved in 3:1:1 THF/water/acetone (165 mL) then treated with *N*-methylmorpholine-*N*-oxide (3.45 g, 29.4 mmol) and osmium tetroxide (4 wt% in water, 5 mL, 0.818 mmol). After stirring at RT for 7 h, the reagents were quenched with 1 M aqueous sodium thiosulfate (~100 mL). The contents of the flask were then poured into a 1 L sep funnel containing water (~300 mL). The aqueous phase was extracted three times with 300 mL dichloromethane. The combined organics were dried over magnesium sulfate and concentrated. The crude residue was purified by silica column chromatography (5% to 45% EtOAc/hexane) to provide 5-aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-methyl ester **603** as a clear oil (5.54g, 19.15 mmol, 65%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 7.36-7.29 (m, 5H), 5.21-5.04 (m, 2H), 4.56-4.47 (m, 1H), 3.75 (s, 1.5H), 3.60 (m, 1.5H), 03.51-3.37 (m, 2H), 2.32-2.25 (m, 1H), 1.87-1.80 (m, 1H), 0.64-0.51 (m, 4H).

d. Preparation of 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester **606**.

5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-methyl ester **603** (244 mg, 0.840 mmol) was dissolved in THF (2.0 mL) / MeOH (1.5 mL). An aqueous solution of LiOH (35.5 mg, 0.84 mmol) was added and stirring at room temperature was continued. After 3 hours, the reaction was neutralized with aqueous HCl (1M) and the organic solvents were removed *in vacuo*. The crude mixture was diluted with water and EtOAc and the organic layer was collected. All volatiles were removed *in vacuo* and the crude acid **606** was used without further purification. LCMS-ESI$^+$: calc'd for $C_{15}H_{17}NO_4$: 275.3 (M^+); Found: 276.3 ($M+H^+$).



607 608 609 610 611 612 613 614

e. Preparation of a 2,7-Dibromo-9,9-difluoro-9H-fluorene **608**.

2,7-Dibromo-fluoren-9-one **607** (4.0 g, 11.8 mmol) was suspended in deoxofluor (12 mL) at room temperature and EtOH (4 drops) was added. The stirred suspension was heated at T = 90° C for 24 hours (**CAUTION: Use of deoxofluor at elevated temperatures, as described above, is cautioned as rapid and violent exotherms may occur**). The reaction was cooled to room temperature and poured onto ice containing sodium bicarbonate. A solid formed and was collected via filtration. The crude material was taken into EtOAc and was washed with aqueous HCl (1M) and brine. The solution was dried over sodium sulfate. Filtration and evaporation of solvents gave crude product, which was purified by silica gel chromatography (eluent: EtOAc / hexanes) to yield **608** (3.2 g). ^{19}F-NMR: 282 MHz, (dmso-d_6)

δ: -111.6 ppm. Before using the material in the next step, it was exposed as a solution in EtOAc to charcoal.

f. Preparation of 5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-[2-(7-bromo-9,9-difluoro-9H-fluoren-2-yl)-2-oxo-ethyl] ester **609**.

2,7-Dibromo-9,9-difluoro-9H-fluorene **608** (372 mg, 1.04 mmol), $Pd(PPh_3)_4$ (30.0 mg, 0.026 mmol), $PdCl_2(PPh_3)_2$ (18.2 mg, 0.026 mmol), $As(PPh_3)_3$ (5.0 mg) were dissolved in dioxane (10 mL) under an argon atmosphere. Ethoxyvinyl-tributyl tin (376.4 mg, 1.04 mmol) was added. The mixture was heated for 140 minutes at 85 °C (oil bath). The reaction was cooled to room temperature. *N*-bromo succinimide (177 mg, 1.0 mmol) was added followed by water (2 mL). The reaction was stirred at room temperature for 3 hours, after which the majority of the dioxane was removed *in vacuo*. The crude reaction mixture was diluted with EtOAc and was washed with water. All volatiles were removed *in vacuo*. Toluene was added and all volatiles were removed *in vacuo* for a second time. The crude material was dissolved in DMF / MeCN (2 mL, 1:1) at room temperature. A solution of *N*-Cbz-4-cyclopropyl (*L*) proline **606** (0.84 mmol) and DIEA (268 mg, 2.08 mmol) in MeCN (2 mL) was added and stirring at room temperature was continued. After 14 hours, most of the MeCN was removed *in vacuo* and the crude reaction mixture was diluted with EtOAc. The mixture was washed with aqueous HCl (1M), aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and evaporation of solvents gave the crude reaction product, which was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield compound **609** (176 mg). LCMS-ESI$^+$: calc'd for $C_{30}H_{24}BrF_2NO_5$: 596.4 (M^+); Found: 595.2 / 597.2 ($M+H^+$).

g. Preparation of 6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester **610**.

5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-benzyl ester 6-[2-(7-bromo-9,9-difluoro-9H-fluoren-2-yl)-2-oxo-ethyl] ester **609** (172 mg, 0.293 mmol) was dissolved in *m*-xylenes (6.0 mL). Ammonium acetate (226 mg, 2.93 mmol) was added and the reaction was stirred at 140 °C for 60 minutes under microwave conditions. The reaction was cooled to room temperature and all volatiles were removed *in vacuo*. The crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield compound **610** (80.3 mg). LCMS-ESI$^+$: calc'd for $C_{30}H_{24}BrF_2N_3O_2$: 576.4 (M^+); Found: 575.2 / 577.2 ($M+H^+$).

h. Preparation of (1-{6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester **612**.

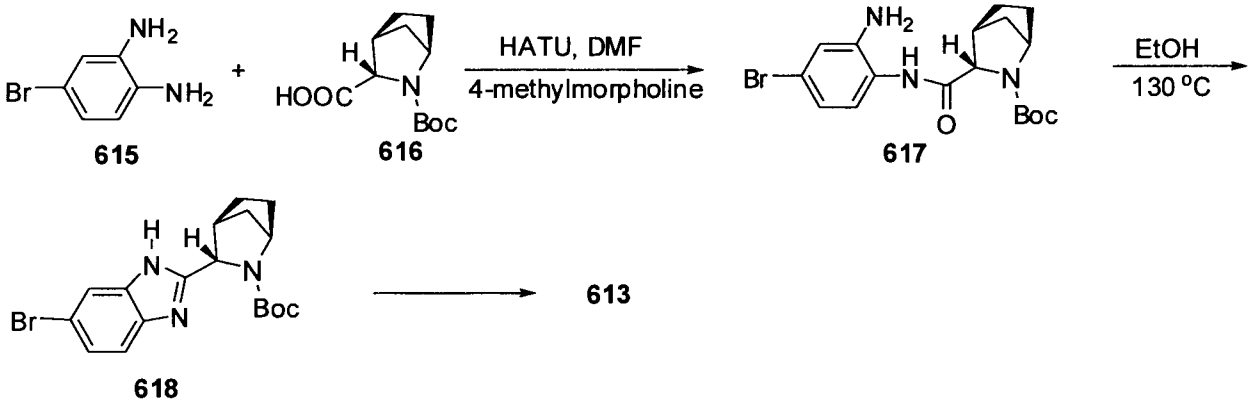
6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester **610** (800 mg, 1.38 mmol) was dissolved in methylene chloride (15 mL) and HBr in AcOH (37%, 2 mL) was added and stirring at room temperature was continued.

After 180 minutes, the suspension was diluted with hexanes and the solid was collected via filtration and was washed with hexanes and subjected to vacuum. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (4.0 mL) and DIEA (356 mg, 2.76 mmol) was added. A solution of 2-(*L*)-Methoxycarbonylamino-3-methyl-butyric acid **611** (242 mg, 1.38 mmol), HATU (524 mg, 1.38 mmol) and DIEA (178 mg, 1.38 mmol) in DMF (1 mL) was added. The reaction was stirred at room temperature. After 50 minutes, the reaction was diluted with EtOAc and was washed with aqueous bicarbonate solution, aqueous LiCl solution (5%), brine, and was dried over sodium sulfate. Filtration and removal of solvents *in vacuo* gave the crude material, which was purified by silica gel chromatography (eluent: EtOAc / hexanes) to yield the slightly impure compound **612** (878 mg). LCMS-ESI$^+$: calc'd for $C_{29}H_{29}BrF_2N_4O_3$: 599.5 (M^+); Found: 598.5 / 600.5 ($M+H^+$).

i. Preparation of 3-[6-(9,9-Difluoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester **614**.

(1-{6-[5-(7-Bromo-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester **612** (840 mg, 1.4 mmol), 3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester **613** (615 mg, 1.4 mmol), $Pd(PPh_3)_4$ (161 mg, 0.14 mmol), K_2CO_3 (579 mg, 4.2 mmol), were dissolved in DME (15 mL) / water (3 mL) under an argon atmosphere. The mixture was heated for 120 minutes at 85 – 90 °C (oil bath). After 120 minutes additional boronate ester (61 mg, 0.14 mmol) was added and heating was continued. After 3 hours, the reaction was cooled to room temperature. Most of the DME was removed *in vacuo* and the crude reaction mixture was diluted with EtOAc. The mixture was washed with brine and was dried over sodium sulfate. Filtration and evaporation of solvents gave the crude reaction product, which was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield compound **614** (878 mg). LCMS-ESI$^+$: calc'd for $C_{47}H_{51}F_2N_7O_5$: 831.9 (M^+); Found: 832.7 ($M+H^+$).

The intermediate compound **613** can be prepared as follows



j. Preparation of 3-(2-Amino-4-bromo-phenylcarbamoyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester **617**.

To a solution of 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester **616** (0.327 g, 1.36 mmol, 1 eq.), 4-Bromo-benzene-1,2-diamine **615** (0.507 g, 2.71 mmol, 2 eq.) and 4-methylmorpholine (0.299 mL, 2 eq.) in 10 mL DMF was added HATU (0.543g, 1.05 eq.). The reaction mixture was stirred at room temperature for 1 hour then concentrated. The reaction mixture was diluted with ethyl acetate and washed with diluted $NaHCO_3$ aqueous solution and brine. The organic layer was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give a mixture of regioisomer 3-(2-Amino-4-bromo-phenylcarbamoyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester **617**.

k. Preparation of 3-(6-Bromo-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester **618**.

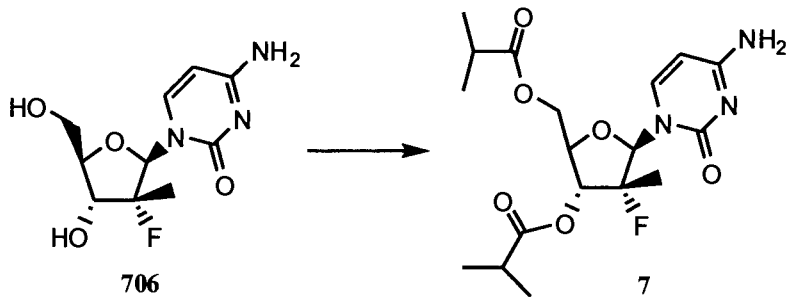
The above mixture of regioisomer 3-(2-Amino-4-bromo-phenylcarbamoyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester **617** was dissolved in ethanol and heated to 130°C in sealed tube overnight and continue heating at 170°C for 3 days. LC-MS showed desired product and Boc cleaved product (about 1:1 ratio). The mixture was concentrated down and dissolved HCL. Di-*tert*-butyl dicarbonate (0.6 eq.) was added and reaction was stirred overnight at room temperature. The reaction mixture was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 3-(6-Bromo-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester **618** (0.383 g, 72%) as an orange foam.

I. Preparation of Compound **613**.

A mixture of 3-(6-Bromo-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester **618** (264 mg, 0.673 mmol), benzene-1,4-diboronic acid dipinocal ester (5 eq., 3.36 g, 6.95 mmol), tetrakis(triphenylphosphine)palladium (5%, 39 mg) and 2M potassium carbonate aqueous solution (3 eq., 1.01 mL) in 5 mL DME was heated to 90°C under Ar for 4 hours. The reaction mixture was cooled and diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 60% ethyl acetate/hexane) to give 3-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester **613** (295 mg, yield 85%). LCMS-ESI$^-$: calc'd for $C_{30}H_{38}BN_3O_4$: 515.45; Found: 516.1 ($M+H^+$).

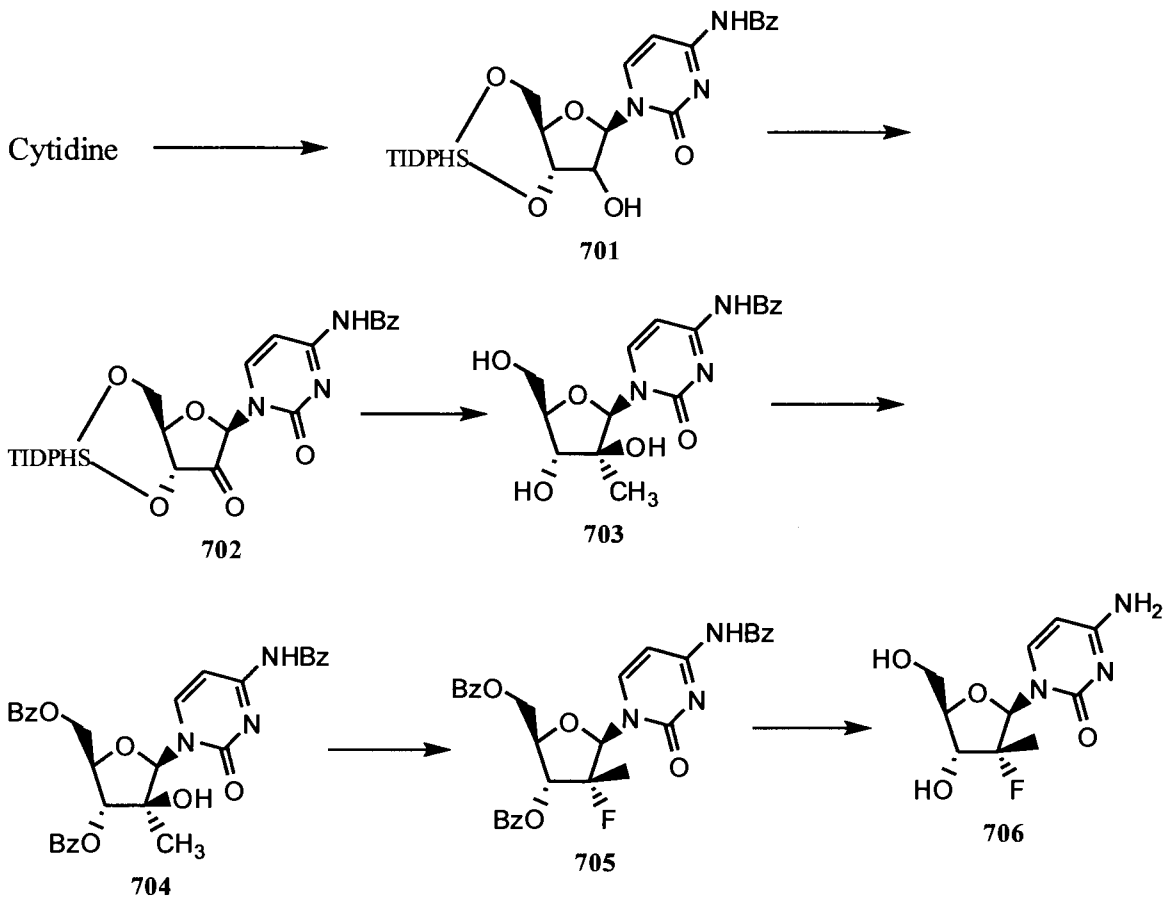
Compound **7** can be prepared using synthetic methods and intermediates like those described in US 7,429,572. Compound **7** can also be prepared as described in the following Example.

Example 7: Preparation of Compound **7**.



To an ice-cold suspension of compound 701 (970 g, 3.74 mol) and DMAP (50 g, 0.412 mol) in THF (10 L) is added TEA (2.3 kg, 16.5 mol) and water (7 L) which produces a clear solution. Isobutyryl chloride (3 equivalents) is added slowly to the stirred mixture while maintaining the temperature at about 0° C. An additional 1.2 then 0.7 equivalents of isobutyl chloride is added until the HPLC indicates the reaction had proceeded essentially to completion (a total of about 1.95 kg). The reaction mixture is acidified with concentrated HCl to a pH of about 6.4 and the organic phase is washed with EtOAc (2 x 10 L). The combined extracts are washed with water (1 x 15 L). The organic phase is filtered and concentrated *in vacuo*. The residue is dissolved in IPA (ca. 20 kg) and heptane (14.2 kg) is added. The solution is heated to about 74-75°C to produce a clear solution, then about 5L is removed by distillation. The resulting solution is cooled slowly to RT. A precipitate is formed at about 42-43° C. Cooling is continued slowly to 5°C then stirred overnight. The resulting solid is filtered and the filtrate is washed with IPA/heptane (1:8) mixture (13.4 kg), and dried under vacuum at about 60- 70°C to afford 1.295 kg (86.65%) of compound **7** which is 99.45% pure by HPLC.

The intermediate compound **706** can be prepared as follows.



a. Preparation of compound **701**.

To a suspension of cytidine (100 g, 0.411 mol) in DMF (2.06 L) is added benzoic anhydride (102.4 g, 0.452 mol). The mixture was stirred at room temperature for 20 hours. The DMF was removed *in vacuo* and the residue was triturated with diethyl ether. The resulting solid was collected by suction filtration and washed with diethyl ether (2 x 200 mL). Further drying *in vacuo* at room temperature gave the N^4 benzamide (140.6 g, 98.3%). A portion of this material (139.3 g, 0.401 mol) was dissolved in anhydrous pyridine (1.2 L) and was treated with 1,3-dichloro-1,1,3,3-tetraisopropyl-disiloxane (141.4 mL, 0.441 mol) at room temperature. The solution was stirred at room temperature overnight. The mixture was concentrated to near dryness *in vacuo* and coevaporated with toluene (3 x 200 mL). The residue was treated with EtOAc (1.8 L) and washed with HCl (2 x 200 mL, 0.05 N), $NaHCO_3$ (5 %, 2 x 400 mL). The organic layer was washed dried (Na_2SO_4), filtered, and evaporated to dryness. Compound **701** (256.5 g, >100%) was isolated as a white foam and used without further purification.

b. Preparation of compound **702**.

Compound **701** (236.5 g, 0.40 mol) was dissolved in dry THF (1.22 L). Anhydrous DMSO (180.8 mL, 2.1 mol) was added and the resulting solution was cooled to between -20°C

and -15°C. Trifluoroacetic anhydride (90.6 mL, 0.64 mol) was added dropwise over 45 minutes and the solution was stirred between -20°C and -15 °C for 2 hrs after which anhydrous triethylamine (223.5 mL, 1.6 mol) was added over 20 minutes. The crude reaction containing ketone **702** was dissolved in EtOAc (500 mL), and the resulting solution was washed with H_2O (3 x 400 mL), dried (Na_2SO_4) and the solvents were removed *in vacuo* to give a yellow solid that was purified on a silica gel column eluting with a stepwise gradient of Et_2O (0-60%) in hexanes followed by a stepwise gradient of EtOAc (50-100%) in hexanes. The crude ketone so-obtained (~192 g) was crystallized from petroleum ether to give ketone **702** (138.91 g, 57.5% from cytidine) as a white solid and 22 g of unreacted starting material, **701,** as a yellow solid.

c. Preparation of compound **703**.

Compound **702** (48.57 g, 8.26 mmol) was dissolved in anhydrous toluene (~400 mL) and the solvent was removed *in vacuo* with exclusion of moisture. The residue was then further dried *in vacuo* (oil pump) for another 2 hours. With strict exclusion of moisture, the residual foam was dissolved in anhydrous diethyl ether (1.03 L) under argon. The resulting solution was cooled to -78°C under argon and MeLi (1.6 M, 258.0 mL, 0.413 mol) was added dropwise *via* additional funnel. After the addition was complete, the mixture was stirred for 2 hours at -78°C. Aqueous 1M NH_4Cl (500 mL) was added slowly. After warming to room temperature, the mixture was washed with H_2O (2 x 500 mL), dried (Na_2SO_4), and then concentrated to dryness to give a brown foam (~60 g, >100%).

The reaction was performed two more times using 37.62 g and 56.4 g of compound **702**. The combined crude products (128.0 g, 0.212 mol) were dissolved in THF (1.28 L) and treated with concd HOAc (23 mL, 0.402 mol). To the solution was added TBAF (384.0 mL, 1 M in THF). The solution was stirred at room temperature for 0.75 hours and the mixture was treated with silica gel (750 g) and concentrated to dryness. The powder was placed on a silica gel column packed in CH_2Cl_2. Elution with 1:7 EtOH-CH_2Cl_2 afforded a dark waxy solid that was pre-adsorbed on silica gel (300 g) and chromatographed as before. Compound **703** (46.4 g, 53.0 % from **702**) was isolated as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 1.20 (s, 3H, CH_3), 3.62-3.69 (m, 2H,), 3.73-3.78 (m, 2H,), 5.19 (t, 1H, *J* = 5.4 Hz, OH-5'), 5.25 (s, 1H, OH-2'), 5.52 (d, 1H, *J* = 5.0 Hz, OH-3'), 5.99 (s, 1H, H-1'), 7.32 (d, 1H, *J* = 5.8 Hz), 7.50 (Ψt, 2H, *J* =7.7 Hz), 7.62 (Ψ, 1H, *J* =7.3 Hz), 8.00 (d, 2H, *J* =7.3 Hz), 8.14 (d, 1H, *J* =6.9 Hz), 11.22 (s, 1H, NH). Anal. Calcd for $C_{17}H_{19}N_3O_6$ • 0.5 H2O: C, 55.13; H, 5.44; N, 11.35. Found: C, 55.21; H, 5.47; N, 11.33.

d. Preparation of compound **704**.

