Timeline: Development of Risdiplam

KEI Research Note 2025:1
April 7, 2025
Arianna Schouten

2003 - Establishment of SMA Foundation (SMAF)

The SMA Foundation (SMAF) was established in 2003 to advance research and development for spinal muscular atrophy (SMA).

2005 - Insights into SMNΔ7 protein

A pivotal study demonstrating that the SMNΔ7 protein, the primary product of the centromeric SMN2 gene, extends survival in a mouse model of spinal muscular atrophy (SMA) and interacts with the full-length SMN protein. This study provided crucial insights into the molecular mechanisms of SMA and the role of SMNΔ7.

Le, T.T., Pham, L.T., Butchbach, M.E., Zhang, H.L., Monani, U.R., Coovert, D.D., Gavrilina, T.O., Xing, L., Bassell, G.J. and Burghes, A.H., 2005. SMNΔ7, the major product of the centromeric survival motor neuron (SMN2) gene, extends survival in mice with spinal muscular atrophy and associates with full-length SMN. Human molecular genetics, 14(6), pp.845-857.	These studies were funded by NIH grant NS3869, Families of SMA and SMA Foundation.

2006 - Partnership between SMAF and PTC Therapeutics

The SMA Foundation entered into a sponsored research agreement with PTC Therapeutics. The purpose of the agreement was to collaborate in the research and preclinical development of small molecule therapeutics for SMA. PTC Therapeutics received $13.3 million in sponsored research funding for its SMA research program from the SMA Foundation. PTC is obligated to pay the SMAF single-digit royalties on worldwide net product sales of any collaboration product that they develop and substantially commercialize.

2008 - Evaluation of drug candidates

A study identified tests for evaluating drug candidates in the SMNΔ7 neonate model of spinal muscular atrophy (SMA). This study contributed to the preclinical development of risdiplam by providing reliable and reproducible methodologies for assessing the efficacy and safety of potential SMA treatments

El-Khodor, B.F., Edgar, N., Chen, A., Winberg, M.L., Joyce, C., Brunner, D., Suárez-Fariñas, M. and Heyes, M.P., 2008. Identification of a battery of tests for drug candidate evaluation in the SMNΔ7 neonate model of spinal muscular atrophy. Experimental neurology, 212(1), pp.29-43.	Supported in part by the SMA Foundation and NIH/NINDS and PsychoGenics Inc.

2011 - Assay tool

Kobayashi et al. (2011) highlights the development and utility of an ELISA (enzyme-linked immunosorbent assay) for measuring survival motor neuron (SMN) protein levels in clinical and preclinical analyses of spinal muscular atrophy (SMA). This is an important assay tool for evaluating potential SMA therapies.

Kobayashi, D.T., Olson, R.J., Sly, L., Swanson, C.J., Chung, B., Naryshkin, N., Narasimhan, J., Bhattacharyya, A., Mullenix, M. and Chen, K.S., 2011. Utility of survival motor neuron ELISA for spinal muscular atrophy clinical and preclinical analyses. PLoS One, 6(8), p.e24269.	Supported by the SMA Foundation.

2011 - Partnership between Roche, PTC and SMAF

Roche entered into a license and collaboration agreement with PTC and SMAF. Pursuant to the license and collaboration agreement, Roche paid PTC Therapeutics an upfront non-refundable payment of $30 million[1]. In addition, PTC is eligible to receive up to an aggregate of $135 million in payments if specified development and regulatory milestones are achieved and up to an aggregate of $325 million in payments if specified sales milestones are achieved. PTC is also entitled to tiered single-digit to mid-teen royalties on worldwide net product sales of products developed pursuant to the collaboration.

2014 - PTC Published Findings on SMA Drug Candidates

[1] https://www.sec.gov/Archives/edgar/data/1070081/000104746913006241/a2215112zs-1.htm

Researchers identified various small molecules that shift the balance of SMN2 splicing towards the production of full-length SMN2 messenger RNA with high selectivity. Early analogs of risdiplam were identified in a phenotypic high-throughput screen of 200,000 small molecules. Three orally available compound series were progressed for further validation.

Administration of these compounds to mice (with a model of severe SMA), led to an increase in SMN protein levels, improvement of motor function and the protection of neuromuscular circuits.

Naryshkin et al. (2014) reports that SMN2 splicing modifiers significantly improve motor function and extend the lifespan of mice with spinal muscular atrophy (SMA). This study demonstrated the therapeutic potential of targeting SMN2 splicing to increase functional SMN protein levels.

Naryshkin, N.A., Weetall, M., Dakka, A., Narasimhan, J., Zhao, X., Feng, Z., Ling, K.K., Karp, G.M., Qi, H., Woll, M.G. and Chen, G., 2014. SMN2 splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy. science, 345(6197), pp.688-693.	Supported by SMA Foundation and the Harvard Stem Cell Institute.

