November 25, 2019

Dear members of the SMA community,

As part of our ongoing partnership and following your request to receive timely information about the risdiplam clinical development program, we are pleased to share with you that the U.S. Food and Drug Administration (FDA) has accepted the filing of the New Drug Application (NDA) for risdiplam for the proposed use in people living with Spinal Muscular Atrophy (SMA). The FDA has granted the application a Priority Review, which means that the agency is currently expected to review the application within 6 months instead of the standard 10 months. The FDA is expected to make a decision on approval by May 24, 2020.

The risdiplam NDA submission incorporates 12-month data from the dose-finding Part 1 sections of the FIREFISH and SUNFISH studies, as well as data from the confirmatory Part 2 of SUNFISH. In addition to the FDA, we will work with health authorities around the world with the objective to determine appropriate pathways for filing a new drug application for our investigational medicine, risdiplam. In Europe, we anticipate to file a Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA) by the middle of 2020. For both regulatory submissions, we are currently seeking a broad label for the treatment of SMA in paediatric and adult patients. We are grateful for the opportunity to collaborate with regulatory agencies throughout our clinical development program and during our preparation for any application submission and/or review.

Advances in medical science are only meaningful when they reach the people who need them. As a company that is driven by the potential to improve the lives of patients and families touched by SMA, we are very excited to take this next step forward toward making risdiplam available to all patients that can benefit from the treatment.

We thank everyone in the community, especially the patients and families who participate in our studies, as well as the patient groups around the world who have supported and worked with us to achieve this milestone. Our journey to develop treatments for people with SMA continues to be inspired by you. We look forward to providing further updates about our program as they become available.

If you have any questions about this update, please do not hesitate to contact me.

Sincerely,

Fani Petridis

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

Frequently Asked Questions and Answers:

1. **What is Priority Review designation?**

   Priority Review designation is granted to medicines that the FDA considers to have the potential to provide significant improvements in the safety and effectiveness of the treatment, prevention or diagnosis of a serious disease.[1] Previously, the FDA also granted Orphan Drug Designation for risdiplam in January 2017, followed by Fast Track Designation in April 2017.

2. **What is risdiplam?**

   Risdiplam is an investigational orally administered liquid survival motor neuron-2 (SMN-2) splicing modifier for SMA, being studied in a broad range of patients with SMA from 1 month to 60 years of age. It is designed to provide sustained increases in survival motor neuron (SMN) protein, which plays an important role in the maintenance of specialized nerve cells (called motor neurons) that transmit signals from the brain and spinal cord to skeletal muscles, allowing the body to move. [2]

   The SMN protein is found throughout the body, with highest levels in the spinal cord and the part of the brain that is connected to the spinal cord (the brainstem).[2]

   Risdiplam increases SMN protein both centrally and peripherally through daily dosing and is being evaluated for its potential ability to help the SMN2 gene produce more functional SMN protein throughout the body.[3]

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

3. **What are the FIREFISH and SUNFISH Studies?**

   FIREFISH is a global, open-label (a type of clinical study where all patients receive the investigational medicine and no placebo – a substance that has no medicinal/therapeutic value, is given), two-part pivotal study in infants aged one to seven months with Type 1 SMA. Part 1 was a dose-finding study in 21 infants where the primary objective was to assess the safety profile of risdiplam and to determine the dose for Part 2. Part 1 also evaluated initial efficacy as an exploratory endpoint. Part 2 of the trial began in March 2018 and is assessing the efficacy and safety of risdiplam in 41 infants at the dose selected from Part 1. Enrolment for Part 2 was completed in November 2018[4] and the study is ongoing with a primary efficacy analyses planned for Q1 2020[4].