Compound **703** (46.0 g, 0.13 mol) was dissolved in anhydrous pyridine and concentrated to dryness *in vacuo*. The resulting syrup was dissolved in anhydrous pyridine under argon and cooled to 0°C with stirring. The brown solution was treated with benzoyl

chloride (30mL, 0.250 mol) dropwise over 10 minutes. The ice bath was removed and stirring continued for 1.5 hours whereby TLC showed no remaining starting material. The mixture was quenched by the addition of water (5 mL) and concentrated to dryness. The residue was dissolved in a minimal amount of CH_2Cl_2 and washed with satd $NaHCO_3$ (1 x 500 mL) and H_2O (1 x 500 mL). The organic phase was dried (Na_2SO_4) and filtered, concentrated to dryness and chromatographed on silica gel eluting with a stepwise gradient of EtOAc-hexanes (25-60%) to provide compound **704** as yellow foam (48.5 g, 67%). ^1H NMR ($CDCl_3$): δ 1.64 (s, 3H, CH_3), 4.50 (m, 1H, H-4), 4.78-4.85 (m, 2H, H-5',5a'), 5.50 (d, 1H, *J* =3.4 Hz, H-3'), 6.42 (s, 1H, H-1'), 7.44-7.54 (m, 7H, Ar), 7.57-7.66 (m, 3H, Ar), 7.94 (d, 2H, *J* =7.8 Hz), 8.05-8.09 (m, 4H, Ar), 8.21 (d, 1H, *J* = 7.3 Hz). Anal. Calcd for $C_{31}H_{27}NO_8$: C, 65.37; H, 4.78; N, 7.38. Found: C, 65.59; H, 4.79; N, 7.16.

e. Preparation of compound **705**.

Compound **704** (7.50 g, 0.013 mol) was dissolved in anhydrous toluene (150 mL) under argon and cooled to -20°C. DAST (2.5 mL, 18.9 mmol) was added slowly and the cooling bath was removed after the addition was complete. Stirring was continued for 1 hours and the mixture was poured into satd $NaHCO_3$ (100 mL) and washed until gas evolution ceased. The organic phase was dried ($Na2SO_4$), concentrated, and purified by silica gel chromatography eluting with 1:1 EtOAc-hexanes. Yield was 1.22 g (16.3%) of pure **705** as a white solid. mp 241°C (CH_2Cl_2-hexanes); ^1H NMR ($CDCl_3$)): δ 1.49 (d, 3H, *J* =22.4 Hz, CH_3), 4.64 (dd, 1H, *J* = 3.44, 12.9 Hz, H-5'), 4.73 (d, 1H, *J* = 9.5 Hz, H-4'), 4.90 (dd, 1H, *J* = 2.4, 12.7 Hz, H-5a'), 5.56 (dd, 1H, *J* = 8.6, 20.7 Hz, H-3'), 6.52 (d, 1H, *J* = 18.0 Hz, H-1'), 7.47-7.57 (m, 7H, Ar), 7.62-7.71 (m, 3H, Ar), 7.89 (d, 2H, *J* = 6.9 Hz), 8.07-8.11 (m, 5H, Ar), 8.67 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$)): δ 3.3 (m). Anal. Calcd for $C_{31}H_{26}FN_3O_7 \cdot 0.7\ H_20$: C, 63.74; H, 4.72; N, 7.20. Found: C, 63.71; H, 4.54; N, 7.20.

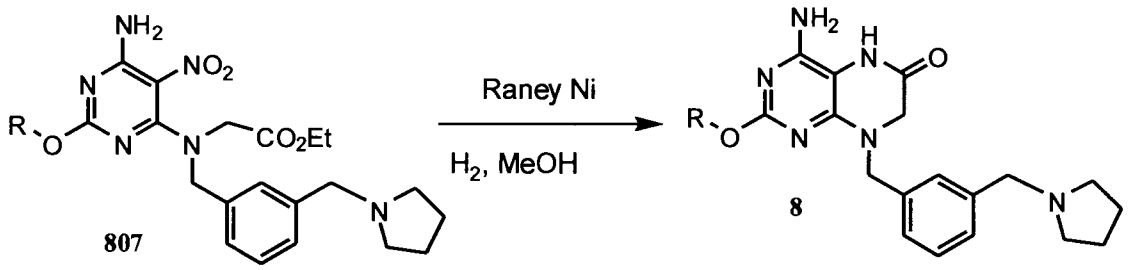
f. Preparation of compound **706**.

Compound **705** (6.30 g, 0.011 mol) was suspended in methanolic ammonia *(ca* 7 N, 150 mL) and stirred at room temperature overnight. The solvent was removed *in vacuo,* co-evaporated with methanol (1 x 20 mL), and pre-adsorbed onto silica gel. The white powder was placed onto a silica gel column (packed in $CHCl_3$) and the column was eluted with 9% EtOH in $CHCl_3$), then 17% EtOH and finally 25% EtOH in CH Cl_3). Concentration of the fractions containing the product, filtration through a 0.4 µm disk, and lyophilization from water afforded compound **706**,2.18 g (76%). ^1H NMR (DMSO-d_6;): δ 1.17 (d, 3H, *J* = 22.3 Hz, CH_3), 3.63 (dd, 1H, *J* =2.7, 13.7 Hz, H-5'), 3.70-3.84 (m, 3H, H-3', H-4', H-5a'), 5.24 (app s, 1H, OH-3'), 5.60 (d, 1H, *J* = 5.4 Hz, H-5'), 5.74 (d, 1H, *J* = 7.71 Hz, H-5), 6.07 (d, 1H, *J* = 18.9 Hz, H-1'), 7.31 (s, 1H, NH2), 7.42 (s, 1H, NH2), 7.90 (d, 1H, *J* = 7.3 Hz, H-6). ^{19}F NMR (DMSO-d_6;): δ 2.60 (m). Anal. Calcd for $C_{10}H_{14}FN_3O_4 \cdot 1.4\ H_2O$: C, 44.22; H, 5.95; N, 14.77. Found: C, 42.24;

H, 5.63; N, 14.54. Compound **706** (0.10 g, 0.386 mmol) was converted to the hydrochloride salt by dissolving in water (2 mL) and adjusting the pH to approximately 3.0 with 1 M HCl. The water was removed *in vacuo* and the residue was crystallized from aqueous EtOH to give Compound **706** as the hydrochloride salt (71.0 mg). mp 243°C (dec); ^{1}H NMR (DMSO-d_6;): δ 1.29 (d, 3H, *J* =22.6 Hz, CH_3), 3.65 (dd, 1H, *J* =2.3, 12.7 Hz, H-5'), 3.76-3.90 (m, 3H, H-3', H-4', H-5a'), 5.96 (d, 1H, *J* = 17.3 Hz, H-1 '),6.15 (d, 1H, *J*= 7.9 Hz, H-5), 8.33 (d, 1H, *J* =7.9 Hz, H-6), 8.69 (s, 1.5H, NH), 9.78 (s, 1.5H, NH). ^{19}F NMR (DMSO-d_6;): δ 1.69 (m). Anal. Calcd for $C_{10}H_{14}FN_3O_4$ • HCl: C, 40.62; H, 5.11; N, 14.21. Found: C, 40.80; H, 5.09; N, 14.23.

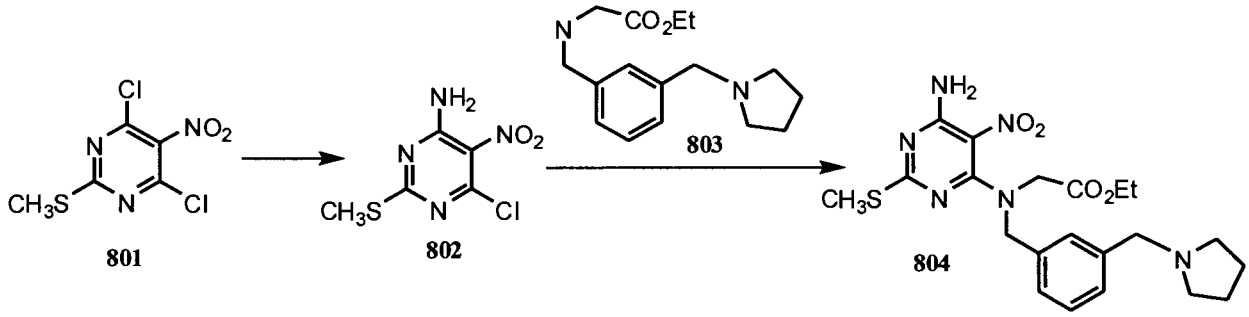
Compound **8** can be prepared using synthetic methods and intermediates like those described in USSN 12/632,194. Compound **8** can also be prepared as described in the following Example.

Example 8: Preparation of 4-amino-2-*n*-butoxy-8-[3'-(pyrrolidin-1''-ylmethyl)-benzyl]-5,6,7,8-tetrahydropteridin-6-one **8**. (R = n-butyl)



To a solution of nitro compound **807** (730 mg, 1.5 mmol) in MeOH (10 mL) was added a Raney Nickel (~200 µL, slurry in H_2O). The reaction vessel was flushed with H_2 and then stirred under an H_2 atmosphere for 1.5 hours. The mixture was filtered through celite with CH_2Cl_2 and MeOH (1:1). The filtrate was concentrated under vacuum and left on lyophilizer overnight. The free base of compound **8** was obtained as a white solid. To obtain the HCl salt of **8**, a sample of the filtrate above was spiked with 1.0 M HCl to pH = 1-2 and lyophilized. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.65 (s, 1H), 7.50 (m, 3H), 4.96 (s, 2H), 4.44 (t, *J* = 7 Hz, 2H), 4.40 (s, 2H), 4.16 (s, 2H), 3.48 (m, 2H), 3.19 (m, 2H), 2.02-2.17 (m, 4H), 1.74 (m, 2H), 1.45 (m, 2H), 0.94 (t, J = 7 Hz, 3H) - [HCl salt]. LCMS-ESI$^+$: calc'd for $C_{22}H_{31}N_6O_2$: 411.5 (M+H$^+$); Found: 411.3 (M+H$^+$).

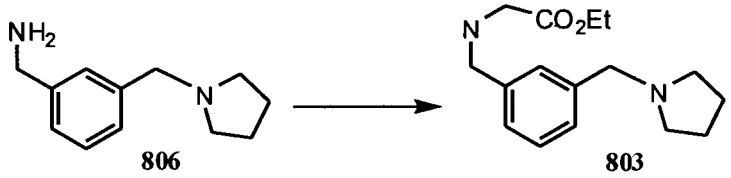
The intermediate compound **807** was prepared as follows.



a. Preparation of compound **802**.

To a solution of compound **801** (2.46 g, 10.2 mmol) in THF (34 mL) at −20 °C was added Et_3N (3.14 mL, 22.5 mmol) followed by a solution of NH_3 (2.0 M in MeOH, 5.4 mL, 11 mmol). The mixture was stirred while warming to 0 °C for 1.5 h (LC/MS indicated consumption of starting materials). The reaction mixture containing compound **802** was taken forward without work-up.

b. Preparation of compound **803**.

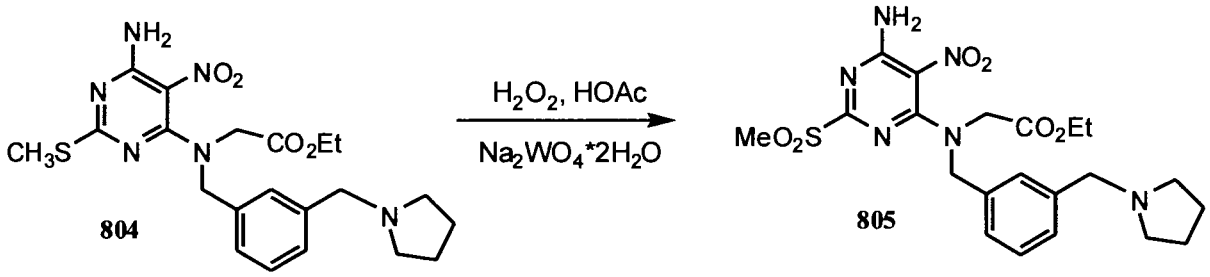


To a solution of 3-((1-pyrrolidinylmethyl)phenyl)methanamine **806** (1.95 g, 10.2 mmol) in THF (34 mL) at 0 °C was added Et_3N (3.14 mmol, 22.5 mmol) followed by methyl bromoacetate (1.04 mL, 22.3 mmol) dropwise. The reaction mixture was stirred until LC/MS indicated consumption of starting materials, approximately 2 hours. The mixture containing compound **803** was taken forward without work up.

c. Preparation of compound **804**.

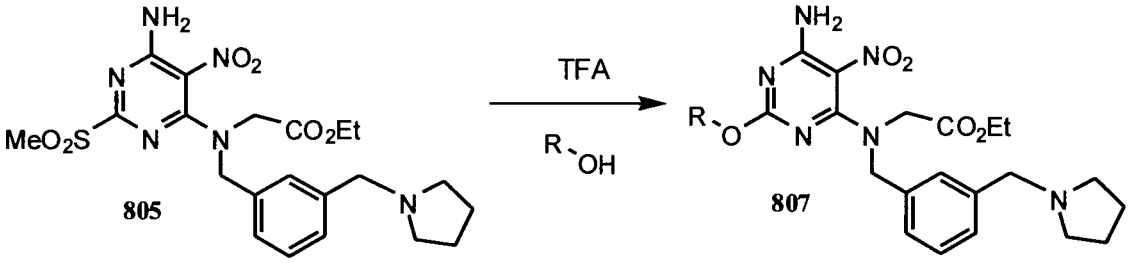
The reaction mixture containing compound **803** was added to the reaction mixture containing compound **802** at 0 °C. The reaction mixture was stirred until LC/MS indicated the consumption of compound **802**, approximately 45 minutes. A saturated solution of NH_4Cl (50 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by silica gel chromatography provided 2.11 g of compound **804**. ^1H NMR (CD_3OD, 300 MHz): δ (ppm) 7.32-7.16 (m, 4H), 4.69 (s, 2H), 4.19 (q, J = 7 Hz, 2H), 4.07 (s, 2H), 3.60 (s, 2H), 2.49 (m, 4H), 2.40 (s, 3H), 1.78 (m, 4H), 1.23 (t, 3 H, J = 7 Hz). LCMS-ESI$^+$: calc'd for $C_{21}H_{29}N_6O_4S$: 461.2 ($M+H^+$); Found: 461.0 ($M+H^+$).

d. Preparation of Ethyl-N_α-[4-amino-2-methanesulfonyl-5-nitropyrimidin-6-yl],N_α-[3′-(pyrrolidin-1″-ylmethyl)-benzyl]-glycinate **805**.



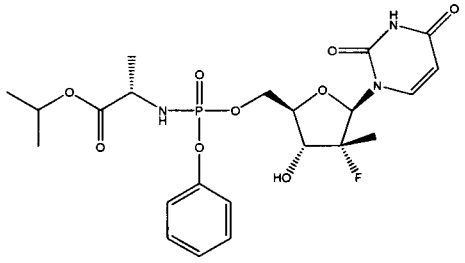
To a solution a suspension of the sulfide **804** (3.68 g, 8.00 mmol) in EtOH (40 mL) at 0 °C was added sodium tungstate dihydrate (792 mg, 2.40 mmol), acetic acid (4.6 mL, 80 mmol), and hydrogen peroxide (3.4 mL, ~40 mmol, 35% w/w in H_2O) sequentially. After 3 hours, additional acetic acid (4.6 mL) and hydrogen peroxide (3.4 mL) were added. The reaction was maintained at 0 °C for 16 hours. A saturated solution of Na_2SO_3 (50 mL) was added carefully while at 0 °C followed by CH_2Cl_2 (75 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to provide a material containing compound **805** that was used without further purification.

e. Preparation of Compound **807**. (R = n-butyl)



To a solution of sulfone **805** (1.0 g, 2.0 mmol) in n-butanol (10 mL) was added TFA (470 μL, 6.1 mmol). The reaction was stirred at 100 °C for 1 hour. The reaction mixture was poured onto a saturated solution of $NaHCO_3$ (20 mL) and CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification was conducted by silica gel chromatography (1 g substrate/10 g SiO_2) (2-15% MeOH/CH_2Cl_2) to provide compound **807**.

Example 9: Preparation of Compound 9 (from US2010/0298257)



9

Preparation of (S)-2-{[(1R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-(R)-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-yl-methoxy]-phenoxyphosphorylamino}-propionic acid isopropyl ester (from US2010/0298257 Example 2)

Synonym: 5'-O-(Isopropyl-L-alanate, phenyl phosphoramidyl)-2'-deoxy-2'-fluoro-2'-C-methyl-uridine diastereomeric mixture.

A 5 L 3-necked flask was fitted with a mechanical stirrer, brine ice bath, internal thermometer, and a nitrogen atmosphere. The flask was charged with L-alanine isopropyl ester hydrochloride (82.0 g, 0.490 moles) and anhydrous dichloromethane (0.80 L). While this was stirring, phenyl dichlorophosphate (85.0 g, 0.40 moles) was added in one lot and stirred. While maintaining the internal temperature between -5 to 5 °C., a solution of N-methylimidazole (NMI, 250 g, 3.07 moles) in dichloromethane (250 mL) was added over a period of a half hour. The solution was allowed to stir for 1 h in this temperature range. 2'-Deoxy-2'-fluoro-2'-C-methyl-uridine (3,80.0 g, 0.307 moles) was added at 0° C. in one portion and then the reaction flask was allowed to warm up slowly in the brine bath. At 1 h, the internal temperature was up to -2° C. TLC (5% Methanol in HCL) at 1 h showed that more than 50% of nucleoside was consumed. The bath was removed and the reaction flask reached ambient temperature over 1 h more. TLC after 3 h and at 5 h total showed 95% of the starting nucleoside was consumed. The reaction mixture was quenched by adding methanol (100 mL) and stirring the reaction for 5 minutes.
The reaction mixture was washed with 1N HCl (2x500 mL) followed by saturated sodium bicarbonate solution (2x500 mL). The separated organic layer was dried over anhydrous sodium sulfate (50 g) and filtered. The solution was evaporated under reduced pressure and then under high vacuum to dryness to give the crude product as a viscous oil (170 g). NMRs of the crude product (^{31}P and ^{1}H) were taken. The ^{31}P-NMR indicated about 1% of the total phosphorus integration was due to the presence of the 3' isomer 5.
To the crude product was added anhydrous pyridine (1700 mL). The solvent was evaporated under reduced pressure and then under high vacuum in order to reduce the water content of the crude mixture through co-evaporation. The resulting oil was re-dissolved in anhydrous pyridine (500 ml) and then was added excess t-butyldimethylsilyl chloride (9.0 g, 60 mM). The reaction was stirred at ambient temperature. Reaction progress was monitored by UPLC/MS.

After 3 hours, the 3' impurity 5 could no longer be detected and the reaction was quenched by the addition of methanol (50 mL).

The reaction was evaporated under reduced pressure to an oil. The residue was dissolved in ethyl acetate (1.5 L) and washed with 1N HCl (2x500 mL), followed by saturated sodium bicarbonate solution (2x500 mL). The organic layer was dried over anhydrous sodium sulfate (50 g), filtered and evaporated under reduced pressure to give the crude product as a pale yellow oil.

The crude oil was diluted with the same volume of dichloromethane and loaded onto a 2.5 Kg silica gel cartridge n a radial compression module at 100 psi of air pressure. Using a gradient pump at 60 psi and a flow rate of 400 ml/min, the cartridge was washed with methylene chloride (4L) followed by a gradient 1-4% methanol in methylene chloride (48 L). Most of the major impurities (di-(isopropylalanyl) phenyl phosphate, 3',5'-bis phosphoramidate, 3'-phosphoramidate-5'-TBDMS adduct (7)) eluted with ~3% gradient. The desired product eluted between 3 and 4% methanol. The product containing fractions were sorted into two lots. The first contained small amounts of upper impurities and the latter was pure product. The first set of fractions contained small amounts of less polar impurities (upper impurities) such as the 3',5'-bis phosphoramidate and the di-alanylphenyl phosphate and a mostly the Rp diastereomer and required a second column purification. (The relative terminology, upper vs. lower refers to the elution on normal phase silica-gel chromatography, where the "upper isomer" means the first eluting isomer.) The second set of fractions did not have a significant amount of impurities-just the remaining *Rp* and mostly the *Sp* diasterereomers. It was later recombined with the twice-columned fractions. The solvent was evaporated under reduced pressure and the resulting white foam was further dried (0.20mmHg) for 1 h to give 42 g of the impure lot (4:1 upper vs lower isomer based on ^{31}P-NMR) and 38 g of the pure lot (1:3 upper vs lower isomer). The impure lot was recolumned in a similar manner to give 3.8 g of 97% pure upper isomer (fraction set aside) and 36 g ofpure product in a 4: 1 ratio. The two main lots were dissolved in HCL, combined, evaporated under reduced pressure and dried (50° C., 0.2 mmHg, 24 h) to get 74 g (45.7%) of pure product (Compound 9) with a diastereomeric ratio of 48:51, as a white foam, mp about 75-85° C.

In order to produce an amorphous solid of the diastereomeric mixture, 74 g of the white foam was stirred in with t-butyl methyl ether (750 mL) resulting in a partial solution and a gummy solid residue. While stirring, heptanes (750 mL) was added slowly and the suspension was mechanically stirred for 1 hour until most of the gum was converted to a white solid. The solid was scraped up with a spatula and the resulting slurry was filtered. The solid was washed with heptanes (4x50mL) and dried under vacuum (50° C., 0.2mmHg, 24 h) to give a white, amorphous powder (64 g) with a broad melting range of ca 70-80° C. ^{1}H and ^{31}P NMR conformed to structure and HPLC showed a purity of 99.8% with a diastereomeric ratio of 46:54 (also confirmed by ^{31}P NMR).

