17 December 2020

Dear members of SMA Europe,

As 2020 draws to a close, based on your requests to receive regular updates, we would like to provide you with a summary of our work in the community throughout this year, including information about the risdiplam clinical development programme and progress towards our goal of making risdiplam available to all patients who can benefit from the treatment. We are hopeful that this information further demonstrates our commitment to transparency, openness and collaboration with the community, which are the cornerstones of our work in SMA.

Supporting the community through COVID-19 and beyond

While this year has been uniquely challenging for the population at large due to the COVID-19 global pandemic, we recognize that circumstances are particularly difficult for people living with or caring for those with serious conditions, such as SMA. Our primary focus over these past several months has been to ensure patient safety, uninterrupted access to treatment and to support the wider community.

Roche has been working closely with clinical trial sites and partners, to safeguard the seamless continuation of our clinical studies, which are ongoing around the world, and mitigate risks where possible. A number of new initiatives were introduced to safely and comfortably enable the continued participation of individuals in our studies. These include a contactless home drug delivery service, remote monitoring to maintain oversight of the general health of participants in situations where visiting the clinic or hospital for a study appointment was no longer feasible, and home nursing services (in countries where this is permitted and feasible).

At the start of 2020, Roche announced the initiation of a global Pre-Approval Access (PAA)/ Compassionate Use (CU) programme for risdiplam in countries where possible (e.g. where applicable laws and regulations allow such programmes, and which fulfil the criteria based on applicable company policy). The programme is offering patients who have no other treatment options and are facing the most urgent medical need, the opportunity to access risdiplam prior to regulatory approval. It is worth highlighting that eligibility criteria vary from country to country. Currently, the risdiplam PAA/CU programme is open in more than 50 countries worldwide.

Additionally, in response to the unique pressures that the COVID-19 pandemic has been exerting on health systems, Roche decided to amend the eligibility criteria for the PAA/CU programme to also include patients whose current treatment has been interrupted as a direct consequence of the COVID-19 outbreak. This change to the risdiplam PAA/CU programme applies to patients who are not able to continue receiving their therapies due to the COVID-19 outbreak and who could subsequently face the risk of their condition worsening due to treatment interruption.

We recommend that people interested in accessing risdiplam via PAA/CU, discuss their options with their treating physician. The decision to apply for the programme is one that should be made by the treating physician after she/he has explored and discussed all possible options with the patient or family.

At the same time, we continue to support the community in its efforts to improve the quality of life of people who live with SMA and advance patient care. One of the key imperatives to achieve optimal clinical outcomes in SMA is early diagnosis. That is why we are proud to have joined the European Alliance for Newborn Screening in SMA, led by SMA Europe, to advocate collectively for newborn screening programmes in Europe to include a test for SMA by 2025.

Clinical Trial Data Updates

During 2020, we announced positive data from three clinical trials, evaluating the efficacy and safety of risdiplam in a broad spectrum of patients living with SMA. Today, more than 450 people are participating

in the risdiplam clinical development programme. Roche leads the clinical development of risdiplam as part of a collaboration with the SMA Foundation and PTC Therapeutics.

FIREFISH assesses risdiplam in infants aged 1-7 months with symptomatic Type 1 SMA.

- In April, we announced that the pivotal Part 2 of the study had met its primary endpoint. The data were selected for the 72nd American Academy of Neurology (AAN) Annual Meeting and were made available online via virtual presentation. By month 12, 29% (12/41) of infants were sitting without support for five seconds, as assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III). In addition, 18 (43.9%) infants were able to hold their head upright, 13 (31.7%) were able to roll to the side and 2 (4.9%) infants were able to stand with support, as measured by the Hammersmith Infant Neurological Examination 2 (HINE-2). Ninety-three percent (38/41) of infants were alive and 85.4% (35/41) were event-free. Without treatment, the median age of death or permanent ventilation was 13.5 months in a natural history cohort. Three infants experienced fatal complications of their disease within the first three months of treatment, none of which have been attributed to risdiplam by the investigator. Of those who were alive at 12 months, 89% (34/38) were able to feed orally. The most common adverse events were upper respiratory tract infection (46.3%), pneumonia (39%), pyrexia (39%), constipation (19.5%) nasopharyngitis (12.2%), rhinitis (12.2%) and diarrhoea (9.8%). The most common serious adverse events were pneumonia (31.7%), bronchiolitis (4.9%), respiratory failure (4.9%) and hypotonia (4.9%).