2015 - PTC, Roche and SMA Foundation Ongoing Collaboration Structure

The research term of the License and Collaboration Agreement between PTC, Roche and SMAF ended on December 31, 2014. The ongoing collaboration between the three entities is governed by a joint steering committee consisting of an equal number of representatives of the three entities. The committee endeavors to make decisions by consensus. As such, the agreement between these entities is an SMAF License Agreement that will expire on the date when no royalty or other payment obligations are or will be due under the agreements.[2]

2015 - RG7800 enters clinical trials

The MOONFISH clinical study, initiated in April 2015, was designed to investigate the safety, pharmacokinetics, and efficacy of RG7800, a small molecule splicing modifier, in individuals with spinal muscular atrophy (SMA). RG7800 was developed to enhance the inclusion of exon 7 in SMN2 mRNA transcripts, thereby increasing the production of functional survival motor neuron (SMN) protein, which is deficient in SMA patients.

During the course of the study, an unexpected safety finding emerged from a separate long-term animal study of RG7800. This animal study revealed adverse effects at exposure levels higher than those used in the MOONFISH study. Due to these safety concerns, the MOONFISH study

[2] https://www.sec.gov/ix?doc=/Archives/edgar/data/0001070081/000155837024002196/tmb-20231231x10k.htm

was placed on hold to prevent any possible harm to the participants and to allow for a thorough investigation of the findings.

Ratni H.; Karp G. M.; Weetall M.; Naryshkin N. A.; Paushkin S. V.; Chen K. S.; McCarthy K. D.; Qi H.; Turpoff A.; Woll M. G.; Zhang X.; Zhang N.; Yang T.; Dakka A.; Vazirani P.; Zhao X.; Pinard E.; Green L.; David-Pierson P.; Tuerck D.; Poirier A.; Muster W.; Kirchner S.; Mueller L.; Gerlach I.; Metzger F. Specific Correction of Alternative Survival Motor Neuron 2 Splicing by Small Molecules: Discovery of a Potential Novel Medicine To Treat Spinal Muscular Atrophy. J. Med. Chem. 2016, 59 (13), 6086–6100.	Supported by Hoffmann-La Roche AG, PTC Therapeutics and the SMA Foundation.

2015 - Decision to move forward with development of a second SMN2 splicing modifier, RG7916

Following the safety concerns with RG7800, the focus shifted to developing a safer and more effective SMN2 splicing modifier. This led to the identification and development of risdiplam (RG7916), which showed superior safety and efficacy profiles in preclinical studies and early clinical trials. The selection of risdiplam was based on its superior in vivo efficacy in the SMAΔ7 mouse model as well as its reduced off-target effects tested in SMA patient fibroblasts as compared to RG7800.

Spellman R, Llorian M, Smith CW. Crossregulation and functional redundancy between the splicing regulator PTB and its paralogs nPTB and ROD1. Mol Cell. 2007;27:420-434	Supported by Hoffmann-La Roche AG, PTC Therapeutics and the SMA Foundation.

2016 - Mechanism of action

Concurrently, a study investigated how small molecule splicing modifiers achieve specificity by binding to the SMN2 pre-mRNA-protein complex. This study provided insight into the molecular mechanism / the mechanism of action of risdiplam.

Sivaramakrishnan, M., McCarthy, K.D., Campagne, S., Huber, S., Meier, S., Augustin, A., Heckel, T., Meistermann, H., Hug, M.N., Birrer, P. and Moursy, A., 2017. Binding to SMN2 pre-mRNA-protein complex elicits specificity for small molecule splicing modifiers. Nature communications, 8(1), p.1476.	This work was supported in part by a grant from the SMA Foundation

2016 & 2017 - Initiation of Phase II/III Trials for Risdiplam

The FIREFISH trial is a Phase II/III clinical study initiated in 2016, focusing on infants aged 1 to 7 months diagnosed with Type 1 SMA. This trial consisted of two parts. Part 1 was a dose-finding study to determine the optimal dose of risdiplam by evaluating its safety, pharmacokinetics, and pharmacodynamics. This component aimed to establish the most effective and safe dosage for further testing. Part 2 was an efficacy and safety assessment using the dose selected from Part 1. The primary objective was to evaluate the impact of risdiplam on motor function and survival rates in infants with Type 1 SMA.

The SUNFISH trial, also initiated in 2016, was a Phase II/III study aimed at children and young adults aged 2 to 25 years with Type 2 or 3 SMA. Similar to FIREFISH, it was divided into two parts. Part 1 was a dose-finding study to determine the optimal dose of risdiplam by assessing safety and pharmacokinetics in the participants. Part 2 was an evaluation of the safety and efficacy of the selected dose from Part 1. The trial measured improvements in motor function and overall health outcomes in the participants.

Launched in 2017, the JEWELFISH trial was a Phase II study that included children and adults aged 6 months to 60 years. This trial focused on evaluating the safety and tolerability of risdiplam in patients who previously participated in the MOONFISH trial or received other SMA treatments such as nusinersen, olesoxime, or AVXS-101.

All the “FISH” trials are industry-sponsored by Roche.