Altemative method to make a solid mixture of Compound 9. After chromatography, the residue was co-evaporated with dichloromethane twice (5 mL/g) and dried for 24 h at 35-40° C. at 35-45 mTorr. The foam residue was sieved through a 250 micron screen and further dried under the same conditions until the residual dichloromethane fell below 400 ppm as measured by headspace GC. The resulting fine off-white to white amorphous powder has a glass transition temperature range of 53.7 to 63.5° C.

Characterization of Compound 9 (mixture of isomers):

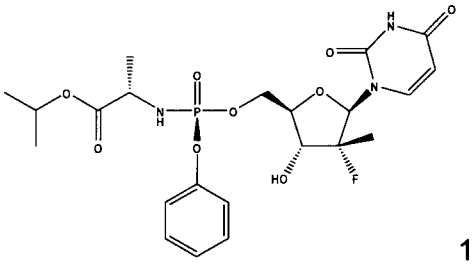
^{1}H-NMR ($CDCl_3$) 010.05 (brs, 1H, NH, *Sp),* 10.00 (brs, 1H, NH, *Rp),* 7.49 (d, 1H, C6-H, *Sp),* 7.36 (m, 5H, C6-H, *Rp,* aromatic), 7.23-7.14 (m, 6H, *Rp/Sp,* aromatic), 6.18 (br d, 2H, Cl'-H, *Rp/Sp),* 5.63 (d, 1H, C5-H, *Sp),* 5.58 (d, 1H, C5-H, *Rp),* 5.01 (m, 2H, CH-$(CH3)_2$ *Rp/Sp),* 4.46-4.33 (m, 8H, C-5'-H_2 , ala-NH, C3'-OH, *Rp/Sp),* 4.12 (m, 2H, ala-$CHCH_3$, *Rp/Sp),* 4.01-3.85 (m, 4H, C3'-H, C4'-H, *Rp/Sp), 1.3*91.22 (m, 12H, all CH_3, *Rp/Sp).*

^{31}P-NMR ($CDCl_3$) 03.60 *(Rp),* 3.20 Sp relative to triphenylphosphate at -17.80 ppm. ES-MS M+1 530.2. Elemental Analysis: Calculated % (including 0.29% water as found by Karl Fisher analysis) C, 49.75; H, 5.54; N, 7.90, F, 3.58, P, 5.84. Found %: C, 49.50; H, 5.44; N, 7.85; F, 3.62; P, 6.05.

Preparation of 2'-deoxy-2'-fluoro-2'-C-methyluridine (from US2010/0298257 Example 1)

In a 10 L flask, was added 3', 5'-O-dibenozyl-2'deoxy-2'-fluoro-2'-C-methyl-N4-benzoylcytidine (500 g, 0.874 mol) and 70% aqueous acetic acid (7.5 L). The solution was heated to reflux (110° C.) for 20 h. TLC indicated a complete reaction (RfO.6 in 5% methanol in dichloromethane (HCL)). The mixture was cooled to ambient temperature and diluted with water (2 L). After stirring for 2 h, the resulting precipitate was collected by filtration and the solid was rinsed with water (5 L) and dried in the atmosphere at ambient temperature for 12 h to afford 360 g (88%). This dibenzoyluridine intermediate was used directly in the next step by adding it all to freshly prepared methanolic ammonia (5.4 L, ca 25%) at 0° C. This temperature was maintained for 3 h and then allowed to warm to 15° C. for 24 h. TLC indicated a complete reaction (Rf 0.4 in 10% methanol in HCL). The reaction mixture was filtered through a Celite bed and concentrated under reduced pressure to give the crude product (216 g). The crude product was stirred with ethyl acetate (325 mL) for 3 h at ambient temperature. The resulting solid was collected by filtration and washed with ethyl acetate (216 mL). The solid was dried under vacuum at ambient temperature for 4 h to afford 160 g (78%) of the desired product in 98.7% HPLC purity. 1H-NMR (DMSO-d6) 011.44 (br s, 1H, NH), 7.95 (d, 1H, C-6H), 5.97 (d, 1H, C-1'H), 5.64 (d, 1H, C-5H), 3.84-3.77 (m, 3H, C-5'-Ha, C-3'H. C-4'H), 3.63-3.60 (m, 1H, C5'-Hb), 1.23 (d, 3H, C-2'-CH3). ES-MS M-I 259.

Example 10: Preparation of Compound 10 (from US2010/0298257)



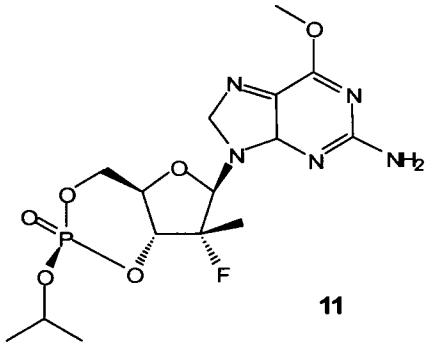
10

Direct precipitation of Compound 10 (from US2010/0298257; Example 4): To a stirred solution of L-alanine isopropyl ester hydrochloride (10.5 g, 61.5 mmol, azeotropically dried, two times, with 50 mL of toluene each time) in dichloromethane (100 mL) was added phenydichlorophosphate (7.5 mL, 50 mmol) at room temperature. The mixture was cooled to -10° C. and then was added a solution of N-Methylimidazole (30.5 mL, 384.3 mmol) in 30 mL of dichloromethane over a period of 30 min. After completion of the addition, the mixture was stirred between -10 and -15° C. for 1 h. To the above mixture was added 2'-deoxy-2'-fluoro-2'-C-methyluridine (10 g, 38.4 mmol) (see US2010/0298257 Example 1) in one lot and the mixture was stirred below -10° C. for 3 h and then slowly allowed to warm to 20° C. (6 h). The mixture was stirred at this temperature overnight (15 h) and then quenched with 10 mL of methanol. The solvent was evaporated and the residue was re-dissolved in EtOAc (200 mL). The EtOAc layer was washed with water (100 mL), 1N HCl (3x75 mL), 2% aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was dried under high vacuum for 2 h to give white foam (22 g).

The above foam was dissolved in 33 mL of HCl and then was added 65 mL of isopropyl ether to give a saturated solution. The solution was filtered though a small pad of Celite and the filtrate was stirred with seeds of Compound 10 for 72 h at ambient temperature (about 22° C.-note that cooling the suspension to 0° C. led to oiling out the crude product). The white solid was filtered, washed with isopropyl ether (20 mL) and dried to give 4.58 g (~85:15 mixture of Compound 10: R isomer at P respectively as determined by ^{31}P NMR) of a white powder. The above solid was suspended in 23 mL of HCL and then refluxed for 3 h. The mixture was cooled to room temperature and stirred for 15 h. The white solid was filtered, washed with 4.5 mL of cold HCl and dried under high vacuum at 45° C. to give pure Compound 10, mp 93.9-104.7° C HPLC purity 99.74% (3.11 g, 15.2% from the uridine nucleoside).

Compound 10: ^1H-NMR ($CDCl_3$) δ 8.63 (br s, ^1H, NH), 7.47 (d, 1H, C6-H), 7.30 (m, 2H, o-aromatic), 7.26-7.18 (m, 3H, m,p-aromatic), 6.18 (br d, lH, Cl'-H), 5.70 (d, lH, C5-H), 5.02 (sept, CH-$(CH_3)_2$), 4.53 (m, 2H, C-5'-H_2), 4.11 (d, lH, C3'-H), 3.97 (m, 3H, C3'-OH, C4'-H, ala-CH-CH_3), 3.77 (br s, lH, ala-NH), 1.39 (d, 3H,C2'- CH_3), 1.37 (d, 3H, ala- CH_3) 1.24 (d, 6H, CH-$(CH_3)_2$).

Example 11: Preparation of Compound 11 (from US 2010/0081628)



11

Synthesis of 6-Ethoxy-9-((4aR,6R,7R,7aR)-7-f1uoro-2-isopropoxy-7-methyl-2-oxo-tetrahydro-2,5-furo[3,2-d][1 ,3,2]dioxaphosphinin-6-yl)-9H-purin-2-yl-amine (Compound 11) (Compound 19, US 2010/0081628)

(2R,3R,4R,5R)-5-(2-Amino-6-ethoxy-purin-9-yl)-4- f1uoro-2-hydroxymethyl-4-methyl-tetrahydro-furan-3-ol (150 mg, 0.46 mmol) was dissolved in anhydrous pyridine (2 ml) at 0° C. A solution of 0.45 M lH-tetrazole in acetonitrile (2.55 mL) was added followed by bis (N,N-diisopropylamino) ispropylphosphoramidite (0.16 mL, 0.55 mmol, 1.2 eq). The mixture was allowed to slowly warm to ambient temperature over 3 h. TLC indicated a complete reaction. The reaction was quenched upon the addition of water (0.1 mL). The reaction solution was concentrated under reduced pres sure and then the residue was triturated with ethyl acetate (5 mL). The resulting white precipitate was removed by filtration and the filtrate was concentrated under reduced pressure.

The resulting intermediate cyclic phosphite residue was dissolved in acetonitrile (2 mL) and then treated with t-butyl hydroperoxide (70% in water, 0.19 mL) for 5 h at ambient temperature. TLC indicated a complete reaction. The reaction solution was concentrated under reduced pressure and the residue was purified by column chromatography (Analogix using a gradient of 0 to 5% IPA in HCL). The two diastereomers (Compound 11 and R-isomer at P) were separable. Fractions containing each diastereomer were separately combined and concentrated under reduced pressure to white solids to give 20 mg of each diastereomer (combined yield 20%).

Compound 11

^{31}P_NMR (162 MHz, DMSO): δ-6.49;

^{1}H-NMR (400 MHz, DMSO): δ =8.17 (s, 1H), 6.47 (bs, 2H), 6.27 (d, J=21.2 Hz, 1H), 4.73-4.62 (m, 4H), 4.45 (q, J=7.0 Hz, 2H), 4.27-4.21 (m, 1H), 1.39-1.34 (m, 9H), 1.20 (d, J=22.8 Hz, 3H).

MS (ESI): m/z 432.4 $[M+H]^+$

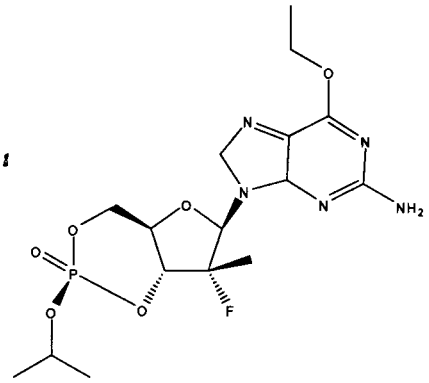
R-isomer at P

^{31}P_NMR (162 MHz, DMSO): δ =-4.68;

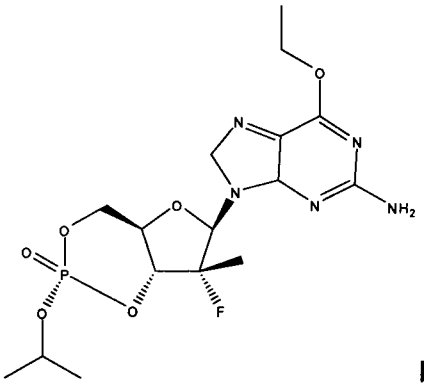
^{1}H -NMR (400 MHz, DMSO): δ =8.15 (s, 1H), 6.63 (s, 2H), 6.27 (d, J=21.2 Hz, 1H), 4.74-4.58 (m, 4H), 4.45 (q, J=6.4 Hz, 2H), 4.42-4.37 (m, 1H), 1.36 (t, J=7.2 Hz, 3H), 1.32 (d, J=3.6 Hz, 3H), 1.30 (d, J=3.6 Hz, 3H), 1.22 (d, J=22.8 Hz, 3H).

MS (ESI): m/z 432.4 $[M+H]^+$

The structures for Compound 11 and the R-Isomer at P are represented below.



11



R-isomer at P

Synthesis of (2R,3R,4R,5R)-5-(2-amino-6-ethoxy-9H-purin-9-yl)-4-f1uoro-2-(hydroxymethyl)-4-methyltetrahydro-furan-3-ol (Compound 16, US 2010/0081628)

To a 500 mL of dry round-bottomed flask was loaded (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (11 g, 20.92 mmol). Anhydrous absolute ethanol (210 mL) was added and followed by anhydrous K_2CO_3 (28.91 g, 209.2 mmol). The suspension was stirred and heated at 75° C under nitrogen for 5.5 h. All the starting material was consumed at that time by TLC test. The mixture was cooled to room temperature and solid was filtered out. The filtrate was neutralized by addition of glacial acetic acid (2.52 g) to pH~7 and concentrated under reduced pressure. The residue was dissolved in methanol and mixed with silica gel (15 g). The dried mixture of crude product and silica gel was transferred to an empty cartridge and separated through column chromatography (Analogix 220 g, gradient of 0 to 15% MeOH in DCM) to afford product (5% MeOH in DCM) as a white foam solid (3.73 g, 54.5%). A second white solid was isolated from column (10% MeOH in DCM, 1.44 g) and it is a mixture of two dimers of nucleoside. A more polar, third white solid was collected from column (15% MeOH in DCM, 0.47 g) and it is a mixture of trimers of nucleoside. HPLC purity of product 99.94%.

^{1}H-NMR (DMSO-d6): δ 8.16 (s, lH, 8-H), 6.55 (s, 2H, NH_2), 6.04 (d, lH, C1'-H), 5.66 (d, lH, 3'-OH), 5.24 (m, lH, 5'-OH), 4.44 (q, 2H, 6-0CH_2), 4.23-4.08 (m, lH, C3'-H), 3.91-3.82 (m, 2H, C4'-H and C5'-H_a,), 3.71-3.66 (m, lH, C5'-Hb), 1.36 (t, 3H, CH_3 of ethyl), 1.06 (d, 3H, C2'-CH_3).

Synthesis of (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (Compound 12, US 2010/0081628)

To a 12 L of three-neck round-bottomed flask was charged 6-chloro-2-aminopurine (225.4 g, 1.329 mol). Anhydrous tert-BuOH (4.5 L) was added and the solution was stirred with a mechanical stirrer at ambient temperature. Potassium tert-butoxide (solid, 151.6 g, 1.35 mol) was added portion-wise under a flow of nitrogen gas while stirring. The mixture was stirred at RT for an additional 30 min. To a 5 L round-bottomed flask was loaded the α-bromide (10, 197 g, 0.451 mol) and 3 L of anhydrous acetonitrile at ambient temperature. The bromide solution was added to the purine base suspension over 1 min at ambient temperature. The 5 L flask was rinsed with acetonitrile (2x1 L) to transfer bromide completely to the reaction mixture. The mixture was heated gradually to 50° C. over 2 h with a heating mantle and controller, and stirred for 20 h. The reaction was almost complete as shown by TLC beta (R_f 0.28, 30% EtOAc in hexanes). The reaction was quenched by the addition of sat. NH4Cl (200 mL) to form a suspension. The suspended solid was removed by filtration through a 3 cm pad of Celite in a 2.5 L porcelain Buchner funnel. The solid was washed with toluene (3x100 mL). The combined filtrate was neutralized by adding 6 N HCl solution until pH 7 (approx 220 mL). The mixture was concentrated under reduced pressure. When the volume of mixture was reduced to about one-third volume, additional precipitated solid was removed by filtration in a similar manner. The filtrate was further concentrated to a volume of about 800 mL. The residue was loaded onto a plug column (1.6 kg flash grade silica gel in a 6 L sintered glass Buchner funnel) and eluted (via suction) with a gradient of 10% ethyl acetate in hexanes (6 L) to remove non-polar impurities, 30% ethyl acetate in hexanes to afford a small amount of lactol (6 L), and then 40%-45% ethyl acetate in hexanes (4 L) to elute the main amount of product. The product containing fractions were combined, concentrated under reduced pressure and dried under vacuum (0.2 mmHg, 24 h, ambient temp.) to a white foam solid (150.7 g, β/α=14:1 by NMR. ^{1}H-NMR. ($CDCl_3$)beta: δ=1.33 (d, 22.4 Hz, 2'-C-CH_3), alpha: 1.55 (d, 22 Hz, 2'-C—CH_3).

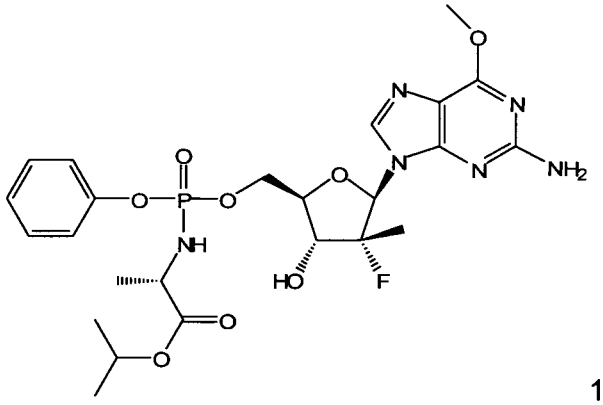
The product mixture foam was dissolved in methanol (700 mL) at ambient temperature. Upon standing, a solid slowly formed over 2 h. The suspension was cooled in a freezer to -5° C. for 17 h. The resulting white solid was collected by filtration and washed with cold MeOH (-5° C 3x60 mL) and ethyl ether (3x100 mL). The solid was dried under vacuum (0.2 mmHg, 24 h, ambient temp.) to afford 110.5 g of β-product with excellent de (β/α 99.8:1 by HPLC). The filtrate was partially concentrated (ca. 400 mL) and then diluted with more MeOH (400 mL) while heating to 60° C. The solution was cooled down to ambient temperature, seeded and the cooled to -5° C. The second crop was collected, washed and dried in a similar manner to give more product as a white solid (12.26 g) with similar diastereomeric purity. The mother liquor was concentrated to dryness under reduced pressure (ca. 25 g). The residue was a mixture of

β and α-isomers. It was subjected to automated silica gel column chromatography (Analogix, 240 g cartridge, 40% to 50% ethyl acetate in hexanes) to afford 14.52 g of product foam which was recrystallized from MeOH, washed and dried in a similar manner to afford an additional 8.46 g of product in high purity.

The three solids were judged to be of similar purity and they were combined to give 131.2 g of white crystalline product, (55% from bromosugar, 49% from lactol). Mp 160.5-162.0° C. HPLC purity 99.5% including 0.20% alpha.

^{1}H-NMR (pure β-anomer, $CDCl_3$): δ=8.03 (m, 2H, arom.), 7.93 (m, 2H, arom.), 7.88 (s, 1H, C8-H), 7.60 (m, 1H, arom.), 7.50 (m, 1H, arom.), 7.44 (m, 2H, arom.), 7.33 (m, 2H, arom.), 6.44 (dd, 1H, CII'-H), 6.12 (d, 1H, C3'-H), 5.35 (s, 2H, NH2), 5.00 (dd, 1H, C5'-Ha), 4.76 (m, 1H, C4'-H), 4.59 (dd, 1H, C5'-Hb), 1.33 (d, 3H, CH_3).

Example 12: Preparation of Compound 12 (from US20110015146)



12

Synthesis of (2S)-isopropyl2-((((2R,3R,4R,5R)-5(2-amino-6-methoxy-9H-purin-9-yl)-4-fluoro-3hydroxy-4-methyltetrahydrofuran-2-yl)methoxy) (phenoxy) phosphorylamino)propanoate

To a 250 mL dry round-bottomed flask were loaded phenyl dichlorophosphate (2.66 g, 12.61 mmol) and anhydrous dichloromethane (40 mL). The amino ester salt (2.60 g, 15.53 mmol) was added to the solution and the mixture was cooled to -5° C. N-Methyl imidazole (7.7 mL, 97 mmol) was then added quickly via a dry syringe at -5° C. and the solution was stirred at -5° C. for 1 h. The nucleoside ((2R,3R,4R,5R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol), 3.04 g, 9.7 mmol) was added from a vial in one portion at -5° C. and the solid was slowly dissolved in 20 minutes. The reaction temperature was allowed to rise to ambient temperature over 2 h. After 17 h, the reaction was not complete. More reagents were made (from phosphate (2.66 g), aminoester (2.60 g), and N-Methyl imidazole (3.8 mL, 48 mmol)) and added to the reaction mixture at -5° C. The reaction was stirred at room temperature for 2 more hours. The reaction was almost complete as shown by TLC result and diluted with 70 mL of dichloromethane. HCl solution (1 N, 70 mL) was added. The aqueous layer was separated and extracted with dichloromethane. The organic layer was

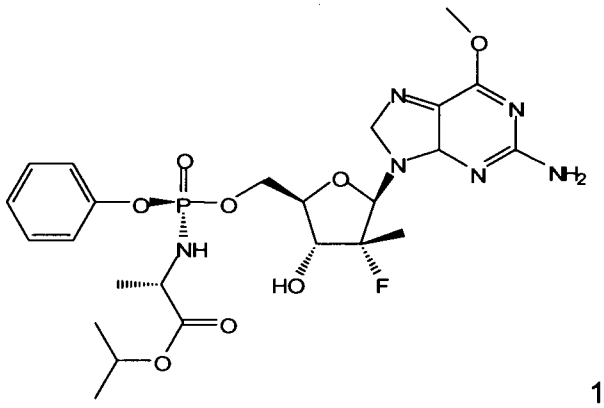
washed with saturated $NaHCO_3$, water, brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the sticky residue was purified through automated column chromatography using a 240 g cartridge and a gradient of 0-8% 2-PrOH in dichloromethane to afford product as a foam solid (4.16 g, 7.14mmol, 73% yield). HPLC purity 97.4%. NMR spectra of product showed it is a mixture of two diastereoisomers with a ratio of 1.2:1.

