18 December 2024

Dear members of SMA Europe,

Following your request for risdiplam and SMA clinical development programme updates, we wanted to take a moment to reflect on the progress of 2024. Please find below a summary of the information you requested, across key data presentations, clinical development, regulatory and access activities during 2024.

International regulatory and access updates

Risdiplam oral solution

We continue to work closely with reimbursement and assessment bodies to expand access to risdiplam for all people living with SMA, and minimise any delay between regulatory approval and national reimbursement. As of December 2024, risdiplam has now:

- Received regulatory approval in >100 countries, including SMA Europe member country, Turkey
- Been reimbursed in 59 countries
- Attained expanded access criteria in Denmark, meaning adults of all ages living with SMA may now also receive treatment

We will continue to work with the community and governments around the world to ensure people living with SMA, of all ages, have access to risdiplam.

Risdiplam tablet formulation

We submitted the 5mg risdiplam tablet to the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) earlier this year. If approved, this would be an additional option to the already available oral solution. We expect updates on the progress of these regulatory submissions in early 2025.

Scientific presentations and study updates

Data from ongoing risdiplam trials and real-world initiatives continue to build on our collective knowledge of SMA, and the role of risdiplam in the wider treatment landscape.

Long-term data from risdiplam pivotal trials

- **FIREFISH** (NCT02913482) - Final five-year efficacy and safety data were presented at Cure SMA's annual congress, confirming the sustained efficacy and safety profile of risdiplam in children with Type 1 SMA, from the open-label extension of the FIREFISH study. The study is now complete.[1]
- **SUNFISH** (NCT02908685) - A post-hoc analysis (further analysis after the data have been collected) from part two of the SUNFISH trial was presented at SMA Europe's annual congress, showing that a larger proportion of those treated with risdiplam were likely to maintain or gain independence when performing activities of daily living, compared to those on placebo.[2]
- **RAINBOWFISH** (NCT03779334) - Two-year data from the RAINBOWFISH trial were presented at the World Muscle Society Congress in October, which confirmed ongoing efficacy and safety of risdiplam in infants treated before symptoms appeared.[3]

Tablet formulation

- **BABE** (NCT04718181) - Bioavailability and bioequivalence data presented at SMA Europe's annual congress concluded that, whether swallowed whole or dispersed in bottled water, the 5mg tablet formulation resulted in the same concentration of risdiplam in the body as the currently available oral solution. No new safety signals were identified for the tablet formulation.[4]

Roche clinical program overview

Please find below a summary table of all complete and ongoing clinical trials. Major updates from 2024 are highlighted in **green**.

Study	What does it assess?	Who does it assess?	Status	Reference
FIREFISH	Safety and efficacy	Type 1 SMA 1–7 months old at enrolment	Complete	NCT02913482
SUNFISH	Safety and efficacy	Type 2 or 3 SMA 2–25 years old at enrolment	Complete	NCT02908685
JEWELFISH	Safety, tolerability, and pharmacokinetics/pharmacodynamics of risdiplam after other SMA therapies	Type 1, 2 or 3 SMA 6 months–60 years at enrolment	Active, not recruiting	NCT03032172
RAINBOWFISH	Safety and efficacy in presymptomatic infants	Type 1, 2 or 3 SMA Birth–6 weeks at enrolment	Active, not recruiting	NCT03779334
Tablet Bioavailability and Bioequivalence (BABE)	Assess bioavailability and bioequivalence of 5mg tablet	Healthy volunteers	Complete	NCT04718181
ACTIVENESS	Long-term effectiveness	Pre- and post-symptomatic patients with 1–4 *SMN2* copies	Ongoing	Website
Pregnancy registry	Learn more about the health of pregnant women who received risdiplam, and the health of their babies	Women exposed to risdiplam during pregnancy	Recruiting	Website
PUPFISH	Pharmacokinetics and safety in newborn infants	Infants <20 days old with SMA	Recruiting	NCT05808764
Hinalea	Safety and effectiveness in children previously treated with gene therapy	2 *SMN2* copies <2 years at enrolment	**Recruiting**	NCT05861986 NCT05861999
MANATEE	Safety and efficacy of an anti-myostatin antibody in combination with risdiplam	• Part 1: Ambulant and non-ambulant patients with SMA aged 2–10 years • Part 2: Ambulant patients with SMA aged 2-25 years	**Active, not recruiting**	NCT05065372

MARLIN **NEW**	Observational study: Fertility journey of adult males living with SMA who are taking or have taken risdiplam.	Males with SMA, ages 18 and 50 years, who are taking or have taken risdiplam, and are trying to conceive a child or have previously conceived a child after taking risdiplam	**Recruiting** (US only)	ISRCTN31399857

Clinical care consensus statements

Roche is supporting a number of Delphi consensus projects regarding care and management of SMA. These activities bring together leading clinicians, patient advocacy leaders, and patients, to define and agree key care recommendations around a specific topic. Two such projects were presented in 2024:

- The methodology for a Delphi consensus on the management of gastrointestinal (GI) adverse events related to the use of risdiplam was presented at Cure SMA's annual congress.[5]
    - This study was initiated following SMA Europe feedback in 2023. It is hoped that the statements generated will help inform clinical decision-making practices related to the management of potential risdiplam-related GI side effects.
- The methodology for a Delphi consensus on assessing clinically meaningful treatment outcomes in adults living with SMA was presented at SMA Europe's annual congress.[6]
    - This study aims to answer key questions: What aspects of SMA (beyond motor function) should be considered when determining meaningful treatment outcomes in adults, and what is a meaningful treatment response/outcome in adults.