- In October, we announced the 2-year results from Part 1 of the study at the virtual World Muscle Society Congress. The 2-year results in infants treated with the therapeutic dose of risdiplam (17/21 infants) showed that these infants continued to improve and achieve motor milestones. This exploratory analysis showed that an estimated 88% of infants were alive and did not require permanent ventilation at two years. In addition, 59% (10/17 vs. 7/17 at 1-year) were able to sit without support for at least 5 seconds (assessed by BSID-III), 65% (11/17 vs. 9/17 at 1-year) had maintained upright head control, 29% (5/17 vs. 2/17 at 1-year) could turn themselves over and 30% (5/17 vs. 1/17 at 1-year) were able to stand, either supporting weight or with support. Of the infants alive at two years (14/17), 100% maintained the ability to swallow and 93% (13/14) were able to feed orally. The most common adverse events included fever (pyrexia; 71%), upper respiratory tract infection (52%), cough (33%), vomiting (33%), diarrhoea (29%) and respiratory tract infection (29%). The most serious adverse event that occurred in 24% of infants was pneumonia.

SUNFISH assesses risdiplam among people with Type 2 or Type 3 SMA aged 2 to 25 years.

- In February, we announced positive initial data from the pivotal randomized, placebo-controlled Part 2 of the study (n=180) at the 2nd International Scientific & Clinical Congress on Spinal Muscular Atrophy. The study met its primary endpoint of change from baseline in the Motor Function Measure 32 (MFM-32) scale after 12 months of treatment with risdiplam, compared to placebo. The Revised Upper Limb Module (RULM), a key secondary endpoint, also showed an improvement (1.59 point difference; p=0.0028). As anticipated, exploratory subgroup analyses showed that the strongest responses in MFM-32 versus placebo were observed in the youngest age group (2-5 years) (78.1% vs 52.9% achieving ≥3 point increase). Importantly, disease stabilisation was observed in the 18-25 years age group (57.1% vs 37.5%, with stabilisation defined as a ≥0 point increase), which is the goal of treatment for those with more established disease. The most common adverse events were upper respiratory tract infection (31.7%), nasopharyngitis (25.8%), pyrexia (20.8%), headache (20%), diarrhoea (16.7%), vomiting (14.2%) and cough (14.2%). While the rate of lower respiratory tract infections overall was similar in both treatment arms (risdiplam 19%, placebo 20%), serious lower respiratory tract infections occurred in more patients in the risdiplam group (risdiplam 10% placebo 2%) but were reported as unrelated and resolved without change to study treatment.

- In June, we presented 2-year data from Part 1 (n=51) of the study at the virtual Cure SMA congress. The results showed that risdiplam significantly improved motor function after 2 years of treatment compared to natural history data, as assessed by the MFM-32 scale. In a weighted analysis comparing the data with a robust natural history comparator cohort, the MFM total change from baseline at month 24 was greater in people receiving risdiplam (3.99 point difference (95% CI: 2.34,

5.65) p< 0.0001). The most common adverse events were fever (pyrexia; 55%), cough (35%), vomiting (33%), upper respiratory tract infections (31%), cold (nasopharyngitis; 24%) and sore throat (oropharyngeal pain; 22%). The most common serious adverse event that occurred in three of the 51 participants exposed to risdiplam was pneumonia.

Preliminary 12-month data from **JEWELFISH** (n=174), a trial in people with all types of SMA aged 1 to 60 years previously treated with nusinersen, olesoxime or AVXS-101, were also presented in June. The results showed that rapid and sustained increases in SMN protein levels were observed among the patients who had completed 12 months of treatment with risdiplam (n=18). The overall adverse event profile was similar to that observed in risdiplam trials of people not previously treated with a SMA-targeting therapy. Twelve-month data from the complete study is expected in the first half of 2021.

No new safety signals were identified in any of the data announcements in 2020 and there have been no ophthalmological adverse events related to risdiplam in the clinical trials programme.

Ongoing clinical trials

The FIREFISH, SUNFISH and JEWELFISH studies are all ongoing so that further long-term efficacy and safety data can be evaluated and shared with the SMA community. Recruitment for these three studies is now closed.

The RAINBOWFISH study is the only global risdiplam study that is currently recruiting. RAINBOWFISH is designed to explore the efficacy and safety of risdiplam in newborn babies up to 6 weeks old with a genetic diagnosis of SMA, who have not yet shown symptoms. More information about RAINBOWFISH and its trial sites can be found on the ClinicalTrials.gov website (ClinicalTrials.gov Identifier: NCT03779334).