^{1}H-NMR (DMSO-d_6): δ=7.98 (1H, s, 8-H of one isomer), 7.95 (1H, s, 8-H of another isomer), 7.37-7.32 (2H, m, arom-H), 7.22-7.15 (3H, m, arom-H), 6.6 (2H, s, NH_2), 6.11 (1H, d, Cl'-H of one isomer), 6.09 (1H, d, Cl'-H of another isomer), 6.09-5.98 (1H, m, amide NH), 5.88 (1H, d, 3'-OH of one isomer), 5.81 (1H, d, 3'-H of another isomer), 4.85-4.75 (1H, hepta, methine H of iso-propyl), 4.46-4.27 (2H, m, C4'-H, α-H of amino ester), 4.15-4.07 (1H, m, C3'-H), 3.96 (3H, s, OCH_3), 3.82-3.72 (2H, m, C5'-H_a and C5'H_b), 1.23-1.06 (9H, m, CH_3's of amino ester), 1.03 (3H, d,C2'-CH_3).

^{31}P-NMR (DMSO-d6): 0=4.91 (one isomer), 4.72 (another isomer).

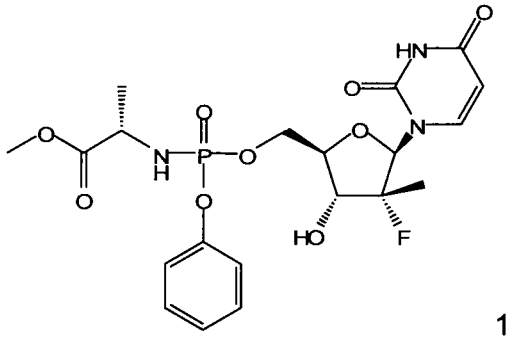
An alternate purification method is to chemically alter the minor 3' phosphoramidate by-product in order to simplify the chromatographic separation. The crude phosphoramidate product is dissolved in anhydrous pyridine (5 mL/g), and is treated with 0.5 molar equivalents of t-butyldimethylsilyl chloride at ambient temperature to react selectively with the free 5' primary hydroxyl of the 3' isomer impurity. Reaction progress can be monitored by LC/MS. Once the 3' isomer is converted to a 5'-tBDMS-3'-phosphoramidate derivative, the reaction is quenched with methanol (3 eq), concentrated under reduced pressure, partitioned between ethyl acetate and 5% citric acid and then the organic layer is concentrated. The residue is then subjected to chromatography which can now be done with a higher loading and a faster gradient and achieve a higher purity.

Example 13: Preparation of Compound 13 (from US20110015146)



13

Example 14: Preparation of Compound 14 (From US 7,964,580, Example 5)

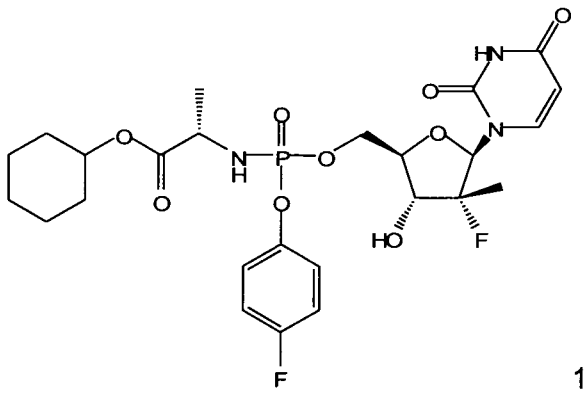


14

Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyluridine-5'-phenyl methoxy-alanyl phosphate)

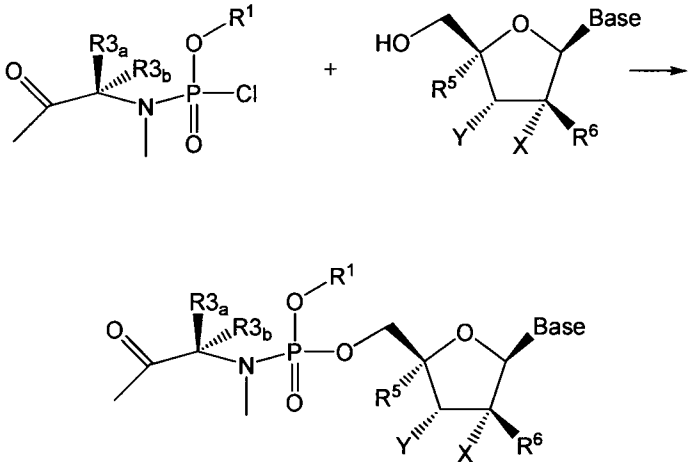
Phenyl methoxyalaninyl phosphorochloridate (1 g, 6.5 eq) dissolved in 3 mL of THF was added to a mixture of 2'-Deoxy-2'-fluoro-2'-C-methyluridine (0.15 g, 1 eq) and N-methylimidazole (0.3 g, 8 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30x2 mm column using a water/acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduce pressure to give the desired product (50.1 mg, 15.6%). ^{1}H NMR (DMSO-d_6) δ 1.20-1.27 (m, 6H), 3.58 (d, J=16.0 Hz, 3H), 3.75-3.92 (m, 2H), 4.015-4.379 (m, 2H), 5.54 (t, J=10.2 Hz, 1H), 5.83-5.91 (m, 1H), 6.00-616 (m, 1H), 7.18 (d, J=8.0 Hz, 2H), 7.22 (s, 1H), 7.35 (t, J=4.4 Hz, 2H), 7.55 (s, 1H), 11.52 (s, 1H); MS, m/e 502 $(M+1)^+$.

Example 15: Preparation of Compound 15 (Example 55, from US 7,964,580)



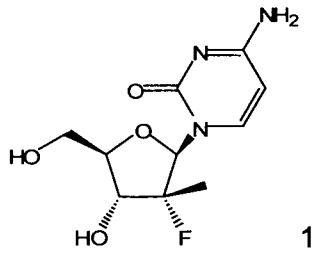
15

^{1}H NMR (DMSO-d_6) δ> 1.20-1.44 (m, 12H), 1.60-1.71 (m, 4H), 3.75-4.02 (m, 2H), 3.94-4.02 (m, 1H), 4.19-4.26 (m, 2H), 4.59-4.61 (m, 1H), 5.57 (t, J = 8.4 Hz, 1H), 5.85-6.06 (m, 3H), 7.17-7.23 (m,4H), 7.54 (d, J = 8.4 Hz, 1H), 11.50 (s, 1H); MS, m/e 587.92 $(M + 1)^+$



A general procedure for nucleoside phosphoramidate derivatives is reported at column 461 of US 7,964,580. A solution of the appropriate phosphorochloridate (6.5 equivalents) in anhydrous tetrahydrofuran (THF) may be added to a mixture of nucleoside (1 equivalent) and N-methylimidazole (8 equivalents) in anhydrous THF with vigorous stirring at room temperature with the reaction mixture stirred overnight. Solvent may be removed *in vacuo* and the crude purified by column chromatography and/or preparative thin layer chromatography to give the desired compound.

Example 16: Preparation of Compound 16 (From US 7,429,572)



16

Synthesis of (2'R)-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine Starting from Cytidine

Step 1: To a suspension of cytidine (100 g, 0.411 mol) in DMF (2.06 L) is added benzoic anhydride (102.4 g, 0.452mol). The mixture was stirred at room temperature for 20 h. The DMF was removed *in vacuo* and the residue was triturated with diethyl ether. The resulting solid was collected by suction filtration and washed with diethyl ether (2x200 mL). Further drying *in vacuo* at room temperature gave the N^4 benzamide (140.6 g, 98.3%). A portion of this material (139.3g, 0.401 mol) was dissolved in anhydrous pyridine (1.2 L) and was treated with 1,3-dichloro-1,1,3,3 -tetraisopropyl-disiloxane (141.4 mL, 0.441 mol) at room temp. The solution was stirred at room temperature overnight. The mixture was concentrated to near

dryness *in vacuo* and coevaporated with toluene (3x200 mL). The residue was treated with EtOAc (1.8L) and washed with HCl (2x200 mL, 0.05 N), $NaHCO_3$ (5%, 2x400 mL). The organic layer was washed, dried (Na_2SO_4), filtered, and evaporated to dryness. Compound 16-1 (Compound 4-1 from US 7,429,572) (256.5 g, >100%) was isolated as a white foam and used without further purification.

Step 2: Compound 16-1 (236.5 g, 0.40 mol) was dissolved in dry THF (1.22 L). Anhydrous DMSO (180.8 mL, 2.1 mol) was added and the resulting solution was cooled to between -20°C. and -15° C. Trifluoroacetic anhydride (90.6 mL, 0.64 mol) was added dropwise over 45 minutes and the solution was stirred between -20° C and -15° C. for 2 hrs after which anhydrous triethylamine (223.5 mL, 1.6 mol) was added over 20 min. The crude reaction containing ketone 16-2 was dissolved in EtOAc (500 mL), and the resulting solution was washed with H_2O (3x400 mL), dried (Na_2SO_4) and the solvents were removed *in vacuo* to give a yellow solid that was purified on a silica gel column eluting with a stepwise gradient of Et_2O (0-60%) in hexanes followed by a stepwise gradient of EtOAc (50-100%) in hexanes. The crude ketone so-obtained (~192 g) was crystallized from petroleum ether to give ketone 16-2 (Compound 4-2 from US 7,429,572) (138.91 g, 57.5% from cytidine) as a white solid and 22 g of unreacted starting material, 16-1, as a yellow solid.

Step 3: Compound 16-2 (48.57 g, 8.26 mmol) was dissolved in anhydrous toluene (~400 mL) and the solvent was removed *in vacuo* with exclusion of moisture. The residue was then further dried *in vacuo* (oil pump) for another 2 h. With strict exclusion of moisture, the residual foam was dissolved in anhydrous diethyl ether (1.03 L) under argon. The resulting solution was cooled to -78° C. under argon and MeLi (1.6 M, 258.0 mL, 0.413 mol) was added dropwise via additional funnel. After the addition was complete, the mixture was stirred for 2 h at -78° C. Aqueous 1M NH_4Cl (500 mL) was added slowly. After warming to room temperature, the mixture was washed with H_2O (2x500 mL), dried (Na_2SO_4), and then concentrated to dryness to give a brown foam (~60 g, >100%).

The reaction was performed two more times using 37.62 g and 56.4 g of compound 16-2. The combined crude products (128.0 g, 0.212 mol) were dissolved in THF (1.28 L) and treated with concd HOAc (23 mL, 0.402 mol). To the solution was added TBAF (384.0 mL, 1 M in THF). The solution was stirred at room temp for 0.75 h and the mixture was treated with silica gel (750 g) and concentrated to dryness. The powder was placed on a silica gel column packed in CH_2Cl_2. Elution with 1:7 EtOH-CH_2Cl_2 afforded a dark waxy solid that was pre-adsorbed on silica gel (300 g) and chromatographed as before. Compound 16-3 (Compound 4-3 from US 7,429,572) (46.4 g, 53.0% from 16-2) was isolated as an off-white solid. ^1H NMR (DMSO-d_6): δ 1.20 (s, 3H, CH_3), 3.62-3.69 (m, 2H,), 3.73-3.78 (m, 2H,), 5.19 (t, 1H, J=5.4 Hz, OH-5'), 5.25 (s, 1H, OH-2'), 5.52 (d, 1H, J=5.0 Hz, OH-3'), 5.99 (s, 1H, H-1'), 7.32 (d, 1H, J=5.8 Hz), 7.05 (Ψt, 2H, J=7.7 Hz), 7.62 (Ψt, 1H, J=7.3 Hz), 8.00 (d, 2H, J=7.3 Hz), 8.14 (d, 1H, J=6.9 Hz), 11.22 (s,

1H, NH). Anal. Calcd for $C_{17}H_{19}N_3O_6.0.5\ H_2O$: C, 55.13; H, 5.44; N, 11.35. Found: C, 55.21; H, 5.47; N, 11.33.

Step 4: Compound 16-3 (46.0 g, 0.13 mol) was dissolved in anhydrous pyridine and concentrated to dryness *in vacuo*. The resulting syrup was dissolved in anhydrous pyridine under argon and cooled to 0°C. with stirring. The brown solution was treated with benzoyl chloride (30 mL, 0.250 mol) dropwise over 10 min. The ice bath was removed and stirring continued for 1.5 h whereby TLC showed no remaining starting material. The mixture was quenched by the addition of water (5 mL) and concentrated to dryness. The residue was dissolved in a minimal amount of CH_2Cl_2 and washed with satd $NaHCO_3$(1x500 mL) and H_2O (1x500mL). The organic phase was dried (Na_2SO_4) and filtered, concentrated to dryness and chromatographed on silica gel eluting with a stepwise gradient of EtOAc-hexanes (25-60%) to provide compound 16-4 as yellow foam (Compound 4-4 from US 7,429,572) (48.5 g, 67%). ^1H NMR ($CDCl_3$): δ 1.64 (s, 3H, CH_3), 4.50 (m, 1H, H-4), 4.78-4.85 (m, 2H, H-5',5a'), 5.50 (d, lH, J=3.4 Hz, H-3'), 6.42 (s, lH, H-1), 7.44-7.54 (m, 7H, Ar), 7.57-7.66 (m, 3H, Ar), 7.94 (d, 2H, J=7.8 Hz), 8.05-8.09 (m, 4H, Ar), 8.21 (d, 1H, J=7.3 Hz). Anal. Calcd for $C_{31}H_{27}N_3O_8$: C, 65.37; H, 4.78; N, 7.38.

Found: C, 65.59; H, 4.79; N, 7.16.

Step 5: Compound 16-4 (7.50 g, 0.013 mol) was dissolved in anhydrous toluene (150 mL) under argon and cooled to -20° C. DAST (2.5 mL, 18.9 mmol) was added slowly and the cooling bath was removed after the addition was complete.

Stirring was continued for 1 h and the mixture was poured into satd $NaHCO_3$ (100 mL) and washed until gas evolution ceased. The organic phase was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography eluting with 1: 1 EtOAc-hexanes. Yield was 1.22 g (16.3%) of pure 16-5 (Compound 4-5 from US 7,429,572 as a white solid. mp 241° C. (CH_2Cl_2-hexanes); ^1H NMR ($CDCl_3$): δ 1.49 (d, 3H, J=22.4 Hz, CH_3), 4.64 (dd, 1H, J=3.44, 12.9 Hz, H-5'), 4.73 (d, 1H, J=9.5 Hz, H-4'), 4.90 (dd, 1H, J=2.4, 12.7 Hz, H-5a'), 5.56 (dd, 1H, J=8.6, 20.7 Hz, H-3'), 6.52 (d, 1H, J=18.0 Hz, H-1'), 7.47-7.57 (m, 7H, Ar), 7.62-7.71 (m, 3H, Ar), 7.89 (d, 2H, J=6.9 Hz), 8.07-8.11 (m, 5H, Ar), 8.67 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$): δ 3.3 (m). Anal. Calcd for $C_{31}H_{26}FN_3O_7.O.7\ H_2O$: C, 63.74; H, 4.72; N, 7.20. Found: C, 63.71; H, 4.54; N, 7.20.

Step 6: Compound 16-5 (6.30 g, 0.011 mol) was suspended in methanolic ammonia (ca 7 N, 150 mnL) and stirred at room temperature overnight. The solvent was removed *in vacuo*, co-evaporated with methanol (1x20 mL), and pre-adsorbed onto silica gel. The white powder was placed onto a silica gel column (packed in $CHCl_3$) and the column was eluted with 9% EtOH in $CHCl_3$, then 17% EtOH and finally 25% EtOH in $CHCl_3$. Concentration of the fractions containing the product, filtration through a 0.4 1am disk, and lyophilization from water afforded compound 16-6 (Compound 4-6 from US 7,429,572), 2.18 g (76%). ^1H NMR (DMSO-d_6): δ 1.17 (d, 3H, J=22.3 Hz, CH_3), 3.63 (dd, 1H, J=2.7, 13.7 Hz, H-5'), 3.70-3.84 (m, 3H, H-3', H-4', H-5a'), 5.24 (app s, 1H, OH-3'), 5.60 (d, 1H, J=5.4 Hz, H-5'), 5.74 (d, 1H, J=7.71 Hz, H-5), 6.07

(d, 1H, J=18.9 Hz, H-1'), 7.31 (s, 1H, NH_2), 7.42 (s, 1H, NH_2), 7.90 (d, 1H, J=7.3 Hz, H-6). ^{19}F NMR (DMSO-d_6): δ 2.60 (m). Anal. Calcd for $C_{10}H_{14}FN_3O_4.4.1.4\ H_20$: C, 44.22; H, 5.95; N, 14.77. Found: C, 42.24; H, 5.63; N, 14.54. Compound 16-6 (0.10 g, 0.386 mmol) was converted to the hydrochloride salt by dissolving in water (2 mL) and adjusting the pH to approximately 3.0 with 1 M HCl. The water was removed *in vacuo* and the residue was crystallized from aqueous EtOH to give 16-6 as the hydrochloride salt (71.0 mg). mp 243° C. (dec); ^1H NMR (DMSO-d_6): δ 1.29 (d, 3H, J=22.6 Hz, CH_3), 3.65 (dd, 1H, J=2.3, 12.7 Hz, H-5'), 3.76-3.90 (m, 3H, H-3', H-4', H-5a'), 5.96 (d, 1H, J=17.3 Hz, H-1'), 6.15 (d, 1H, J=7.9 Hz, H-5), 8.33 (d, 1H, J=7.9 Hz, H-6), 8.69 (s, 1.5H, NH), 9.78 (s, 1.5H, NH). ^{19}F NMR (DMSO-d_4): δ 1.69 (m). Anal. Calcd for $C_{10}H_{14}FN_3O_4.HCl$: C, 40.62; H, 5.11; N, 14.21. Found: C, 40.80; H, 5.09; N, 14.23.

BIOLOGICAL EXAMPLES

Assay Protocol

High throughput replicon assay (HTBS)

Replicon cells harboring H77 (genotype 1a) or Con1 (genotype 1b) HCV RNA and Renilla luciferase reporter were seeded in 384-well black plates at a density of 1.6 × 103 cells per well in 90 µl of DMEM culture medium, excluding G-418. Compounds were serially diluted in 100% DMSO and added to cells at a 1:225 dilution, achieving a final concentration of 0.44% DMSO in a total volume of 90 µL with a Biotek µFlow Workstation. Cell plates were incubated at 37°C with 5% CO2 for 3 days, after which culture media were removed and cells were assayed for luciferase activity as a marker for replication level. Luciferase expression was measured using Dual-Glo luciferase assay reagents (Promega, Madison, WI). Briefly, 20 µL of Dual-Glo luciferase buffer was added to lyse the cells for 10 min and subsequently 20 µL of a diluted Dual-Glo Stop & Glo substrate (1:100) was added to each well. Luminescence signal was measured on a Perkin Elmer Envision Plate Reader after incubation for10 minute. Luciferase levels were converted into percentages relative to the untreated controls (defined as 100%) and data were fit to the logistic dose response equation y = a/(1+(x/b)c) using XLFit4 software (IDBS, Emeryville, CA). EC_{50} values were calculated from the resulting equations. Alternatively, antiviral activity may be analyzed by HCV NS3 Protease IC_{50} Determination. HCV NS3 protease activity was monitored using a fluorescence resonance energy transfer (FRET) depsipeptide substrate (RET S1, Anaspec, San Jose, CA) based on the method of Taliani, Taliani M, Bianchi E, Narjes F, Fossatelli M, Urbani A, Steinkuhler C, et al. A continuous assay of hepatitis C virus protease based on resonance energy transfer depsipeptide substrates. Anal. Biochem. 1996; 240 (1):60-7, herein incorporated by reference with regard to performing such assay.

Briefly, 2–10 nM of purified NS3 protease domains were pre-incubated at 37°C for 10 minutes with 20µM isogenic NS4A peptide cofactors (Sigma, St. Louis, MO), in 40% glycerol

buffer with 50 mM HEPES pH 7.5 and 10 mM DTT. Compounds were diluted serially 1:3 in DMSO, incubated with the enzyme/cofactor mixture for 10 minutes and reactions were started by the addition of 2 μM RET S1 substrate (final concentration). Fluorescence increase was measured continuously over one hour using a Victor3 V fluorescence plate reader (Perkin Elmer, Waltham, MA). Initial velocities were calculated for each inhibitor concentration using Workout 1.5 software (DAZDAQ, East Sussex, UK) with the maximal slope algorithm. Velocity data were converted into percentages relative to the untreated control (defined as 100%) and non-linear regression was performed to calculate 50% inhibitory concentrations (IC_{50} values).

NS3 Enzymatic Potency: Purified NS3 protease is complexed with NS4A peptide and then incubated with serial dilutions of the compounds (DMSO used as solvent). Reactions are started by addition of dual-labeled peptide substrate and the resulting kinetic increase in fluorescence is measured. Non-linear regression of velocity data is performed to calculate IC_{50}s. Activity is initially tested against genotype 1b protease. Depending on the potency obtained against genotype 1b, additional genotypes (1a, 2a, 3) and or protease inhibitor resistant enzymes (D168Y, D168V, or A156T mutants) may be tested. BILN-2061 is used as a control during all assays. Compounds of the Examples were evaluated in this assay and were found to have IC_{50} values of less than about 1 μM.

Replicon Potency and Cytotoxicity: Huh-luc cells (stably replicating Bartenschlager's I389luc-ubi-neo/NS3-3'/ET genotype 1b replicon) are treated with serial dilutions of compound (DMSO is used as solvent) for 72 hours. Replicon copy number is measured by bioluminescence and non-linear regression is performed to calculate EC_{50}s. Parallel plates treated with the same drug dilutions are assayed for cytotoxicity using the Promega CellTiter-Glo cell viability assay. Depending on the potency achieved against the 1b replicon, compounds may be tested against a genotype 1a replicon and/or inhibitor resistant replicons encoding D168Y or A156T mutations. BILN-2061 is used as a control during all assays. Compounds of the Examples were evaluated in this assay and were found to have EC_{50} values of less than about 5 μM.

Effect of serum proteins on replicon potency

Replicon assays are conducted in normal cell culture medium (DMEM + 10%FBS) supplemented with physiologic concentrations of human serum albumin (40 mg/mL) or α-acid glycoprotein (1 mg/mL). EC_{50}s in the presence of human serum proteins are compared to the EC_{50} in normal medium to determine the fold shift in potency.