2017 - Pharmacokinetic and Pharmacodynamic studies

Studies evaluated a novel class of benzamide derivatives, including risdiplam, which restored SMN protein levels in mouse models of SMA. Risdiplam displayed excellent pharmacokinetic and pharmacodynamic properties, suggesting potential benefits for chronic treatment of SMA patients.

Pinard, E., Green, L., Reutlinger, M., Weetall, M., Naryshkin, N.A., Baird, J., Chen, K.S., Paushkin, S.V., Metzger, F. and Ratni, H., 2017. Discovery of a novel class of survival motor neuron 2 splicing modifiers for the treatment of spinal muscular atrophy. Journal of Medicinal Chemistry, 60(10), pp.4444-4457.	Supported by Hoffmann-La Roche AG, PTC Therapeutics and the SMA Foundation.

2018 - Discovery of Risdiplam published: cellular activity, selectivity, pre-clinical efficacy and safety data first published

Risdiplam showed enhancement in expression of SMN in brain and quadriceps muscle upon oral administration in a mild SMA mouse model (allele C model). Intraperitoneal (IP) administration of risdiplam at a concentration as low as 1 mg/kg of body weight produced a robust enhancement in SMN levels in brain and quadriceps muscle of these mice. This study also reported favorable pharmacokinetic properties of risdiplam, including on positive bioavailability and a suitable safety profile for chronic treatment.

Ratni H.; Ebeling M.; Baird J.; Bendels S.; Bylund J.; Chen K. S.; Denk N.; Feng Z.; Green L.; Guerard M.; Jablonski P.; Jacobsen B.; Khwaja O.; Kletzl H.; Ko C.-P.; Kustermann S.; Marquet A.; Metzger F.; Mueller B.; Naryshkin N. A.; Paushkin S. V.; Pinard E.; Poirier A.; Reutlinger M.; Weetall M.; Zeller A.; Zhao X.; Mueller L. Discovery of Risdiplam, a Selective Survival of Motor Neuron-2 (SMN2) Gene Splicing Modifier for the Treatment of Spinal Muscular Atrophy (SMA). J. Med. Chem. 2018, 61 (15), 6501–6517.	Supported by Hoffmann-La Roche AG, PTC Therapeutics and the SMA Foundation.

2018 - In vitro characteristics and in vivo characteristics

In further studies in several SMA mouse models as well as in rats and non-human primates, risdiplam displayed excellent pharmacokinetic and pharmacodynamic properties, such as body-wide distribution and stable plasma levels over extended dosing periods. The in vitro and in vivo preclinical data suggest that function SMN protein increases seen in patients' blood flow following risdiplam treatment should reflect similar increases in functional SMN protein in the CNS, muscle and other peripheral tissues. These results were sufficient to launch clinical trials of risdiplam for its evaluation in SMA patients.

Safety assessment of risdiplam. Pharmacokinetics was evaluated by in vitro and in vivo studies. In mouse models of SMA and in healthy monkeys, risdiplam was shown to distribute to brain, muscle and peripheral organs at concentration at or above those expected for pharmacologic benefit.

Poirier, A., Weetall, M., Heinig, K., Bucheli, F., Schoenlein, K., Alsenz, J., Bassett, S., Ullah, M., Senn, C., Ratni, H. and Naryshkin, N., 2018. Risdiplam distributes and increases SMN protein in both the central nervous system and peripheral organs. Pharmacology research & perspectives, 6(6), p.e00447.	Supported by F. Hoffmann-La-Roche Ltd.

2019 - RAINBOWFISH

The RAINBOWFISH study is a global clinical trial investigating the safety and efficacy of risdiplam in pre-symptomatic infants with SMA, aged from birth to 6 weeks. This trial aims to evaluate whether early intervention with risdiplam can prevent the onset of SMA symptoms and improve long-term motor function and survival outcomes. The primary objectives include assessing the pharmacokinetics (PK) and pharmacodynamics (PD) of risdiplam, as well as monitoring the development of motor milestones.

2020 - FDA approval of Evrysdi

In August 2020, the FDA approved risdiplam under the brand name Evrysdi for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older. The trials cited in the FDA approval were FIREFISH, SUNFISH, and JEWELFISH.

2022 - FDA approval of Evrysdi extended indication

In May 2022, the FDA expanded the approved use of Evrysdi (risdiplam) to include patients with SMA from birth onward.[3]

2024 - PUPFISH

The PUPFISH study is a Phase II clinical trial designed to evaluate the pharmacokinetics (PK) and safety of risdiplam in newborns with SMA who are under 20 days of age at the first dose. This trial aims to gather critical data on how risdiplam is absorbed, distributed, metabolized, and excreted in this very young patient population. Additionally, the study will monitor for any potential adverse effects and assess the overall safety profile of risdiplam in these infants. The ultimate goal is to extend the therapeutic benefits of risdiplam to the youngest SMA patients as early as possible.

[3] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/213535Orig1s003,%20s005ltr.pdf