Regulatory approvals for risdiplam

In 2020, we have made significant progress towards our goal of ensuring broad and rapid access to risdiplam.

In August, we received the first regulatory approval of risdiplam when the U.S. Food and Drug Administration (FDA) approved risdiplam for the treatment of SMA in adults and children 2 months of age and older under the brand name Evrysdi™. Six additional countries (Chile, Brazil, Ukraine, South Korea, Georgia and Russia) have also approved the use of risdiplam in the last few months. Furthermore, we have 29 existing regulatory applications under review for marketing authorization in 55 countries worldwide, including: the 27 member states of the European Union, Iceland, Norway, Indonesia, Taiwan, China, UK, Australia, Canada, Israel, Malaysia, Switzerland, Thailand, UAE, Macedonia, Kuwait, Singapore, New-Zealand, Japan, Peru, South Africa, Pakistan, Botswana, Namibia, Mauritius, Bolivia, Qatar, Saudi Arabia and India (where the first step of approval towards marketing authorization was granted).

As always, our sincere gratitude and appreciation goes out to the many patients and families who are participating in our ongoing clinical studies. As we work towards our goal of enabling access to risdiplam for people around the world, we continue to be humbled by the resilience of the SMA community and are grateful for everything we have achieved by working together.

We wish you a happy and healthy holiday season and look forward to the year ahead.

Sincerely,

Fani Petridis

Fani Petridis, on behalf of the Roche Global SMA Team
Senior Global Patient Partnership Director, Rare Diseases

Overview of risdiplam clinical trials

FIREFISH (NCT02913482):

- A global two-part open-label study evaluating the efficacy and safety of risdiplam in symptomatic infants with Type 1 SMA aged 1 to 7 months
- Part 1 (n=21) assessed the safety profile of risdiplam and determined the dose for Part 2
- Part 2 (n=41) is a pivotal open label study (no placebo arm) assessing the safety and efficacy of risdiplam at the dose selected from Part 1

SUNFISH (NCT02908685):

- A large (n=231) global two-part open-label study evaluating the efficacy and safety of risdiplam in in people with Type 2 or 3 SMA aged 2 to 25 years
- Part 1 (n=51) assessed the safety profile of risdiplam and determined the dose for Part 2
- The pivotal Part 2 (n=180) is the only double-blind, placebo-controlled trial in this broad population, evaluating the safety and efficacy of the dose selected in Part 1. Specifically, it assesses the ability of risdiplam to improve the overall MFM-32 score after one year of treatment

JEWELFISH (NCT03032172):

- An open-label exploratory trial (n=174) in people with SMA aged 6 months-60 years who have previously been treated with SMA-targeted therapies. The study will determine the safety of risdiplam, its levels in the blood and its metabolism
- BSID-III, HINE-2, MFM and HFMSE scales are being used to assess motor function and milestones expected of normal individuals at the same age

RAINBOWFISH (NCT03779334):

- An open-label, single-arm, multicentre study (n=25) investigating the efficacy, safety, pharmacokinetics and pharmacodynamics of risdiplam in infants from birth to 6 weeks old who have been genetically tested and diagnosed with SMA but have not yet shown disease symptoms
- The main analysis will assess the proportion of infants (with two copies of the SMN2 gene) that are able to sit without support for five seconds after one year of treatment with risdiplam
- This is the only global clinical trial with risdiplam currently recruiting. More information about RAINBOWFISH and its trial sites can be found on the ClinicalTrials.gov website.

About the risdiplam PAA/ CU Programme:

- The PAA/CU programme provides access to risdiplam for eligible patients with Type 1 SMA, and who have no other treatment options. In addition, the programme is expanded in countries where applicable, to patients with Type 2 SMA at the moment of filing of the regulatory application for risdiplam in that respective country.
- In order to participate in the risdiplam PAA/CU programme, specific criteria must be met in order secure patient safety. We recommend that people with SMA interested in accessing risdiplam via PAA/CU, discuss their options with their treating physician who will determine the best path forward. The decision to apply for the programme is one that should be made by the treating physician.
- PAA/CU to unlicensed medicines must always comply with the applicable country-specific laws, which differ across different countries, and as a result, the eligibility criteria of the risdiplam PAA/ CU programme vary from country to country.