Enzymatic Selectivity: The inhibition of mammalian proteases including Porcine Pancreatic Elastase, Human Leukocyte Elastase, Protease 3, and Cathepsin D are measured at K_m for the respective substrates for each enzyme. IC_{50} for each enzyme is compared to the IC_{50} obtained with NS3 1b protease to calculate selectivity.

MT-4 Cell Cytotoxicity: MT4 cells are treated with serial dilutions of compounds for a five day period. Cell viability is measured at the end of the treatment period using the Promega CellTiter-Glo assay and non-linear regression is performed to calculate CC_{50}.

Compound Concentration Associated with Cells at EC_{50}: Huh-luc cultures are incubated with compound at concentrations equal to EC_{50}. At multiple time points (0 – 72 hours), cells are washed 2X with cold medium and extracted with 85% acetonitrile; a sample of the media at each time-point is also extracted. Cell and media extracts are analyzed by LC/MS/MS to determine the molar concentration of compounds in each fraction

Solubility and Stability: Solubility is determined by taking an aliquot of 10 mM DMSO stock solution and preparing the compound at a final concentration of 100 µM in the test media solutions (PBS, pH 7.4 and 0.1 N HCl, pH 1.5) with a total DMSO concentration of 1%. The test media solutions are incubated at room temperature with shaking for 1 hr. The solutions are then centrifuged and the recovered supernatants are assayed on the HPLC/UV. Solubility can be calculated by comparing the amount of compound detected in the defined test solution compared to the amount detected in DMSO at the same concentration. The stability of compounds after 1 hour incubation in the test media at 37°C is also determined.

Stability in Cryo-preserved Human, Dog, and Rat Hepatocytes: Each compound is incubated for up to 1 hour in hepatocyte suspensions (100 µl, 80,000 cells per well) at 37°C. Cryopreserved hepatocytes are reconstituted in the serum-free incubation medium. The suspension is transferred into 96-well plates (50 µL/well). The compounds are diluted to 2 µM in incubation medium and then are added to hepatocyte suspensions to start the incubation. Samples are taken at 0, 10, 30 and 60 minutes after the start of incubation and reaction can be quenched with a mixture consisting of 0.3% formic acid in 90% acetonitrile/10% water. The concentration of the compound in each sample is analyzed using LC/MS/MS. The disappearance half-life of the compound in hepatocyte suspension is determined by fitting the concentration-time data with a monophasic exponential equation. The data is also scaled up to represent intrinsic hepatic clearance and/or total hepatic clearance.

Stability in Hepatic S9 Fraction from Human, Dog, and Rat: Each compound is incubated for up to 1 hour in S9 suspension (500 µl, 3 mg protein/mL) at 37°C (n = 3). The compounds are added to the S9 suspension to start the incubation. Samples are taken at 0, 10, 30, and 60 minutes after the start of incubation. The concentration of the compound in each sample is analyzed using LC/MS/MS. The disappearance half-life of the compound in S9 suspension is determined by fitting the concentration-time data with a monophasic exponential equation.

Caco-2 Permeability: Both forward (A-to-B) and reverse (B-to-A) permeability is measured. Caco-2 monolayers are grown to confluence on collagen-coated, microporous, polycarbonate membranes in 12-well Costar Transwell® plates. The compounds are dosed on the apical side for forward permeability (A-to-B), and are dosed on the basolateral side for reverse permeability (B-to-A). The cells are incubated at 37°C with 5% CO_2 in a humidified incubator. At the

beginning of incubation, at 1 hr and 2 hr after incubation, a 200-µL aliquot is taken from the receiver chamber and replaced with fresh assay buffer. The concentration of the compound in each sample is determined with LC/MS/MS. The apparent permeability, Papp, is calculated.

Plasma Protein Binding: Plasma protein binding is measured by equilibrium dialysis. Each compound is spiked into blank plasma at a final concentration of 2 µM. The spiked plasma and phosphate buffer is placed into opposite sides of the assembled dialysis cells, which is then rotated slowly in a 37°C water bath. At the end of the incubation, the concentration of the compound in plasma and phosphate buffer is determined. The percent unbound is calculated using the following equation:

$$\% \text{ Unbound} = 100 \bullet \left(\frac{C_f}{C_b + C_f} \right)$$

Where C_f and C_b are free and bound concentrations determined as the post-dialysis buffer and plasma concentrations, respectively.

CYP450 Profiling: Each compound is incubated with each of 5 recombinant human CYP450 enzymes, including CYP1A2, CYP2C9, CYP3A4, CYP2D6 and CYP2C19 in the presence and absence of NADPH. Serial samples can be taken from the incubation mixture at the beginning of the incubation and at 5, 15, 30, 45 and 60 min after the start of the incubation. The concentration of the compound in the incubation mixture is determined by LC/MS/MS. The percentage of the compound remaining after incubation at each time point is calculated by comparing with the sampling at the start of incubation.

Stability in Rat, Dog, Monkey and Human Plasma: Compounds are incubated for up to 2 hour in plasma (rat, dog, monkey, or human) at 37°C. Compounds are added to the plasma at final concentrations of 1 and 10 µg/mL. Aliquots are taken at 0, 5, 15, 30, 60, and 120 min after adding the compound. Concentration of compounds and major metabolites at each timepoint are measured by LC/MS/MS. Biological data (antiviral potency [EC_{50}] is determined using a *Renilla* luciferase (RLuc)-based HCV replicon reporter assay – HCV 1b RLuc).

Biological Example 1: Anti-HCV Activity of the Combination of Compound 1 and Compound 2

Materials and Methods

Compound 1 and Compound 2 were synthesized by Gilead Sciences (Foster City, CA).

Cell Lines

HCV genotype 1b replicon cells (Huh-luc) were obtained from Reblikon (Mainz, Germany). The replicon in these cells is designated I389luc-ubi-neo/NS3-3'/ET and encodes a selectable resistance marker (neomycin phosphotransferase) as well as the firefly luciferase reporter gene. Huh-luc cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM; GIBCO, Carlsbad, CA) supplemented with 10% fetal bovine serum (FBS; Hyclone, Logan, UT) and 0.5 mg/mL of G-418 (GIBCO). Cells were passaged twice a week and maintained at subconfluent levels.

EC_{50} Determinations

Replicon cells were seeded in 96-well plates at a density of 5×10^3 cells per well in 100 μL of DMEM culture medium, excluding G-418. Compounds 1 and 2 were serially diluted 1:3 in 100% DMSO (Sigma). These serial dilutions were added to the cells at a 1:200 dilution to achieve a final concentration of 0.5% DMSO in a total volume of 200 μL. Plates were incubated at 37°C for 3 days, after which culture media were removed and cells were lysed and assayed for luciferase activity using a commercial luciferase assay (Promega, Madison, WI). HCV replication levels in drug-treated samples were expressed as a percentage of those in untreated controls (defined as 100%), and data were fit to the logistic dose response equation y=a/(1+(x/b)c) using XLFit4 software (IDBS, Emeryville, CA). EC_{50} values were calculated from the resulting equations as described previously (Delaney, W.E., et al., Antimicrobial Agents Chemotherapy, 45(6):1705-1713 (2001)).

Antiviral Combination Studies

Replicon cells were seeded in 96-well plates at a density of 5×10^3 cells per well in 100μL of culture medium. Compounds 1 and 2 were serially diluted in 100% DMSO as described above and added in a matrix format to 96-well plates, achieving a defined set of different drug concentrations and ratios in a final volume of 200μL and a final DMSO concentration of 0.5%. For each individual drug, the EC_{50} value was selected as the midpoint for the concentration range tested. Cells were incubated for three days and analyzed for luciferase expression as indicated above. For the combination study, two independent experiments were performed in triplicate.

Combination Data Analysis

Data were analyzed using the MacSynergy II program developed by Prichard and Shipman (Prichard MN, Aseltine KR, Shipman C, Jr., MacSynergyTM II, Version 1.0. University of Michigan, Ann Arbor, Michigan, 1993; Prichard M.N., Shipman C., Jr., Antiviral Res 14 (4-5):181-205 (1990); Prichard M.N., Shipman C, Jr., Antivir Ther 1 (1):9-20 (1996); Prichard M.N., et al., Antimicrob Agents Chemother 37 (3):540-5 (1993). The software calculates theoretical inhibition assuming an additive interaction between drugs (based on the Bliss Independence model) and quantifies statistically significant differences between the theoretical and observed inhibition values. Plotting these differences in three dimensions results in a surface where elevations in the Z-plane represent antiviral synergy and depressions represent antiviral antagonism between compounds. The calculated volumes of surface deviations are expressed in $nM^2\%$. Per Prichard and Shipman, combination effects are defined as:

- Highly synergistic if volumes > 100 nM^2.
- Slightly synergistic if volumes are > 50 and ≤ 100 nM^2.
- Additive if volumes are > –50 nM^2 and ≤ 50 nM^2.
- Slightly antagonistic if volumes are > –100 nM^2 and ≤ –50 nM^2.
- Antagonistic if volumes are ≤ –100 nM^2.

Results

Prior to initiating combination experiments, EC_{50} values in Huh-luc replicon cells were determined for Compound 1 and Compound 2 and results are shown in Table II. Both compounds had an antiviral effect.

Table II

Individual EC_{50}s for Anti-HCV Compounds 1 and 2 in Huh-luc Replicon Cells

Compound	EC_{50} (nM)[a]
Compound 1	3 ± 2
Compound 2	11 ± 3

[a] EC_{50} indicates average ± standard deviation for two or more independent experiments.

The antiviral effect of the combination of Compound 1 and Compound 2 was measured, and the resulting data were analyzed using MacSynergy II, which provides surface plots displaying significant deviations from additivity. Quantification of statistically significant deviations from

additivity indicated that the combination of Compounds 1 and 2 had synergy/antagonism volumes between -50 nM^2 and 50 nM^2 indicating additive antiviral effects as shown in Table III.

Table III

Quantification of Antiviral Synergy and Antagonism and Drug Interactions for Combination of Compound 1 and Compound 2

Drug(s) Used in Combination with Compound 2	**Synergy Volume (nM^2)[a]**	**Antagonism Volume (nM^2)[a]**	**Interaction**
Compound 1	13.5 ± 10.5	0.07 ± 0.07	Additive

[a] Values represent the mean ± standard deviation of two independent experiments performed in triplicate

The results of the *in vitro* experiments set forth in Table III indicate that Compound 2 has additive antiviral activity when combined with Compound 1.

Biological Example 2: Combinations with Compound 3

Materials and Methods

Antiviral Compounds

Compound 1 and Compound 3 were synthesized by Gilead Sciences (Foster City, CA). Ribavirin and IFN-α were purchased from Sigma (St. Louis, MO).

Cell Lines

HCV genotype 1b replicon cells (Huh-luc) were obtained from Reblikon (Mainz, Germany). The replicon in these cells is designated I389luc-ubi-neo/NS3-3'/ET and encodes a selectable resistance marker (neomycin phosphotransferase) as well as the firefly luciferase reporter gene. Huh-luc cells were maintained in Dulbecco's Modified Eagle Medium (D-MEM) with GlutaMAX™ (Invitrogen, Carlsbad, CA) supplemented with 10% fetal bovine serum (FBS, Hyclone, Logan, UT) and 0.5 mg/mL of G-418 (Invitrogen). Cells were passaged twice a week and maintained at subconfluent levels.

EC_{50} Determinations

Replicon cells were seeded in 96-well plates at a density of 5×10^3 cells per well in 100 μL of DMEM plus 10% FBS culture medium, excluding G-418. Compounds were serially diluted 1:3 in 100% DMSO (Sigma). These serial dilutions were added to the cells at a 1:200 dilution to achieve a final concentration of 0.5% DMSO in a total volume of 200 μL. Plates were incubated at 37°C for 3 days, after which culture media were removed and cells were lysed and assayed for luciferase activity using a commercial luciferase assay (Promega, Madison, WI). HCV replication levels in drug-treated samples were expressed as a percentage of those in untreated controls (defined as 100%), and data were fit to the logistic dose response equation $y=a/(1+(x/b)^c)$ using XLFit4 software (IDBS, Emeryville, CA). EC_{50} values were calculated from the resulting equations as described previously.

Antiviral Combination Studies

Replicon cells were seeded in 96-well plates at a density of 5×10^3 cells per well in 100μL of culture medium, excluding G-418. Compound 3 and other compounds were serially diluted in 100% DMSO as described above and added in a matrix format to 96-well plates, achieving a defined set of different drug concentrations and ratios in a final volume of 200μL and a final DMSO concentration of 0.5%. For each individual drug (with the exception of Ribavirin), the EC_{50} value was selected as the midpoint for the concentration range tested. For Ribavirin, which did not have a selective antiviral effect, a top dose of 6.2 μM was selected since this was approximately 3-fold below the concentration at which cytotoxicity started to be observed. Cells

were incubated with drugs for three days and analyzed for luciferase expression as indicated above. For each combination study, two independent experiments were performed in triplicate.

Combination Data Analysis

Data were analyzed using the MacSynergy II program developed by Prichard and Shipman. The software calculates theoretical inhibition assuming an additive interaction between drugs (based on the Bliss Independence model) and quantifies statistically significant differences between the theoretical and observed inhibition values. Plotting these differences in three dimensions results in a surface where elevations in the Z-plane represent antiviral synergy and depressions represent antiviral antagonism between compounds. The calculated volumes of surface deviations are expressed in $nM^2\%$. Per Prichard and Shipman, combination effects are defined as follows:

- Strong synergy if volumes > 100 nM^2; this amount of synergy is probably important *in vivo*
- Moderate synergy if volumes are > 50 and ≤ 100 nM^2; this amount of synergy may be important *in vivo*
- Minor synergy if volumes are > 25 and < 50 nM^2
- Additivity if volumes are > –25 nM^2 and ≤ 25 nM^2
- Minor antagonism if volumes are < -25 and > -50 nM^2
- Moderate antagonism if volumes are > -100 nM^2 and ≤ -50 nM^2; this amount of antagonism may be important *in vivo*
- Strong antagonism if volumes are ≤ -100 nM^2; this amount of antagonism is probably important *in vivo*

Results

EC_{50} Values for Individual Compounds in Huh-luc Replicon Cells.

Prior to initiating combination experiments, EC_{50} values in Huh-luc replicon cells were determined for each compound as shown in Table IV. All compounds had an antiviral effect with the exception of Ribavirin, which had no antiviral activity up to concentrations which were beginning to show cytotoxicity.

Table IV

Individual EC_{50}s for Anti-HCV Compounds in Huh-luc Replicon Cells

Compound	**EC_{50} (nM)[a]**
Compound 3	2.3 ± 2.6
IFN-α	0.105 ± .003 (U/mL)[b]
Ribavirin	> 12,500
Compound 1	0.4 ± 0.14

[a] EC_{50} indicates average ± standard deviation for two or more independent experiments.

[b] INF-α EC_{50} is expressed in Units (U) per milliliter (mL) instead of a nanomolar concentration.

Combination Antiviral Effects and Drug Interactions

The antiviral effects of Compound 3 when combined with IFN-α, Ribavirin, and Compound 1 were assayed. The resulting data were analyzed using MacSynergy II, which provides surface plots displaying significant deviations from additivity. Quantification of statistically significant deviations from additivity indicated that combinations of Compound 3 with IFN-α resulted in minor synergy (synergy volumes of 32 and 36.5 nM^2, respectively; Table V). The combination of Compound 3 with the non-nucleoside NS5B inhibitor Compound 1 yielded an synergy volume of 14.5 nM^2 which indicates an additive antiviral interaction. None of the compounds yielded antiviral antagonism volumes outside of the additive range (> –25 nM^2) when combined with Compound 3 as shown in Table V.

Table V

Quantification of Antiviral Synergy and Antagonism and Drug Interactions for Drug Combinations with Compound 3

Drug(s) Used in Combination with Compound 3	**Synergy Volume (nM^2)[a]**	**Antagonism Volume (nM^2)[a]**	**Interaction**
IFN-α	32 ± 4.2	0.15 ± 0.2	Minor synergy
Ribavirin	54 ± 14.1	1.6 ± 2.3	Moderate synergy
Compound 1	14.5 ± 0.7	4.22 ± 5.0	Additive

[a] Values represent the mean ± standard deviation of two independent experiments performed in triplicate

These *in vitro* antiviral combination experiments indicate that the novel HCV NS3 protease inhibitor Compound 3 has minor synergy when combined with IFN-α and moderate synergy when combined with Ribavirin. These results suggest that Compound 3 could potentially be used in combination with the current standard of care (PEG-IFN-α plus ribavirin) in HCV patients to achieve enhanced viral load suppression without reducing the efficacy of any of the individual drugs. Combinations of Compound 3 with non-nucleoside (Compound 1) NS5B polymerase inhibitors resulted in additivity. These results indicate that Compound 3 may also be suitable for exploring drug combinations comprised of multiple classes of specific HCV inhibitors in patients.

Biological Example 3: Compound 4 Combinations

Materials and Methods

Anti-HCV Agents

Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, and Compound 6 were synthesized by Gilead Sciences (Foster City, CA). Puromycin, IFN-α and Ribavirin were purchased from Sigma (St. Louis, MO). Calcein AM was purchased from Anaspec (Fremont, CA).

Cell Line and Cell Culture

The HCV genotype 1a replicon cell line used in this study was described previously. The cells were grown in cell culture medium containing Dulbecco's Modified Eagle Medium (DMEM) with GlutaMAX (Gibco, Carlsbad, CA, Cat# 10569-044), supplemented with 10% FBS (HyClone, Logan, UT, Cat#SH30071.03), 100 Units/mL Penicillin, 100 μg/mL Streptomycin (Gibco, Carlsbad, CA, Cat# 15140-122), and 0.1 mM non-essential amino acids (Gibco, Carlsbad, CA, Cat#11140-050). Replicon cells were maintained in 0.5 mg/mL Geneticin (Invitrogen, Carlsbad, CA, Cat# 10131-035) to prevent the loss of HCV replicon. The cells were passaged every 3-4 days before reaching confluency.

HCV Replicon Assay for EC_{50}, CC_{50} Determinations and Combination Studies

All compounds were supplied in 100% DMSO except for IFN-α, which was supplied in buffer specified by the manufacture (Sigma, St. Louis, MO, Cat#I4276). Compound serial dilutions were performed in 100% DMSO except for IFN-α, which was serially diluted in cell culture medium described in section 3.2. All serial dilutions were performed in 384-well polypropylene plates (Thermo Scientific, Hudson, NH, Cat#4341) using a Biomek FX Workstation. For EC_{50} and CC_{50} determinations, test compounds were serially diluted in ten steps of 1:3 dilutions in columns 3-20 of the 384-well plates. For combinational studies, one compound was serially diluted in nine steps of 1:2 dilutions toward the horizontal direction with the other compound serially diluted in seven steps of 1:2 dilutions toward the vertical direction. This achieved a defined set of different drug concentrations and ratios. For each individual drug, the EC_{50} value was selected as the midpoint for the concentration range tested. All serial dilutions were performed in four replicates per compound within the same 384-well plate. 100% DMSO was added into column 1-2 of each serial dilution 384-well plate. A HCV protease inhibitor ITMN-191 at 100 μM was added into column 23 as a control of 100% inhibition of HCV replication while puromycin at 10 mM was added into column 24 as a control of 100% cytotoxicity.

To each well of a black polystyrene 384-well plate (Greiner Bio-one, Monroe, NC, Cat#781086, cell culture treated), 90 μL of cell culture medium (without geneticin) containing 2000

suspended HCV replicon cells was added with a Biotek μFlow Workstation. For compound transfer into cell culture plates, 0.4 μL of compound solution from the compound serial dilution plate was transferred to the cell culture plate on a Biomek FX Workstation. The DMSO concentration in the final assay wells was 0.44%. The plates were incubated for 3 days at 37 °C with 5% CO_2 and 85% humidity.

The HCV replicon assay was a multiplex assay which can assess both cytotoxicity and anti-replicon activity from the same well. The CC_{50} assay was performed first. The media in the 384-well cell culture plate was aspirated and the wells were washed four times with 100 μL 1 X PBS each, using a Biotek ELX405 plate washer. A volume of 50 μL of a solution containing 400 nM calcein AM (Anaspec, Fremont, CA, Cat#25200-056) in 1 X PBS was added to each well of the plate with a Biotek μFlow Workstation. The plate was incubated for 30 minutes at room temperature before the fluorescence signal (excitation 490 nm, emission 520 nm) was measured with a Perkin Elmer Envision Plate Reader.

EC_{50} assay was performed in the same wells as CC_{50} assay. The calcein-PBS solution in the 384-well cell culture plate was aspirated with a Biotek ELX405 plate washer. A volume of 20 μL of Dual-Glo luciferase buffer (Promega, Madison, WI, Cat#E298B) was added to each well of the plate with a Biotek μFlow Workstation. The plate was incubated for 10 minutes at room temperature. A volume of 20 μL of a solution containing 1:100 mixture of Dual-Glo Stop & Glo substrate (Promega, Madison, WI, Cat#E313B) and Dual-Glo Stop & Glo buffer (Promega, Madison, WI, Cat#E314B) was then added to each well of the plate with a Biotek μFlow Workstation. The plate was then incubated at room temperature for 10 minutes before the luminescence signal was measured with a Perkin Elmer Envision Plate Reader.

Data Analysis

The cytotoxicity effect was determined by calcein AM conversion to fluorescent product. The percent cytotoxicity was calculated by equation 1:

$$\% \text{ cytotoxicity or } \% \text{ inhibition} = 100 \times (1 - \frac{X_C - M_B}{M_D - M_B}) \quad (1)$$

where X_C is the fluorescence signal from the compound-treated well; M_B is the average fluorescence signal from puromycin-treated wells; M_D is the average fluorescence signal from DMSO-treated wells. The anti-HCV replication activity was determined by the luminescence signal generated from the reporter renilla luciferase of the HCV replicon. The percent inhibition on HCV replicon was calculated using equation 1, where X_C is the luminescence signal from compound-treated well; M_B is average luminescence signal from the ITMN-191-treated wells; M_D is the average luminescence signal from DMSO-treated wells.