Real world evidence (RWE)

A number of risdiplam RWE studies were presented in 2024. These included real-world treatment with risdiplam in adults (including demographic, clinical characteristics, and motor outcomes)[7,8], infants under two months of age[9], fertility outcomes in males treated with risdiplam[10], and WeSMA[11] - a prospective study investigating long-term safety and effectiveness of risdiplam in adult and pediatric SMA populations.

Our ongoing commitment to the SMA community

We are proud to collaborate with our partners in the community to positively impact the lives of individuals living with SMA. In addition to the national projects led by our local Roche teams, we engaged in a number of international projects aiming to drive meaningful advancements in care and support.

Adults living with SMA

- We proudly published the Care for Adults Living with SMA in Europe benchmarking report, a collaborative effort between SMA Europe and Roche. It has been wonderful to see this advocacy tool in action across Europe, from advocacy workshops to national media coverage.
- Together with SMA Europe and seven amazing adults living with SMA, we developed video testimonials to raise awareness of the everyday challenges adults face when seeking care and treatment: How adult SMA patients break down barriers to care and treatment.

SMA My Way

- We remain committed to raising awareness and understanding of SMA and are proud to continue our support of SMA My Way. In 2024, the Champions published five new podcast episodes, discussing love, life, travel, entrepreneurship, and more.

Global advocacy

- It was our pleasure to support the Global SMAdvocacy event in Ghent, Belgium, which brought together 70 patient advocates from 50 countries to address critical issues in SMA advocacy. We look forward to seeing your continued progress in 2025 and beyond!

It's been another year of meaningful progress for those living with SMA, and we extend our heartfelt gratitude to the entire community for your partnership. We wish you all a happy holiday season and may 2025 bring you much happiness and success.

Sincerely,

Louisa Danielle Townson

Louisa Townson, on behalf of the Roche Global SMA Team

Global Patient Partnership, SMA & FSHD

References

1. Mazurkiewicz-Bełdzińska W, et al. FIREFISH Parts 1 and 2: 5-year efficacy and safety of risdiplam in Type 1 SMA. Presented at Cure SMA Research & Clinical Care Meeting, 2024.
2. Sully K, et al. Post hoc analysis of the SMA Independence Scale-Upper Limb Module (SMAIS-ULM) in individuals with Type 2 and non-ambulant Type 3 SMA using SUNFISH Part 2 data. Presented at SMA Europe 4th Scientific International Congress, 2024
3. Servais L, et al. RAINBOWFISH: 2-year efficacy and safety data of risdiplam in infants with presymptomatic SMA. Presented at World Muscle Society Annual Congress, 2024.
4. Kletzl H, et al. Bioequivalence and food effect assessment for a new risdiplam tablet formulation in healthy volunteers. Presented at SMA Europe 4th Scientific International Congress, 2024.
5. Hewamadduma C and Korb M. International evidence-based consensus on the management of gastrointestinal adverse events related to the use of risdiplam in patients with spinal muscular atrophy: methodology. Presented at Cure SMA Research & Clinical Care Meeting, 2024.
6. Sully K, et al. Protocol for a Delphi consensus panel on assessing clinically meaningful treatment outcomes in adults living with SMA. Presented at SMA Europe 4th Scientific International Congress, 2024.
7. Gorni K, et al. Demographic and clinical characteristics of risdiplam-treated and untreated adult patients with Spinal Muscular Atrophy. Presented at World Muscle Society Annual Congress, 2024.
8. Gorni K, et al. Real-world treatment with risdiplam in adults with SMA: A multicentre study. Presented at World Muscle Society Annual Congress, 2024.
9. Dickendesher T, et al. Real-world use of risdiplam for the treatment of spinal muscular atrophy (SMA) in infants under 2 months of age in the US. Presented at SMA Europe 4th Scientific International Congress, 2024.
10. Erdler M, et al. Fertility outcomes in risdiplam-treated male patients with spinal muscular atrophy: a multicenter case series. Presented at World Muscle Society Annual Congress, 2024.
11. Tanvir I, et al. Long-term follow-up study of risdiplam in participants with spinal muscular atrophy (WeSMA). Presented at the Muscular Dystrophy Association (MDA) Clinical and Scientific Conference, 2024.

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