15 December 2023

Dear Members of SMA Europe,

As the year draws to a close, and following your request for regular updates, we wanted to take a moment to reflect on the progress of 2023. Please find enclosed a summary of key risdiplam data presentations and clinical development activities, and international projects we have partnered on with the SMA community in 2023.

Our work to secure access to risdiplam as a treatment option for those who need it is an ongoing priority. Risdiplam is now approved in more than 100 countries, with reimbursement secured in 56 and counting. We could not make these strides forward without the partnership of the SMA community, and we are so grateful for your ongoing collaboration and support to make this possible. In 2024, we will continue to work relentlessly to enable broader and sustainable access to risdiplam for people living with SMA around the world.

Scientific presentations:
Throughout the year, we have been committed to sharing data from ongoing risdiplam trials to build on the collective knowledge about SMA and the role of risdiplam in the treatment landscape.

- **SUNFISH** (NCT02908685) – Long-term, four-year data presented at the Muscular Dystrophy Association (MDA) Clinical and Scientific Conference in March.[1]
- **FIREFISH** (NCT02913482) – Data in children with Type 1 SMA presented at the Cure SMA Research & Clinical Care Meeting in June.[2]
- **RAINBOWFISH** (NCT03779334) – Data on risdiplam's efficacy and safety in babies with presymptomatic SMA, aged from birth to 6 weeks, was presented at the World Muscle Society Congress (WMS) in October.[3]
- Pooled safety data from FIREFISH, SUNFISH, JEWELFISH (NCT03032172) (open-label extension) and RAINBOWFISH were presented at the WMS Congress in October.[4]
- **ACTIVENESS** (EUPAS47916) – The study design for a prospective, longitudinal cohort study to assess the long-term effectiveness of risdiplam in SMA was presented at the Cure SMA Research & Clinical Care Meeting in June.[5] Challenges and strategies for conducting a study of this kind were presented at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) in August.[6]

Clinical programme overview:

Study	What does it assess?	Who does it assess?	Status	Reference
FIREFISH	Safety and efficacy	Type 1 SMA 1–7 months old at enrolment	Ongoing	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	Ongoing	NCT03032172
RAINBOWFISH	Safety and efficacy in presymptomatic infants	Type 1, 2 or 3 SMA Birth–6 weeks at enrolment	Ongoing	NCT03779334

5mg Tablet bioequivalence and bioavailability	Assess bioavailability and bioequivalence of two 5mg tablet formulations vs the approved oral solution	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	Activating	NCT05808764
Hinalea	Safety and effectiveness in children previously treated with gene therapy	2 *SMN2* copies <2 years at enrolment	Activating	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	Recruiting	NCT05065372

Clinical study updates:

- **Study amendment**: Recruitment started for Part 1 of the MANATEE clinical study (NCT05115110) – a two-part, global Phase 2/3 study evaluating the safety and efficacy of GYM329 (RO7204239), an investigational anti-myostatin antibody targeting muscular growth, in combination with risdiplam. We are pleased to share that the trial design was amended to include non-ambulant individuals in Part 1 and that recruitment for this additional group of participants is underway. Results from Part 1 of the study will inform if we move forward into Part 2.
- **New studies:** HINALEA 1 (NCT05861986) and HINALEA 2 (NCT05861999) are two new studies that aim to evaluate the safety and efficacy of risdiplam in children aged between 3 months and 2 years, who have previously been treated with gene therapy. Recruitment is expected to commence in 2024.
- **Study completions**: Two risdiplam clinical trials documented last study visits, marking the conclusion of SUNFISH and the 5mg Tablet bioequivalence and bioavailability study. Data from both of these studies will be presented at scientific meetings in 2024. Our sincere thanks go to the people and their families who have participated in these clinical trials.