The CC_{50} values were determined as the testing compound concentration that caused a 50% decrease of cell viability. The EC_{50} values were determined as the testing compound concentration that caused a 50% decrease in HCV replication. Both CC_{50} and EC_{50} values were obtained using Pipeline Pilot 5.0 software package (Accelrys, San Diego, CA) by nonlinear regression fitting of experimental data to equation 2:

$$y = d + \frac{a - d}{[1 + (\frac{x}{c})^b]} \quad (2)$$

where *y* is the observed % inhibition of HCV replicon at *x* concentration of compound; *d* is estimated response at zero compound concentration; *a* is estimated response at infinite compound concentration; *c* is the mid-range concentration (CC_{50} or EC_{50}); *b* is the Hill slope factor.

The combination study experimental data were analyzed using the MacSynergy II program developed by Prichard and Shipman. The software (MacSynergy™ II, University of Michigan, MI) calculates theoretical inhibition assuming an additive interaction between drugs (based on the Bliss Independence model) and quantifies statistically significant differences between the theoretical and observed inhibition values. Plotting these differences in three dimensions results in a surface where elevations in the Z-plane represent antiviral synergy and depressions represent antiviral antagonism between compounds. The calculated volumes of surface deviations are expressed in $nM^2\%$. Per Prichard and Shipman, combination effects are defined as:

- Strong synergy: > 100 $nM^2\%$
- Moderate synergy: > 50 and ≤ 100 $nM^2\%$
- Minor synergy: > 25 and ≤ 50 $nM^2\%$
- Additivity: ≤ 25 and > –25 $nM^2\%$
- Minor antagonism: ≤ –25 and > –50 $nM^2\%$
- Moderate antagonism: ≤ –50 and > –100 $nM^2\%$
- Strong antagonism: ≤ –100 $nM^2\%$

For each combination study, three independent experiments were performed with four replicates in each experiment.

Results

Antiviral Activity and Cytotoxicity of Individual Compounds in HCV Genotype 1a Replicon Assay.

The anti-HCV activity and cytotoxicity of Compound 4 and other compounds were tested in Huh-7 cells carrying a HCV genotype 1a replicon. The EC_{50} and CC_{50} values are listed in Table VI. There is no significant cytotoxicity observed for all compounds up to the highest concentrations tested.

Table VI

EC_{50} and CC_{50} of Compounds used in this Study against HCV Genotype 1a Replicon

Compounds	EC_{50}[a] (nM)	CC_{50}[a] (nM)
Compound 1	19 ± 8	>44400
Compound 2	496 ± 135	>22200
Compound 3	49 ± 18	>22200
Compound 4	201 ± 74	>44400
Compound 5	15 ± 2.4	>44400
Compound 6	0.033 ± 0.011	>44400
IFN-α	1.4 ± 0.3[b]	>50[b]
Ribavirin	36482 ± 17507	>88800

[a] Values are average ± standard deviation for three or more independent experiments

[b] IFN-α values are expressed in Units (U) per milliliter (mL) instead of a nanomolar concentration

Antiviral Activity and Cytotoxicity of Compound 4 in Combination with Other Classes of Anti-HCV Agents.

The antiviral effects of Compound 4 in combination with other anti-HCV compounds were evaluated using the HCV genotype 1a replicon. The results were analyzed using MacSynergy II, which provides surface plots displaying significant deviations from additivity. Synergy and antagonism volumes (nM^2%) calculated from deviations from additive surface are summarized in Table VII. At 95% confidence interval, the mean synergy and antagonism volumes are between 25 and –25 nM^2 % when Compound 4 was combined with IFN-α, Compound 2 and Compound 6, indicative of additive interaction with those compounds. Furthermore, Compound 4 shows synergy volumes in the range of 25 to 50 nM^2% when combined with Compound 1, Compound 5 or Compound 3, suggesting minor synergistic interaction.

Table VII

Quantification of Antiviral Synergy and Antagonism and Drug Interactions for Drug Combinations with Compound 4

Drug(s) Used in Combination with Compound 4	**Synergy Volume (nM^2%)[a]**	**Antagonism Volume (nM^2%)[a]**	**Interaction**
Compound 1	34 ± 26	–1 ± 2	Minor synergy
Compound 2	22 ± 14	–2 ± 3	Additivity
Compound 3	26 ± 6	–3 ± 2	Minor synergy
Compound 5	26 ± 28	–1 ± 3	Minor synergy
Compound 6	19 ± 17	–7 ± 7	Additivity
IFN-α	12 ± 6	0 ± 0	Additivity
Ribavirin	1 ± 1	–43 ± 20	Minor antagonism

Values represent the mean ± standard deviation of three independent experiments performed in four replicates

In all combination studies, the cell viability is higher than 85% at all concentration ratios and all drug combinations show additive effects on the cytotoxicity as shown in Table VIII.

Table VIII

Quantification of Cytotoxicity Synergy and Antagonism and Drug Interactions for Drug Combinations with Compound 4

Drug(s) Used in Combination with Compound 4	**Synergy Volume (nM^2%)[a]**	**Antagonism Volume (nM^2%)[a]**	**Interaction**
Compound 1	13 ± 11	0 ± 1	Additivity
Compound 2	17 ± 14	0 ± 0	Additivity
Compound 3	3 ± 5	0 ± 0	Additivity
Compound 5	15 ± 8	-10 ± 7	Additivity
Compound 6	8 ± 4	0 ± 0	Additivity
IFN-α	8 ± 12	-7 ± 13	Additivity
Ribavirin	4 ± 3	-1 ± 2	Additivity

[a] Values represent the mean ± standard deviation of three independent experiments performed in four replicates

However, Compound 4 shows an antagonism volume of -43 $nM^2\%$ when combined with Ribavirin, suggesting a minor antagonistic interaction.

Table IX

Quantification of Cytotoxicity Synergy and Antagonism and Drug Interactions for Drug Combinations with Ribavirin

Drug Used in Combination with Ribavirin	**Synergy Volume ($\mu M^2\%$)[a]**	**Antagonism Volume ($\mu M^2\%$)[a]**	**Interaction**
Compound 4	4 ± 3	-1 ± 2	Additivity

[a] Values represent the mean ± standard deviation of three independent experiments performed in four replicates

The Ribavirin concentration that shows the highest antagonism with Compound 4 is around 0.5 to 1 μM, which is about 10-fold lower than the steady-state plasma concentration of Ribavirin (6-11 μM) observed in human at a dose of 800 mg/day. At this physiological concentration of Ribavirin (6-11 μM), the antagonistic interaction between Ribavirin and Compound 4 is minimal across a wide range of Compound 4 concentrations (0-0.44 μM). Therefore, the observed minor antagonism between Ribavirin and Compound 4 in the *in vitro* replicon system is unlikely to have clinical significance.

Conclusions

The antiviral activity of Compound 4 (in a diastereomeric mixture) was tested in combination with the current standard of care (IFN-α/Ribavirin), as well as Gilead Sciences' internal developmental candidates Compound 1 and Compound 5 (non-nucleoside NS5B inhibitors), Compound 2 and Compound 3 (NS3 protease inhibitors), and Compound 6 (NS5A inhibitor). As summarized in Table VIII, Compound 4 showed additive antiviral activity in combination with IFN-α, Compound 2 and Compound 6 and minor synergy with Compound 1, Compound 5 and Compound 3.

The combination of Compound 4 with Ribavirin resulted in a minor antagonism at Ribavirin concentrations between 0.5 to 1 μM, which is approximately 10-fold lower than its steady-state physiological concentration (6-11 μM) in human plasma. At the clinically relevant Ribavirin concentration, the antagonistic interaction between the two compounds became negligible.

Biological Example 4: Compound 5 Combinations

The antiviral activity of Compound 5 was tested in GT-1b Huh-lunet cells (using substantially the same methods as in the assays for Compound 4) in combination with the internal developmental compounds Compound 1, Compound 2 and Compound 3 (NS3 protease inhibitors), Compound 6 (NS5A inhibitor), Compound 4 (C-nuc NS5B inhibitor) and also the approved HCV therapeutics PEG-IFN-α and Ribavirin. Combination data were analyzed based on the Bliss Independence model using MacSynergy II software. Results of the combination assays were expressed as mean synergy and antagonism volumes (nM^2) calculated at 95% confidence from two independent experiments performed in triplicate. Combination effects are defined as:

- Strong synergy if volumes > 100 nM^2; this amount of synergy is probably important *in vivo*
- Moderate synergy if volumes are > 50 and ≤ 100 nM^2; this amount of synergy may be important *in vivo*
- Minor synergy if volumes are > 25 and < 50 nM^2
- Additivity if volumes are > –25 and ≤ 25 nM^2
- Minor antagonism if volumes are < -25 and > -50 nM^2
- Moderate antagonism if volumes are > -100 nM^2 and ≤ -50 nM^2; this amount of antagonism may be important *in vivo*
- Strong antagonism if volumes are ≤ -100 nM^2; this amount of antagonism is probably important *in vivo*.

The combination of the allosteric NS5B inhibitors Compound 1 and Compound 5 resulted in moderate synergy in the replicon assay. Studies with other HCV inhibitors, including PEG-IFN-α and Ribavirin, revealed additive to minor synergistic interactions.

Table X

Antiviral effects of Compound 5 in combination with other anti-HCV drugs in 1b Huh-luc replicon cells

Drug used in combination with Compound 5	Synergy Volume (nM^2) [a]	Antagonism Volume (nM^2) [a]	Interaction
Compound 1	70 ± 26	0 ± 0	Moderate synergy
Compound 2	22 ± 12	-7 ± 7	Additive
Compound 3	19 ± 13	-2 ± 2	Additive
Compound 4	26 ± 28	-1 ± 3	Minor synergy
Compound 6	34 ± 19	0 ± 0	Minor synergy
PEG-IFN-α	31 ± 23	-2 ± 4	Minor synergy
Ribavirin	12 ± 8	-12 ± 9	Additive

[a] Values represent the mean ± standard deviation of two independent experiments performed in triplicate

Biological Example 5: Compound 6, Combinations

Materials and Methods

Compounds

Compound 1, Compound 2, Compound 3, Compound 6 and Compound 7 were synthesized by Gilead Sciences (Foster City, CA). IFN-α and Ribavirin were purchased from Sigma (St. Louis, MO).

Cell Lines

HCV genotype 1b replicon cells (Huh-luc) were obtained from Reblikon (Mainz, Germany). The replicon in these cells is designated I389luc-ubi-neo/NS3-3'/ET and encodes a selectable resistance marker (neomycin phosphotransferase) as well as the firefly luciferase reporter gene. Huh-luc cells were maintained in Dulbecco's Modified Eagle's Medium GlutaMax (DMEM; Invitrogen, Carlsbad, CA) supplemented with 10% fetal bovine serum (FBS; Hyclone, Logan, UT), 1X penicillin/streptomycin, 1X nonessential amino acids and 0.5 mg/mL of G-418 (all from Invitrogen, Carlsbad, CA). Cells were passaged twice a week and maintained at subconfluent levels.

Assays

Antiviral Activity Assay in HCV Huh-luc Replicon Cells

Replicon cells were seeded in 96-well plates at a density of 7×10^3 cells per well in 100 μL of DMEM culture medium, excluding G-418. Compounds were serially diluted 1:2 in 100% DMSO. Serial dilutions were added to the cells at a 1:200 dilution to achieve a final concentration of 0.5% DMSO in a total volume of 200 μL. Plates were incubated at 37°C for 3 days, after which culture media were removed and cells were lysed and assayed for luciferase activity using a commercial luciferase assay (Promega, Madison, WI).

Antiviral Combination Studies

Replicon cells were seeded in 96-well plates at a density of 7×10^3 cells per well in 100 μL culture medium, excluding G-418. Compound 6 and other compounds were serially diluted 1:2 in 100% DMSO and added in a matrix format to 96-well plates, achieving a defined set of different drug concentrations and ratios in a final volume of 200 μL and a final DMSO concentration of 0.5%. For each individual drug, the EC_{50} value was selected as the midpoint for the concentration range tested. Cells were incubated for 3 days and analyzed for luciferase expression using a commercial luciferase assay (Promega). For each combination study, two independent experiments were performed in triplicate.

Cellular Cytotoxicity Determination

Replicon cells were seeded and treated with drugs as described for the antiviral combination studies above. After three day incubation at 37°C, the culture media was removed and cells were lysed and assayed for cytotoxicity using a CellTiter-Glo Luminescent Cell Viability Assay (Promega) according to the manufacturer's instructions. Relative Light Units were converted into percentages relative to the untreated controls (defined as 100%).

Data Analysis

EC_{50} Calculations

Following EC_{50} assays, luciferase levels in drug-treated samples were expressed as a percentage of those in untreated controls (defined as 100%). EC_{50} values were calculated by nonlinear regression analysis of replicate data sets using XLfit 4 software (IDBS, Emeryville, CA).

Calculation of Antiviral Synergy and Antagonism

Following combination assays, luciferase levels in drug-treated samples were expressed as a percentage of those in untreated controls (defined as 100%). Replicate data sets were then analyzed using the MacSynergy II program developed by Prichard and Shipman. The software (MacSynergy™ II, University of Michigan, MI) calculates theoretical inhibition assuming an additive interaction between drugs (based on the Bliss Independence model) and quantifies statistically significant differences between the theoretical and observed inhibition values. Plotting these differences in three dimensions results in a surface where elevations in the Z-plane represent antiviral synergy and depressions represent antiviral antagonism between compounds. The calculated volumes of surface deviations are expressed in nM^2%. Per Prichard and Shipman, combination effects are defined as:

- Strong synergy if volumes > 100 nM^2; this amount of synergy is probably important *in vivo*
- Moderate synergy if volumes are > 50 and ≤ 100 nM^2; this amount of synergy may be important *in vivo*
- Minor synergy if volumes are > 25 and < 50 nM^2
- Additivity if volumes are > –25 nM2 and ≤ 25 nM^2
- Minor antagonism if volumes are < -25 and > -50 nM^2
- Moderate antagonism if volumes are > -100 nM^2 and ≤ -50 nM^2; this amount of antagonism may be important *in vivo*
- Strong antagonism if volumes are ≤ -100 nM^2; this amount of antagonism is probably important *in vivo.*

Results

Antiviral Activity of Individual Compounds in Huh-luc Replicon Cells.

Prior to initiating combination experiments, the antiviral activity of individual compounds was determined in Huh-luc replicon cells. EC_{50} values consistent with historical results were observed with all seven compounds.

Table XI

Individual EC_{50} Values for Anti-HCV Compounds in Huh-luc Replicon Cells

Compound	**EC_{50} (nM)[a]**
IFN-α [b]	0.05 U/ml ± 0.04
Ribavirin	> 12 ± 2.4
Compound 1	0.96 ± 0.39
Compound 2	5.0 ± 0.0
Compound 3	3.0 ± 1.2
Compound 6	0.0018 ± 0.0007
Compound 7	1245 ± 341

[a] EC_{50} indicates arithmetic mean ± standard deviation for three or more independent experiments.

[b] IFN-α EC_{50} is expressed in Units (U) per milliliter (mL) instead of a nanomolar concentration.

Combination Antiviral Effects and Drug Interactions

The antiviral effects of Compound 6 in combination with other HCV inhibitors were evaluated using the HCV 1b replicon system. The resulting data were analyzed using MacSynergy II, which provides surface plots displaying significant deviations from additivity. Quantification of statistically significant deviations from additivity from two independent experiments is summarized in Table XII. Combinations of Compound 6 with IFN-α or Compound 1 resulted in synergy volumes of 32 and 34 nM^2, respectively, indicating minor synergy. Ribavirin, Compound 2 and Compound 7 yielded synergy volumes of 61, 52 and 51 when combined with Compound 6, respectively, indicating a moderate synergistic interaction between Compound 6 and these three HCV inhibitors. The combination of Compound 6 with Compound 3 resulted in a synergy volume of 132 nM^2 % signifying a strongly synergistic antiviral interaction. None of

the compounds yielded antiviral antagonism volumes outside of the additive range (> -25 nM) when combined with Compound 6.

Table XII

Quantification of Antiviral Synergy and Antagonism and Drug Interactions for Drug Combinations with Compound 6

Drug(s) Used in Combination with Compound 6	**Synergy Volume (nM^2)[a]**	**Antagonism Volume (nM^2)[a]**	**Interaction**
IFN-α	32 ± 1.4	0.0 ± 0.0	Minor Synergy
Ribavirin	61 ± 0.5	–0.5 ± 0.1	Moderate Synergy
Compound 1	34 ± 9.9	–17 ± 0.7	Minor Synergy
Compound 2	52 ± 5.1	–0.7 ± 0.7	Moderate Synergy
Compound 3	132 ± 44	–0.1 ± 0.2	Strong Synergy
Compound 7	51 ± 7.8	–0.2 ± 0.1	Moderate Synergy

[a] Values represent the arithmetic mean ± standard deviation of two independent experiments performed in triplicate.

Cell Viability Percentages for Compound 6 in Combination with Other HCV Inhibitors

To ensure that antiviral combination results were not confounded by combination cytotoxicity, the cytotoxicity was investigated in parallel using the same compound concentrations tested in the antiviral assays (Table XIII). For all compounds, cell viability was at least 98% of untreated controls for combinations at the highest concentrations tested. Therefore, no significant *in vitro* cytotoxicity was observed while testing Compound 6 alone, or in combination with these agents.

Table XIII

Cell Viability Percentages for Compound 6, Combinations in Huh-luc Replicon Cells

Compounds	Concentration(s) (nM)	Cell Viability %[a]
Compound 6	0.014	99 ± 1
Compound 6 + IFN-α[b]	0.014 + 0.8	102 ± 3
Compound 6 + Ribavirin	0.014 + 8000	105 ± 4
Compound 6 + Compound 1	0.014 + 4.0	99 ± 3
Compound 6 + Compound 2	0.014 + 24.0	103 ± 3
Compound 6 + Compound 3	0.014 + 12.8	104 ± 4
Compound 6 + Compound 7	0.014 + 8800	103 ± 3

[a] Cell viability % indicates arithmetic mean ± standard deviation for at least two independent experiments performed in triplicate.

[b] IFN-α is expressed in Units (U) per milliliter (mL) instead of a nanomolar concentration.

Conclusions

Results of these *in vitro* experiments indicate that Compound 6 has minor antiviral synergy when combined with IFN-α or the non-nucleoside NS5B polymerase inhibitor Compound 1. Combinations of Compound 6 with Ribavirin, the NS3 protease inhibitor Compound 2 or the nucleoside NS5B polymerase inhibitor Compound 7 resulted in moderate antiviral synergy. Strong antiviral synergy was observed between Compound 6 and the NS3 protease inhibitor Compound 3. No significant *in vitro* cytotoxicity was identified while testing these drug combinations. These results suggest that Compound 6, Could rationally be combined with the current standard of care.

Biological Example 6:

Compounds

Compound 1, Compound 3, Compound 4, and Compound 6 were synthesized by Gilead Sciences (Foster City, CA)

Cell Lines

HCV genotype 1b replicon cells (Huh-luc) were obtained from Reblikon (Mainz, Germany). The replicon in these cells is designated I389luc-ubi-neo/NS3-3'/ET and encodes a selectable

resistance marker (neomycin phosphotransferase) as well as the firefly luciferase reporter gene. Huh-luc cells were maintained in Dulbecco's Modified Eagle's Medium GlutaMax (DMEM; Invitrogen, Carlsbad, CA) supplemented with 10% fetal bovine serum (FBS; Hyclone, Logan, UT), 1X penicillin/streptomycin, 1X nonessential amino acids and 0.5 mg/mL of G-418 (all from Invitrogen, Carlsbad, CA). Cells were passaged twice a week and maintained at subconfluent levels.

Assays

Determination of compound concentration required to suppress replicon RNA by 1-1.5 log over 6 days of treatment

Genotype 1b replicon cells were seeded in T-75 flasks at a cell densitiy of $2.5x10^5$ cells/ flask, excluding G418. Compounds were individually added to the cells at variable concentrations: Compound 6 was added at concentrations of either 1pM, 2pM, 4pM, 6pM, 8pM, or 12pM, Compound 4 was added at 125nM, 250nM, 375nM, 500nM or 1000nM, Compound 1 was added at 1.25nM, 2.5nM, 5nM, 2.75nM or 10nM, and Compound 3 was added at concentrations of 3.75nM, 7.5nM, 11.25nM, 15nM, 30nM or 60nM. Flasks were incubated at 37°C, media and compounds were refreshed every two days. After 6 days of incubation the replicon cells were collected for RNA extraction and replicon RNA QRT-PCR analysis.

Compound combination replicon cure assay

Genotype 1b replicon cells were seeded in T-75 flasks at a density of $2.5x10^5$ cells/flask Compounds were added to the T-75 flasks at the following concentrations: Compound 6 at 4pM, Compound 4 at 1000nM, Compound 1 at 10nM, and Compound 3 at 26.25nM. Flasks were incubated at 37°C and compounds and media were refreshed every two days. All experiments were performed in duplicate and will be noted in as flask 1 and flask 2. On day 6 all cells were collected form flask 1 for RNA extraction followed by HCV replicon specific QRT-PCR analysis and the cells form flask 2 were replated on a 10cm tissue culture dishes in the presence of G418 for 14 days to record colony formation of uncured replicon cells.

QRT-PCR assay

Total RNA was extracted with the RiboPure kit (AM1924 Life Technologies Corporation Carlsbad, CA) following the manufacturer's protocol. Extracted RNA samples were stored at -80°C until use. For the Quantitative RT-PCR assay the Qiagen One-step QRT-PCR kit was used according to manufacturer's protocol (Qiagen, Valencia CA). The genotype 1b HCV NS3 gene specific primers, forward primer NS3_180FL 5'-CGGCGGACTGTCTATCATGGTGC[FAM]G-'3 (SEQ ID NO:1) and reverse NS3_180 5'-

GGTCCTGGTCCACATTGGTGT-'3 (SEQ ID NO:2) and 18S rRNA LUX™ [FAM] endogenous control primer set (115HM-01) were produced by Invitrogen corporation (Carlsbad, CA). For the reverse transcriptase step, the reactions were incubated at 44°C for 30 min, the reverse transcriptase enzyme was then degraded by heating the sample to 94°C for 10 min. The Q-PCR step included 38 cycles at 94°C for 15 s and 58°C for 30 s.

Results

Prior to initiating combination replicon cure experiments the compound concentration required to suppress genotype 1b replicon RNA by 1-1.5 log was determined for Compound 6, Compound 4, Compound 1, and Compound 3. The replicon RNA log drop is relative to the RNA levels in DMSO control treated replicon cells maintained for 6 days.

Table XIV

Individual compound dose able to induce replicon RNA 1-1.5 log drop in a 6 day assay

Compound	Replicon RNA log drop	Compound concentration (nM)
Compound 1	-1.0	10
Compound 3	-0.9	26.25
Compound 4	-1.2	1000
Compound 6	-1.4	0.004

Combination genotype 1b replicon cure assay

The replicon RNA suppression by compounds Compound 6, Compound 4, Compound 1 and Compound 3 was determined in a 6 day assay as individual compounds and in various double, triple, and quadruple combinations. The replicon RNA log drop is relative to the RNA levels in DMSO control treated replicon cells maintained for 6 days alongside the treatment flasks. The ability of the various compound combinations to cure the cells from the HCV replicon was determined by colony formation. Colony formation occurred after compound treatment was removed and G418 pressure was returned for 14 days. If a compound combination completely cures the cell population from the HCV replicon no colonies will develop since the cells lack resistance to G418.

Table XV

Quantification of compound combination in the replicon cure assay

Compounds	Replicon RNA log drop	Uncured colony number
Compound 6	-1.4	634
Compound 4	-1.2	1054
Compound 1	-1.0	657
Compound 3	-0.9	989
Compound 4+Compound 6	-2.67	15
Compound 1+Compound 4	-2.022	14
Compound 3+Compound 4	-2.26	23
Compound 1+Compound 6	-2.3	148
Compound 3+Compound 6	-2.62	13
Compound 1+Compound 3	-1.8	113
Compound 1+Compound 4+Compound 6	-2.66	0
Compound 3+Compound 4+Compound 6	-2.71	0
Compound 1+Compound 3+Compound 4	-2.69	0
Compound 1+Compound 3+Compound 6	-2.69	0
Compound 1+Compound 3+Compound 4+Compound 6	-2.71	0
DMSO (0.2% to match Quadruple combination)	0	6330

Conclusions

Results of these *in vitro* experiments indicate that combination of two compounds increases the viral RNA log drop over 6 day treatment and increases the rate of cured replicon cells. The dual combinations of Compound 6 with Compound 4 or Compound 3 results in larger replicon RNA log supression and lowest number of uncured colonies compared to all other dual compound combinations. The combination of three or four compounds cures all replicon cells and the combination treatments suppress the replicon RNA levels to the assay limit of detection.

Biological Example 7: Compound 10 and Compound 6 Cross-Resistance

This study was conducted to determine the in vitro cross-resistance profiles of Compound 10 and Compound 6. A panel of HCV mutant replicons bearing the signature NS5B nucleoside HCV drug resistance mutation S282T or the most common *in vitro* and *in vivo* NS5A HCV drug resistance mutations was investigated via transient replicon assay to determine whether cross-resistance exists between mutations conferring reduced susceptibility to

Compound 10 or Compound 6. No cross-resistance was observed between these compound with S282T mutant replicons remaining fully susceptible to Compound 6 and NS5A mutants showing no reduced susceptibility to Compound 10.

Materials and Methods

Reagents

Compounds

Compound 6 and Compound 10 were synthesized at Gilead Sciences, Inc. in Foster City, CA.

Cell Lines

Huh-lunet, a Huh-7 clone that is highly permissive for HCV replication, was obtained from ReBLikon GmbH (Mainz, Germany). Huh-lunet cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM; GIBCO, Carlsbad, CA) supplemented with 10% fetal bovine serum (FBS; Hyclone, Logan, UT). Cells were maintained at 37°C in humidified incubators (85% humidity) and under a 5% CO_2 atmosphere.

PI-hRluc, a bicistronic replicon encoding the Renilla luciferase gene downstream of the polio IRES and the genotype 1b (Con-1 strain) HCV nonstructural genes (NS3 - NS5B) downstream of the EMCV IRES, was used for transient transfection studies. The plasmid pPI-hRluc was generated from the plasmid pFKI341 PI-Luc/NS3-3'/ET, which encodes a genotype 1b (Con-1 strain) subgenomic replicon and was obtained from ReBLikon (Friebe et al., J Virol 2001;75 (24):12047-57). The hRluc gene was PCR amplified from pF9 CMV hRluc-neo Flexi(R) (Promega, Madison, WI) by PCR using Accuprime Super Mix I (Invitrogen, Carlsbad, CA) and the primers PV_Rluc_Top and 3'-Rluc(NotI). These two primers have the following sequences and carry restriction sites for subsequent cloning: PV_Rluc_Top: 5' ATC AGA CAA TTG TAT CAT AAT GGC TTC CAA GGT GTA CG 3' (SEQ ID NO:3); 3'-Rluc(NotI): 5' ACG TCA CTA TCT ACG CGG CCG CTT ACT GCT CGT TCT TC3' (NotI site underlined) (SEQ ID NO:4). The T7 Promoter, 5'UTR and Polio Virus IRES were PCR amplified from the plasmid pFKI341 PI-Luc/NS3-3'/ET using the primers 5'-P7(SbfI) and PV_Rluc_Bottom. These two primers have the following sequences and carry restriction sites for subsequent cloning: 5'-P7(SbfI): 5' CAA GCT AAG CTG CCT GCA GG T 3' (SbfI site underlined) (SEQ ID NO:5); PV_Rluc_Bottom: 5' CGT ACA CCT TGG AAG CCA TTA TGA TAC AAT TGT CTG AT (SEQ ID NO:6). The subsequent PCR fragments from the two above reactions were then joined together using overlapping PCR and the primers 5'- P7(SbfI) and 3'-Rluc(NotI). The completed P7-5'UTR-Polio Virus IRES-hRluc amplification product was subcloned into pCR2.1-TOPO. The resulting plasmid was digested with SbfI and NotI, and the excised fragment (P7-5'UTR-Polio Virus IRES-hRluc) were ligated using T4 DNA ligase into pFKI341 PI-Luc/NS3-3'/ET digested with the same enzymes. The resulting vector, pPI-hRluc, was sequenced to confirm the correct orientation and sequence of the P75'UTR-Polio Virus IRES-hRluc region of the plasmid.

GT 1a and 2a replicons containing hRluc have been described previously (Robinson M, Yang H, Sun SC, Peng B, Tian Y, Pagratis N, et al. Novel HCV Reporter Replicon Cell Lines Enable Efficient Antiviral Screening against Genotype 1a. Antimicrob Agents Chemother 2010.)

The PI-hRluc replicon was used as a backbone for chimera construction. An internal deletion was made in NS5B rendering it replication deficient. The last 413 base pairs (encoding last 137 NS5A amino acids) of 1b-con-1 NS5A were synthesized in frame with NS5B sequences from genotypes 2b, 3a, 4a, 5a, and 6a (Genscript Inc. Piscataway NJ). Consensus NS5B sequences for each of these genotypes were derived by aligning sequences deposited in the European HCV database and extracting a consensus. These novel consensus sequences for NS5B, as well as sequences derived from individual clinical isolates (Herlihy et al., Antimicrob Agents Chemother 2008;52 (10):3523-31) were used to construct the NS5B chimeric replicons. A unique XhoI site was used at the 5' end and a unique AseI site at the 3' end to directionally clone into the 1b-hRLuc/NeoR NS5B vector via standard molecular biology techniques.

NS5B S282T mutations were introduced replicon plasmids using the QuikChange II XL mutagenesis kit according to the manufacturer's instructions (Stratagene, La Jolla, CA). The entire mutated replicon was sequenced to confirm the presence of the S282T mutation and absence of any secondary site mutations.

NS5A mutant replicons were created by synthesizing a sequence encoding the first 149 amino acids of NS5A containing the desired mutation flanked by a 5' and 3' BsrGI and EcoRI site, respectively (Genscript, Piscataway, NJ). Synthesized fragments were then cloned by standard molecular biology techniques into a 1a Rluc replicon plasmid modified to enable cloning into unique BsrGI and EcoRI restriction sites. Mutations were confirmed by DNA sequencing.

Replicons were linearized using the following enzymes: Spe I (1b PI-Rluc-based replicons), Hpa I (1a-Rluc-based replicons), and XbaI/HpaI (2a Rluc replicon). Replicon RNAs were transcribed *in vitro* from replicon-encoding plasmids using a T7 Ribomax in vitro transcription kit (Promega; Madison, WI) followed by purification using an RNAeasy column (Qiagen; Valencia, CA).

Assays

Drug Susceptibility Determination using Transient Transfection Replicon Assay

RNA was transfected into Huh-lunet cells using the method of Lohmann et al. (Lohmann et al., Science 1999;285 (5424):110-3) Briefly, cells were trypsinized and washed twice with PBS. A suspension of 4 x 10^6 cells in 400 µL of PBS were mixed with 5 µg of RNA and subjected to electroporation using settings of 960 µF and 270 V. Cells were transferred into 40 mL of pre-warmed culture medium and then seeded into 96-well or 384-well plates. Compounds were 3-fold serially diluted in 100% DMSO and added to cells to achieve a final

DMSO concentration of 0.5%. Cells were treated for three days after which culture media were removed, cells were lysed, and Renilla luciferase activity was quantified using commercially available reagents (Promega) and a Victor or Envision instrument (Perkin Elmer, Waltham, MA).

Data Analysis

Data were converted into percentages relative to untreated controls (defined as 100%), and EC_{50} values were calculated by non-linear regression of two replicate data sets using GraphPad Prism software or Pipeline Pilot. Resistance fold changes were calculated as the ratio of mutant to wild-type replicon EC_{50}.

Results

Activity of Compound 10 and Compound 6 against S282T

Previous in vitro resistance selection with Compound 10 has consistently identified S282T in NS5B as primary mutation in multiple genotypes (GT 1b, 1a and 2a). The NS5B S282T mutation was subsequently introduced into the full-length GT 1a, 1b, and 2a replicons and chimeric replicons containing a 2b, 3a, or 4a NS5B sequence cloned into a GT1b backbone. The susceptibility to Compound 10, Compound 6, and ribavirin (RBV) was evaluated using a transient replication assay. The S282T mutation displayed a reduced susceptibility to Compound 10 with EC_{50} values across all five genotypes ranging from 117.1 nM to 346.1 nM. The fold increase in EC_{50} for S282T ranged from 2.4 to 16.0 compared to the wild-type from the corresponding genotypes demonstrating decreased replicon susceptibility to Compound 10 when the NS5B S282T mutation is present.

For the wild-type replicon, the EC_{50} values for RBV were also similar across the five genotypes tested with the lowest EC_{50} being against GT 2b. Interestingly, the EC_{50} values for S282T replicons were 5- to 10-fold more sensitive to treatment with RBV than their corresponding wild-type for all five genotypes. No significant differences were observed in Compound 6 EC_{50}s between the wild-type and S282T replicons indicating that this mutation does not alter susceptibility to Compound 6. In conclusion, while the S282T replicon conferred reduced susceptibility to Compound 10, the mutant replicon demonstrated wild-type sensitivity to Compound 6 and an increased susceptibility to inhibition by RBV over wild-type.

Table 7.1. Antiviral activity of Compound 10 and RBV against wild-type and S282T mutant of GT1b, 2a, 2b, 3a and 4a

Replicon	Compound 10			RBV			Compound 6		
	EC_{50} nM[a]		Fold change[b]	EC_{50} nM[a]		Fold change[b]	EC_{50} nM[a]		Fold change[b]
	WT	S282T		WT	S282T		WT	S282T	
GT1b	21.5	189.2	8.8	6.6	1.6	0.2	0.5	0.4	0.8
GT2a	146.8	346.1	2.4	8.3	0.6	0.1	5165	2336	0.5
GT2b	13.3	215.6	16.2	2.6	0.6	0.2	0.5	0.5	0.9
GT3a	33.9	117.1	3.5	6.7	1.0	0.2	0.4	0.2	0.6
GT4a	35.8	217.5	6.1	6.2	0.6	0.1	0.5	0.4	0.8

a EC_{50} indicates average for two or more independent experiments.

b Fold change from the corresponding wild type

Activity of Compound 10 and Compound 6 against NS5A Mutants

To determine if NS5A drug resistance mutations are cross resistant to Compound 10, a panel of NS5A mutant replicons was assayed for susceptibility to both Compound 6 and Compound 10. All seven NS5A mutants displayed a reduced susceptibility to Compound 6 with an increase in EC_{50} ranging from 25- to 3029-fold. In contrast, no significant shift in EC_{50} was observed for the NS5A mutants to Compound 10 or to a RBV control.

Table 7.2 In Vitro Activity of Compound 10 or Compound 6 against NS5A Mutants in Genotype 1a

Compound	Fold Shift in EC_{50} (DRM EC_{50} / 1a-H77 EC_{50})						
	M28T	Q30H	Q30R	Q30E	L31M	Y93C	Y93H
Compound 6	25	73	170	997	140	327	3029
Compound 10	0.9	1.0	0.8	1.0	1.1	ND	0.7
RBV	0.4	0.7	0.8	0.8	0.5		1.0

Conclusions

In this example, the cross-resistance profiles of Compound 10 and Compound 6 were evaluated using transient HCV replicons encoding known resistance mutations in NS5A and NS5B conferring reduced susceptibility to Compound 6 and Compound 10, respectively. NS5B S282T replicons conferred reduced susceptibility to Compound 10, while there were no significant differences in Compound 6 EC_{50}s measured from wild-type and S282T replicons.

Reciprocally, mutations conferring reduced susceptibility to Compound 6 remained sensitive to treatment with Compound 10.

Overall, these results indicate that resistance mutations for Compound 10 and Compound 6 do not demonstrate cross-resistance and support the use of these compounds in future combination therapy for the treatment of HCV.

Biological Example 8: Combination Activity

Combination study data of Compound 10 with the NS5A inhibitor Compound 6, the non-nucleoside inhibitors Compound 1 or Compound 5, the protease inhibitor Compound 3, or ribavirin (RBV) is shown for an in vitro replicon assay which remains the standard for evaluating the cell-based antiviral activity of HCV inhibitors. These results indicated that Compound 10 has additive antiviral activity when combined with Compound 6, Compound 1, Compound 5, or Compound 3. In addition, Compound 10 demonstrated minor synergy in combination with RBV in vitro.

Materials and Methods

Cell Line and Cell Culture

The HCV genotype 1a replicon cell line used in this study was described previously (Robinson M, Yang H, Sun SC, Peng B, Tian Y, Pagratis N, et al. Novel HCV Reporter Replicon Cell Lines Enable Efficient Antiviral Screening against Genotype 1a. Antimicrob Agents Chemother 2010). The cells were grown in cell culture medium containing Dulbecco's Modified Eagle Medium (DMEM) with GlutaMAX (Gibco, Carlsbad, CA, Cat# 10569-044), supplemented with 10% FBS (HyClone, Logan, UT, Cat# SH30071.03), 100 Units/mL Penicillin, 100 μg/mL Streptomycin (Gibco, Carlsbad, CA, Cat# 15140-122), and 0.1 mM non-essential amino acids (Gibco, Carlsbad, CA, Cat#11140-050). Replicon cells were maintained in 0.5 mg/mL Geneticin (Invitrogen, Carlsbad, CA, Cat# 10131-035) to prevent the loss of HCV replicon. The cells were passaged every 3-4 days before reaching confluency.

HCV Replicon Assay for EC_{50}, CC_{50} Determinations and Combination Studies

All compounds were supplied in 100% DMSO. Compound serial dilutions were performed in 100% DMSO. All serial dilutions were performed in 384-well polypropylene plates (Thermo Scientific, Hudson, NH, Cat#4341) using a Biomek FX Workstation. For EC_{50} and CC_{50} determinations, test compounds were serially diluted in ten steps of 1:3 dilutions in columns 3-20 of the 384-well plates. For combinational studies, one compound was serially diluted in nine steps of 1:2 dilutions toward the horizontal direction with the other compound serially diluted in seven steps of 1:2 dilutions toward the vertical direction. This achieved a defined set of different drug concentrations and ratios. For each individual drug, the EC_{50} value was selected as the midpoint for the concentration range tested. All serial dilutions were performed in four replicates

per compound within the same 384-well plate. 100% DMSO was added into column 1-2 of each serial dilution 384-well plate. A HCV protease inhibitor ITMN-191 at 100 μM was added into column 23 as a control of 100% inhibition of HCV replication while puromycin at 10 mM was added into column 24 as a control of 100% cytotoxicity.

To each well of a black polystyrene 384-well plate (Greiner Bio-one, Monroe, NC, Cat#781086, cell culture treated), 90 μL of cell culture medium (without geneticin) containing 2000 suspended HCV replicon cells was added with a Biotek μFlow Workstation. For compound transfer into cell culture plates, 0.4 μL of compound solution from the compound serial dilution plate was transferred to the cell culture plate on a Biomek FX Workstation. The DMSO concentration in the final assay wells was 0.44%. The plates were incubated for 3 days at 37 °C with 5% CO_2 and 85% humidity.

The HCV replicon assay was a multiplex assay which can assess both cytotoxicity and anti-replicon activity from the same well. The CC_{50} assay was performed first. The media in the 384-well cell culture plate was aspirated and the wells were washed four times with 100 μL 1 X PBS each, using a Biotek ELX405 plate washer. A volume of 50 μL of a solution containing 400 nM calcein AM (Anaspec, Fremont, CA, Cat#25200-056) in 1 X PBS was added to each well of the plate with a Biotek μFlow Workstation. The plate was incubated for 30 minutes at room temperature before the fluorescence signal (excitation 490 nm, emission 520 nm) was measured with a Perkin Elmer Envision Plate Reader.

EC_{50} assay was performed in the same wells as CC_{50} assay. The calcein-PBS solution in the 384-well cell culture plate was aspirated with a Biotek ELX405 plate washer. A volume of 20 μL of Dual-Glo luciferase buffer (Promega, Madison, WI, Cat#E298B) was added to each well of the plate with a Biotek μFlow Workstation. The plate was incubated for 10 minutes at room temperature. A volume of 20 μL of a solution containing 1:100 mixture of Dual-Glo Stop & Glo substrate (Promega, Madison, WI, Cat#E313B) and Dual-Glo Stop & Glo buffer (Promega, Madison, WI, Cat#E314B) was then added to each well of the plate with a Biotek μFlow Workstation. The plate was then incubated at room temperature for 10 minutes before the luminescence signal was measured with a Perkin Elmer Envision Plate Reader.

Data Analysis

The cytotoxicity effect was determined by calcein AM conversion to fluorescent product. The percent cytotoxicity was calculated by equation 1:

$$\%\ \text{cytotoxicity or}\ \%\ \text{inhibition} = 100 \times (1 - \frac{X_C - M_B}{M_D - M_B}) \qquad (1)$$

where X_C is the fluorescence signal from the compound-treated well; M_B is the average fluorescence signal from puromycin-treated wells; M_D is the average fluorescence signal from

DMSO-treated wells. The anti-HCV replication activity was determined by the luminescence signal generated from the reporter renilla luciferase of the HCV replicon. The percent inhibition on HCV replicon was calculated using equation 1, where X_C is the luminescence signal from compound-treated well; M_B is average luminescence signal from the ITMN-191-treated wells; M_D is the average luminescence signal from DMSO-treated wells.

The CC_{50} values were determined as the testing compound concentration that caused a 50% decrease of cell viability. The EC_{50} values were determined as the testing compound concentration that caused a 50% decrease in HCV replication. Both CC_{50} and EC_{50} values were obtained using Pipeline Pilot 5.0 software package (Accelrys, San Diego, CA) by nonlinear regression fitting of experimental data to equation 2:

$$y = d + \frac{a-d}{[1+(\frac{x}{c})^b]} \qquad (2)$$

where y is the observed % inhibition of HCV replicon at x concentration of compound; d is estimated response at zero compound concentration; a is estimated response at infinite compound concentration; c is the mid-range concentration (CC_{50} or EC_{50}); b is the Hill slope factor.

The combination study experimental data were analyzed using the MacSynergy II program developed by Prichard and Shipman (Prichard MN, Aseltine KR, Shipman C, Jr. MacSynergyTM II, Version 1.0. University of Michigan, Ann Arbor, Michigan, 1993). The software (MacSynergy™ II, University of Michigan, MI) calculates theoretical inhibition assuming an additive interaction between drugs (based on the Bliss Independence model) and quantifies statistically significant differences between the theoretical and observed inhibition values. Plotting these differences in three dimensions results in a surface where elevations in the Z-plane represent antiviral synergy and depressions represent antiviral antagonism between compounds. The calculated volumes of surface deviations are expressed in $\mu M^2\%$. Per Prichard and Shipman, combination effects are defined as:

- Strong synergy: $> 100\ \mu M^2\%$
- Moderate synergy: > 50 and $\leq 100\ \mu M^2\%$
- Minor synergy: > 25 and $\leq 50\ \mu M^2\%$
- Additivity: ≤ 25 and $> -25\ \mu M^2\%$
- Minor antagonism: ≤ -25 and $> -50\ \mu M^2\%$
- Moderate antagonism: ≤ -50 and $> -100\ \mu M^2\%$

- Strong antagonism: $\leq -100\ \mu M^2\%$

For each combination study, three independent experiments were performed with four replicates in each experiment.