Regulatory and product updates:

We have continued to work to expand the label of risdiplam for those living with SMA:

- In August 2023, the European Medicines Agency (EMA) approved a label extension for risdiplam to include infants from birth, based on interim data from the RAINBOWFISH study.[7] Risdiplam is now approved from birth in 52 countries.
- The European Union label for risdiplam was also updated to include two-year data from JEWELFISH, an ongoing, open-label study evaluating risdiplam in the broadest population ever studied in an SMA clinical trial, to reflect safety and efficacy data in patients previously treated with other SMA-modifying therapies.

Access to risdiplam:
We continue to work closely with reimbursement and assessment bodies to expand access to risdiplam for all groups living with SMA, with a focus on adults and newborns, and minimise any delay between regulatory approval and national reimbursement. Risdiplam has now:

- received regulatory approval in 104 countries with marketing authorisation applications under review in 13 countries
- been reimbursed in 56 countries, including 15 middle income and lower income countries such as Brazil, Georgia, Iran, Iraq, Serbia, Ukraine.

Our ongoing commitment:

- ***SMA My Way:*** As part of our commitment to raise awareness and understanding of SMA, we are proud to support SMA My Way, a platform where the SMA community can share their experiences, support and empower each other. In 2023 the website received over 56,000 views and in partnership with the SMA My Way Champions, the first episode of a podcast series launched. Across the first season, you'll hear the Champions discuss love, life, travel, entrepreneurship and more. You can listen here or search for *SMA My Way* on your favourite podcasting platform to subscribe and catch each episode as it's released.
- ***Adults living with SMA:*** we are incredibly proud to be working in partnership with SMA Europe on a pan-European benchmarking project to assess how care is provided to adults living with SMA. The benchmarking report will augment the important work done by the OdySMA project and add to the understanding of SMA care across Europe.[8]
- ***Newborn Screening:*** as a founding member of the European Alliance for Newborn Screening in SMA, we continue to support the group's urgent work to identify infants born with SMA and enable timely treatment initiation.
- ***2023 International SMA Patient Advocacy Group Meeting:*** the value of sharing experiences and strengthening global community connections cannot be overstated and it was our pleasure to support this inaugural meeting of international advocates, hosted by Cure SMA in Orlando on June 27th.

2023 has been another busy year! Our heartfelt gratitude goes to the entire community for the meaningful progress we continue to make for all of those living with SMA. We wish you all a joyous holiday season and that the coming year brings happiness and success.

Sincerely,

Louisa Danielle Townson

Louisa Townson, on behalf of the Roche Global SMA Team

Global Patient Partnership, SMA & FSHD

References

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3) Finkel S, et al. RAINBOWFISH: Primary efficacy and safety data in risdiplam-treated infants with presymptomatic spinal muscular atrophy (SMA). Presented at the 28th International Annual Congress of the World Muscle Society (WMS), Charleston, USA; October 3–7, 2023.
4) Baranello G, et al. Safety update: Risdiplam clinical trial program for spinal muscular atrophy. Presented at 28th International Annual Congress of the World Muscle Society (WMS), Charleston, USA; October 3 – 7, 2023.

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5) Salem L, et al. ACTIVENESS: A prospective, observational, long-term post-authorization efficacy study of risdiplam in patients with SMA. Presented at Cure SMA Research & Clinical Care Meeting, Orlando, USA; June 28 – 30, 2023.
6) Salem L, et al. Challenges and Mitigations of Conducting a Long-Term Effectiveness Study in a Rare Disease (Spinal Muscular Atrophy). Presented at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), Halifax, Canada; August 23 - 27, 2023.
7) Evrysdi. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf. Accessed December 2023.
8) Petridis F, et al. Benchmarking care for adults living with spinal muscular atrophy (SMA) in Europe. Presented at the 9th Congress of the European Academy of Neurology, Budapest, Hungary; July 1-4 2023. Available at: https://medically.gene.com/global/en/unrestricted/neuroscience/EAN-2023/ean-2023-poster-petridis-benchmarking-care-for-adults-l.html. Accessed December 2023.