Results

Antiviral Activity and Cytotoxicity of Individual Compounds in HCV Genotype 1a Replicon Assay

The anti-HCV activity and cytotoxicity of Compound 10 combined with other anti-HCV compounds were tested in Huh-7 cells carrying an HCV genotype 1a replicon. The EC_{50} and CC_{50} values for all compounds are listed in the following Table. There is no significant cytotoxicity observed for all individual compounds up to the highest concentrations tested in the combination assay.

Table 8.1. EC_{50} and CC_{50} of Compounds used in this Study against HCV Genotype 1a Replicon

Compounds	Class	EC_{50}[a] (nM)	CC_{50}[a] (nM)
Compound 10	NS5B Nucleoside Prodrug	39	>82446
Compound 6	NS5A Inhibitor	0.032	>44400
Compound 1	NS5B Non-nucleoside	18	>44400
Compound 5	NS5B Non-nucleoside	14	>44400
Compound 3	NS3 Protease Inhibitor	46	>22200
RBV	Nucleoside Analog	33626	>88800

a Values are geometric means for three or more independent experiments

Antiviral Activity and Cytotoxicity of Compound 10 in Combination with Other Classes of Anti-HCV Agents.

The antiviral effects of Compound 10 in combination with other anti-HCV compounds were evaluated using the HCV genotype 1a replicon. The results were analyzed using MacSynergy II, which provides surface plots displaying significant deviations from additivity. Synergy and antagonism volumes ($\mu M^2\%$) calculated from deviations from additive surface are summarized in the following Table. At 95% confidence interval, the mean synergy and antagonism volumes were between 25 and –25 μM^2 % when Compound 10 was combined with Compound 6, Compound 1, Compound 5, or Compound 3 indicative of additive interaction with Compound 10. Furthermore, Compound 10 shows a synergy volume in the range of 25 to 50 $\mu M^2\%$ when combined with RBV, suggesting a minor synergistic interaction. In combination studies using direct acting antivirals with Compound 10, cell viability was greater than 93% at the highest concentrations of compound combinations tested while studies analyzing the

combined effects of Compound 10 and RBV showed cell viability greater than 85% at the highest combined drug concentrations.

Table 8.2. Quantification of Antiviral Synergy and Antagonism and Drug Interactions for Drug Combinations with Compound 10

Compound Used in Combination with Compound 10	Class	Synergy Volume (nM^2)[a]	Antagonism Volume (nM^2)[a]	Interaction
Compound 6	NS5A Inhibitor	3.3 ± 4.2	-7.7 ± 13.3	Additive
Compound 1	NS5B Non-nucleoside	4.7 ± 8.1	-11.7 ± 10.0	Additive
Compound 5	NS5B Non-nucleoside	1.3 ± 2.3	-5.7 ± 9.0	Additive
Compound 3	NS3 Protease Inhibitor	1.0 ± 1.7	-3.0 ± 4.4	Additive
RBV	Nucleoside Analog	35.3 ± 3.2	-2.0 ± 2.0	Minor synergy

a Values represent the mean ± standard deviation of three independent experiments performed in four replicates

Table 8.3. Quantification of Cytotoxicity In Compound Combinations

Compound Used in Combination with Compound 10	Highest Concentration of Compound Used With Highest Concentration (320 nM) of Compound 10	Cytotoxicity at Highest Concentration of Compound Combinations (% inhibition on cell growth)
Compound 6	0.16 nM	5.0 ± 5.0
Compound 1	120 nM	7.0 ± 4.6
Compound 5	64 nM	4.3 ± 2.9
Compound 3	240 nM	2.0 ± 3.5
RBV	16000 nM	14.0 ± 4.4

a Values represent the mean ± standard deviation of three independent experiments performed in four replicates

Conclusions

The antiviral activity of Compound 10 was tested in combination with Compound 6, Compound 1, Compound 5, Compound 3, or RBV. Compound 10 showed additive antiviral activity in combination with Compound 6, Compound 1, Compound 5, or Compound 3, and minor synergy with RBV.

In summary, these findings support the potential of Compound 10 to be used in combination with Compound 6, Compound 1, Compound 5, Compound 3 or RBV to achieve enhanced viral suppression without reducing the efficacy of any of the individual drugs.

Clinical Example 1: Clinical Testing of Anti-HCV Activity of the Combination of Compound 1 and Compound 2

This Clinical Example shows that the combination of Compound 1 and Compound 2 plus ribavirin is more effective at reducing HCV viral load, and suppressing HCV viral rebound, than the combination of Compound 1 plus Compound 2 without ribavirin.

Clinical Trial Design:

A Phase 2, randomized, open-label trial of Compound 2 plus Compound 1 alone and in combination with ribavirin for 28 days in treatment-naive subjects with chronic genotype 1 HCV infection. Subjects in Arm 1 received Compound 2 at 75 mg + Compound 1 at 40 mg, both administered twice daily (BID) (double regimen) and subjects in Arm 2 received Compound 2 at 75 mg + Compound 1 at 40 mg, both administered BID, and plus ribavirin, also administered BID (triple regimen) for 28 days.

On Day 28, all subjects were to initiate PEG/Ribavirin. Additionally, the protocol called for subjects with an insufficient virologic response (< 2 $\log_{10}$ IU/mL reduction from baseline HCV RNA by Day 5) or virologic rebound (HCV RNA increase of > 0.5 $\log_{10}$ IU/mL from nadir confirmed over two time points occurring after Day 5 with an absolute value > 1000 IU/mL) to initiate PEG/RIBA prior to Day 28.

For subjects with insufficient virologic response, the combination of pegylated interferon (PEG) and ribavirin (RIBA) was initiated prior to Day 28 with or without continuation Compound 2 + Compound 1. As a result, by Day 28 of the study, subjects were receiving one of four treatments:

(i) Compound 2 + Compound 1,

(ii) Compound 2 + Compound 1 + RIBA,

(iii) Compound 2 + Compound 1 + PEG/RIBA, or

(iv) PEG/RIBA.

A total of 31 subjects were enrolled and started dosing (16 subjects received the double regimen in Arm 1 and 15 subjects received the triple regimen in Arm 2). Preliminary subject demographics and baseline characteristics (Table XVI) were generally comparable between Arms 1 and 2, aside from a greater number of subjects with genotype 1b in Arm 2. Four subjects were identified as HCV genotype 1b at screening (one subject on the dual regimen and three subjects on the triple regimen), but have not been confirmed as genotype 1a or 1b upon further analysis, with further assessment ongoing.

No subjects have experienced serious adverse events. Study medications have been generally well-tolerated, with all adverse events being Grade 1-2 in severity, except for a single Grade 3 fatigue, which was the only treatment emergent adverse event leading to study drug discontinuation. Prior to the initiation of PEG/Ribavirin, the most common treatment-emergent adverse events occurring in more than one subject were headache (n=5), and diarrhea or nausea (n=3 each) in Arm 1 and headache (n=7), diarrhea or fatigue (n=3 each), nausea,

asthenia, pruritis or insomnia (n=2 each) in Arm 2. When Compound 2 + Compound 1 were given in combination with PEG/RIBA, the only adverse events occurring in more than one subject were influenza-like illness (n=5) and myalgia (n=3), both common adverse events with PEG/RIBA therapy. With regard to laboratory abnormalities, there were no Grade 4 events during the 28-day treatment period. Among subjects receiving the study drugs, there were two treatment-emergent Grade 3 elevations in total bilirubin in the ribavirin containing Arm 2 (occurring at Day 7, but resolving with continued dosing of study drug). There were also 2 Grade-1 elevations and a single Grade-2 elevation in total bilirubin among other subjects in this dosing Arm (with ribavirin). Among subjects in Arm-1 (no ribavirin), there were four Grade-1 total bilirubin elevations. ALT values were reduced approximately 40 U/L from baseline in both arms by Day 14. Median QTcF was not significantly changed from baseline in either study arm and no subjects discontinued study drugs due to QTc abnormalities. Preliminary safety data are summarized in Table XVIII.

Plasma HCV RNA was monitored approximately twice weekly to gauge virologic response in relation to the protocol-specified criteria for early initiation of PEG/RIBA. From preliminary analysis of the HCV RNA values, the median maximal decline in HCV RNA was 3.9 $\log_{10}$ IU/mL for the dual regimen and 5.0 $\log_{10}$ IU/mL for the triple regimen. The median time to maximal decline in HCV RNA was 7 days for the dual regimen and 14 days for the triple regimen, with the difference attributed to delayed incidence and onset of viral breakthrough in the ribavirin containing arm. Three of 15 (20%) subjects receiving the dual regimen and 10 of 13 (77%) subjects receiving the triple regimen had nadir HCV RNA values ≤30 IU/mL (excluding non-GT1 subjects). 13/16 (81%) subjects receiving Compound 2/Compound 1 and 6/15 (40%) subjects receiving Compound 2/Compound1/Ribavirin initiated PEG or PEG/Ribavirin prior to the scheduled start on Day 28 of the study. Additional details of virologic outcomes are provided in

Results. Compound 2 + Compound 1 alone and in combination with RIBA were well-tolerated for up to 28 days by HCV subjects in this study, both before and following the addition of PEG or PEG/Ribavirin. Both regimens yielded potent suppression of HCV RNA, with greater and more sustained activity in the three drug regimen.

Table XVI Preliminary Subject Demographics and Baseline Characteristics

	Arm #1: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID (n=16)	**Arm #2: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID + RIBA (n=15)**
Age in years - Median (range)	47 (30,66)	55 (27, 63)
Sex	14 male 2 female	11 male 4 female
Ethnicity	16 Non-Hispanic/Latino	15 Non-Hispanic/Latino
Race	13 White 2 Black 1 Asian	13 White 2 Black 0 Asian
Baseline Weight in kg – Median (range)	86.1 (57.8, 110.5)	79.0 (51, 127.5)
Baseline BMI in kg/M^2 – Median (range)	27.1 (21.5, 34.1)	24.7 (19.9, 37.6)
Baseline Log_{10} HCV RNA (IU/mL) from Central lab– Median (range) Central lab	6.17 (5.25, 7.26)	6.34 (5.41, 7.19)
Baseline HCV Genotype	8 1a 8 1b	3 1a 12 1b

Table XVII Preliminary Safety Results

	Arm 1: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID (n=16)	**Arm 2: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID + RIBA (n=15)**
Grade 3 Adverse Events (AEs): Fatigue	1	0
Grade 1/Grade 2 (AEs):		
Headache	5 (31%)	7 (47%)
Diarrhea	3 (19%)	3 (20%)
Nausea	3 (19%)	2 (13%)
Fatigue	0	3 (20%)
Asthenia	0	2 (13%)
Pruritis	1 (6%)	2 (13%)
Insomnia	0	2 (13%)
Grade 3 Laboratory Abnormalities: Bilirubin	0	2
Grade 1/Grade 2 Laboratory Abnormalities:		
Bilirubin	4	3
Hemoglobin	0	2
Glucose (nonfasting)	8	5

Table XVIII Preliminary Virologic Outcomes

	Arm 1: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID (n=16)	**Arm 1: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID** ***Unconfirmed GT1 Subjects Excluded (n=15)****	**Arm 2: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID + Ribavirin (n=15)**	**Arm 2: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID + Ribavirin** ***Unconfirmed GT1 Subjects Excluded (n=13)***
Median maximal HCV RNA decline Mean maximal HCV RNA decline	-3.9 $\log_{10}$ IU/mL -3.4 $\log_{10}$ IU/mL	-4.0 $\log_{10}$ IU/mL -3.6 $\log_{10}$ IU/mL	-5.0 $\log_{10}$ IU/mL -4.5 $\log_{10}$ IU/mL	-5.0 $\log_{10}$ IU/mL -4.9 $\log_{10}$ IU/mL
Mean time to Breakthrough	16 days	16 days	23 days	23 days
Subjects with HCV RNA nadir <50 IU/mL	3/16 (19%)	3/15 (20%)	10/15 (63%)	10/13 (77%)
Subjects with Breakthrough**	12 (75%)	12/15 (80%)	6/15 (40%)	6/13 (46%)
Day 28 Response: RVR at < 25 IU/mL	1/16 (6%) 1/16 (6%)	1/15 (7%) 1/15 (7%)	5/15 (33%) 6/15 (40%)	5/13 (38%) 6/13 (46%)

	Arm 1: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID (n=16)	**Arm 1: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID** ***Unconfirmed GT1 Subjects Excluded (n=15)****	**Arm 2: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID + Ribavirin (n=15)**	**Arm 2: Compound 2 at 75 mg BID + Compound 1 at 40 mg BID + Ribavirin** ***Unconfirmed GT1 Subjects Excluded (n=13)***
RVR at < 50 IU/mL				

* GT1 is an abbreviation for HCV Genotype 1.
Subjects 1011, 1012, and 1043 at one French study center were excluded;
Subject 1004 was not excluded

** Breakthrough defined as > 1 log increase in HCV RNA above nadir value or HCV RNA > 25 IU/mL following a nadir of < 25 IU/mL

The data presented in Table XVIII show that there was an approximately 10 fold greater decline in both the median maximal HCV RNA level and the mean maximal HCV RNA level in response to the combination of Compound 2 + Compound 1 in the presence of ribavirin compared to the absence of ribavirin. Also, the number of study subjects having an HCV RNA nadir below 50 IU/mL is greater in the presence of ribavirin than in the absence of ribavirin. These results show that ribavirin, in the absence of interferon, significantly potentiates the antiviral activity of the combination of Compound 1 and Compound 2.

Additionally, the mean time to HCV breakthrough, which is a measure of the eventual increase in HCV viral load as the virus mutates and becomes less susceptible to the antiviral drugs, is greater in the presence of ribavirin than in the absence of ribavirin. Further, the number of subjects showing viral breakthrough is substantially less in the presence of ribavirin than in the absence of ribavirin. These results show that the HCV virus is less able to develop resistance to the combination of Compound 1 and Compound 2 in the presence of ribavirin.

Further, the data presented in Table XVIII shows that the number of patients achieving a Rapid Virologic Response (RVR) in the presence of ribavirin is significantly greater than in the absence of ribavirin. Achievement of RVR positively correlates with cure of HCV infection.

Taken together the data presented in Table XVIII show that the combination of Compound 1, Compound 2, and ribavirin causes a rapid and clinically significant reduction in HCV viral load, with a reduced viral rebound, even in the absence of administration of interferon.

Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any

limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

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CLAIMS

What is claimed is:

1. A composition comprising: 1) compound 10 or a pharmaceutically acceptable salt thereof and 2) compound 5 or a pharmaceutically acceptable salt thereof, or compound 6 or a pharmaceutically acceptable salt thereof.

2. The composition of claim 1 which comprises: 1) compound 10 or a pharmaceutically acceptable salt thereof, and 2) compound 5 or a pharmaceutically acceptable salt thereof.

3. The composition of claim 1 which comprises: 1) compound 10 or a pharmaceutically acceptable salt thereof, and 2) compound 6 or a pharmaceutically acceptable salt thereof.

4. The composition of claim 1 which comprises: 1) compound 10 or a pharmaceutically acceptable salt thereof, 2) compound 5 or a pharmaceutically acceptable salt thereof, and 3) compound 6 or a pharmaceutically acceptable salt thereof.

5. The composition of any one of claims 1-4 which further comprises one or more pharmaceutically acceptable diluents or carriers.

6. The composition of claim 5 which is formulated as a unit dosage form for once daily administration.

7. The composition of any one of claims 5-6 which is formulated for oral administration.

8. The composition of any one of claims 5-7 which is formulated as a tablet.

9. The composition of any one of claims 1-8 which further comprises ribavirin.

10. A method of treating an HCV infection in a human, comprising administering to the human: 1) a compound 10 or a pharmaceutically acceptable salt thereof and 2) a compound 5 or a pharmaceutically acceptable salt thereof, or compound 6 or a pharmaceutically acceptable salt thereof.

11. The method of claim 10 wherein: 1) compound 10 or a pharmaceutically acceptable salt thereof, and 2) a compound 5 or a pharmaceutically acceptable salt thereof are administered.

12. The method of claim 10 wherein: 1) a compound 10 or a pharmaceutically acceptable salt thereof, and 2) a compound 6 or a pharmaceutically acceptable salt thereof are administered.

13. The method of claim 10 wherein: 1) a compound 10 or a pharmaceutically acceptable salt thereof, 2) a compound 5 or a pharmaceutically acceptable salt thereof, and 3) a compound 6 or a pharmaceutically acceptable salt thereof are administered.

14. The method of claim 10 wherein a composition as described in any one of claims 1-8 is administered to the human.

15. A method of ameliorating one or more symptoms of an HCV infection in a human, comprising administering to the human: 1) a compound 10 or a pharmaceutically acceptable salt thereof and 2) a compound 5 or a pharmaceutically acceptable salt thereof, or compound 6 or a pharmaceutically acceptable salt thereof.

16. The method of claim 15 wherein: 1) compound 10 or a pharmaceutically acceptable salt thereof, and 2) a compound 5 or a pharmaceutically acceptable salt thereof are administered.

17. The method of claim 15 wherein: 1) a compound 10 or a pharmaceutically acceptable salt thereof, and 2) a compound 6 or a pharmaceutically acceptable salt thereof are administered.

18. The method of claim 15 wherein: 1) a compound 10 or a pharmaceutically acceptable salt thereof, 2) a compound 5 or a pharmaceutically acceptable salt thereof, and 3) a compound 6 or a pharmaceutically acceptable salt thereof are administered.

19. The method of claim 15 wherein a composition as described in any one of claims 1-8 is administered to the human.

20. A method of reducing viral load in a human with HCV, comprising administering to the human: 1) a compound 10 or a pharmaceutically acceptable salt thereof and 2) a compound 5 or a pharmaceutically acceptable salt thereof, or compound 6 or a pharmaceutically acceptable salt thereof.

21. The method of claim 20 wherein: 1) compound 10 or a pharmaceutically acceptable salt thereof, and 2) a compound 5 or a pharmaceutically acceptable salt thereof are administered.

22. The method of claim 20 wherein: 1) a compound 10 or a pharmaceutically acceptable salt thereof, and 2) a compound 6 or a pharmaceutically acceptable salt thereof are administered.

23. The method of claim 20 wherein: 1) a compound 10 or a pharmaceutically acceptable salt thereof, 2) a compound 5 or a pharmaceutically acceptable salt thereof, and 3) a compound 6 or a pharmaceutically acceptable salt thereof are administered.

24. The method of claim 20 wherein a composition as described in any one of claims 1-8 is administered to the human.

25. A method for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents in a human, comprising administering to the human: 1) a compound 10 or a pharmaceutically acceptable salt thereof and 2) a compound 5 or a pharmaceutically acceptable salt thereof, or compound 6 or a pharmaceutically acceptable salt thereof.

26. The method of claim 25 wherein: 1) compound 10 or a pharmaceutically acceptable salt thereof, and 2) a compound 5 or a pharmaceutically acceptable salt thereof are administered.

27. The method of claim 25 wherein: 1) a compound 10 or a pharmaceutically acceptable salt thereof, and 2) a compound 6 or a pharmaceutically acceptable salt thereof are administered.

28. The method of claim 25 wherein: 1) a compound 10 or a pharmaceutically acceptable salt thereof, 2) a compound 5 or a pharmaceutically acceptable salt thereof, and 3) a compound 6 or a pharmaceutically acceptable salt thereof are administered.

29. The method of claim 25 wherein a composition as described in any one of claims 1-8 is administered to the human.

30. The method of any one of claims 10-29 wherein an interferon is not administered to the human.

31. The method of any one of claims 10-29 further comprising administering ribavirin to the human.

32. The method of any one of claims 10-29 further comprising administering one or more additional agents selected from ribavirin, an interferon, alpha-glucosidase 1 inhibitors, hepatoprotectants, TLR-7 agonists, cyclophilin inhibitors, HCV viral entry inhibitors, HCV maturation inhibitors, and HCV IRES inhibitors to the human.

33. A composition as described in any one of claims 1-9 for use in medical therapy.

34. A composition as described in any one of claims 1-9 for the prophylactic or therapeutic treatment of an HCV infection.

35. The use of a composition as described in any one of claims 1-9 to prepare a medicament for treating an HCV infection in a human.

36. The use of a composition as described in any one of claims 1-9 to prepare a medicament for ameliorating one or more symptoms of an HCV infection in a human.

37. A composition as described in any one of claims 1-9 for reducing viral load.

38. The use of a composition as described in any one of claims 1-9 to prepare a medicament for reducing viral load in a human.

39. A composition as described in any one of claims 1-9 for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents.

40. The use of a composition as described in any one of claims 1-9 to prepare a medicament for reducing emergence of HCV quasispecies with resistance to coadministered oral antiviral agents in a human.

41. The composition of claim 34, 37, or 39 which is not for administration with an interferon.

42. The composition of claim 34, 37, or 39 which is for administration with ribavirin.

43. The composition of claim 34, 37, or 39 which is for administration with one or more additional agents selected from ribavirin, an interferon, alpha-glucosidase 1 inhibitors, hepatoprotectants, TLR-7 agonists, cyclophilin inhibitors, HCV viral entry inhibitors, HCV maturation inhibitors, and HCV IRES inhibitors.

44. The use of any one of claims 35, 36, 38, and 40 wherein the medicament is not for administration with an interferon.

45. The use of any one of claims 35, 36, 38, and 40 wherein the medicament is for administration with ribavirin.

46. The use of any one of claims 35, 36, 38, and 40 wherein the medicament is for administration with one or more additional agents selected from ribavirin, an interferon, alpha-glucosidase 1 inhibitors, hepatoprotectants, TLR-7 agonists, cyclophilin inhibitors, HCV viral entry inhibitors, HCV maturation inhibitors, and HCV IRES inhibitors.