   SUNFISH is a two-part, double-blind, placebo-controlled (a type of clinical study where neither the participants nor the researchers know who is being treated with the investigational medicine or a placebo), pivotal clinical trial in children and young adults aged 2 to 25 years old with Type 2 or 3 SMA. Part 1, which included 51 patients, determined the dose for the confirmatory Part 2 and evaluated initial efficacy as an exploratory endpoint. The primary objective of Part 2 was to evaluate motor function using total score of Motor Function Measure 32 (MFM-32) at 12 months. MFM-32 is a validated scale used to evaluate fine and gross motor function in people with neurological disorders, including SMA. SUNFISH Part 2 recently met its primary endpoint of change from baseline in the Motor Function Measure 32 (MFM-32) scale after one year of treatment with risdiplam, compared to placebo. No treatment-related safety findings leading to study withdrawal have been seen in any risdiplam trial to date. Safety for risdiplam was consistent with its known safety profile and no new safety signals were identified. Results will be presented at an upcoming medical congress[5].

4. When are you planning to file for regulatory approval in Europe and the rest of the world?

Different health authorities follow different processes and have different filing requirements, which largely reflect differences in procedure and timelines of each application.

Following previous discussions with the European Medicines Agency (EMA), we are targeting a Marketing Authorization Application (MAA) submission for risdiplam by the middle of 2020. The EMA had indicated their support for the MAA including both FIREFISH and SUNFISH Part 1 and 2 in the initial application, to best support their overall review.

At the same time, we will work closely with health authorities across the world with the objective to determine appropriate pathways for filing a new drug application and make risdiplam available as soon as possible to all patients with SMA who would be appropriate for the treatment.

5. When do you anticipate regulatory approval?

If a pharmaceutical company has evidence from its early tests and preclinical and clinical research that a drug is considered safe and effective for its intended use, the company can file an application to market the drug. Once a pharmaceutical company submits its application, health authorities will initially check the submitted application and decide whether the file is complete (a process sometimes referred to as 'validation'). If complete, the evaluation process and ultimately the timing to reach a decision as to whether the investigational medicine may be authorized or not, varies across health authorities, their procedures and timelines. For example, in the U.S. the FDA review team has 6 to 10 months (after validation) to make a decision on whether to approve the drug[6] whereas in Europe it may take up to 210 active days.[7] These timelines do not include the time required to answer potential questions requested by the health authorities. As a result, the total time from submission to approval can be approximately 8-12 months for the U.S. (dependent on whether Priority Review or Standard Review) and approximately 8-15 months in Europe (dependent on whether Accelerated Assessment or Standard Assessment).

6. When will risdiplam be commercially available in my country?

Regulatory approval is only the first step towards commercial availability. National access to investigational medicines is determined by the local authorities who are responsible for granting reimbursements in each country and usually involves many incremental steps. As such, timelines of national reimbursement can vary significantly from country to country and, at the moment, we cannot speculate on reimbursement timings. Roche is actively collaborating with health authorities, government agencies and other key stakeholders around the world with the aim to ensure broad and rapid access to risdiplam to all patients who can benefit from the treatment.

7. Will it be possible to obtain access to risdiplam prior to approval, on compassionate grounds?

We understand the urgency of addressing the needs and daily challenges of people with SMA and their families, and the concerns they have about accessing investigational medicines as soon as possible.

Our primary goal is to conduct the necessary clinical studies to generate the medical data that will support regulatory approval and reimbursement.

At this stage, we are looking to introduce risdiplam via a Pre-Approval Access (PAA) programme or for Compassionate Use (CU) and we are investigating the feasibility of running such as a programme with health authorities. As mechanisms for PAA/CU to new medicines vary across different countries, differences in the programme and timelines may occur. Ultimately, we will continue to work with

health authorities to hopefully bring risdiplam to patients as a licensed product as soon as we can. We are committed to come back to the community and share updates once information is available.

For more information on the criteria for pre-approval access, please refer to 'Roche's Position on Pre-Approval Access to Investigational Medicinal Products' on the official Roche website:

http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/access_to_investigational_medicines.htm

8. Are the risdiplam clinical studies still recruiting? Where can I obtain further information about the risdiplam studies that are recruiting?

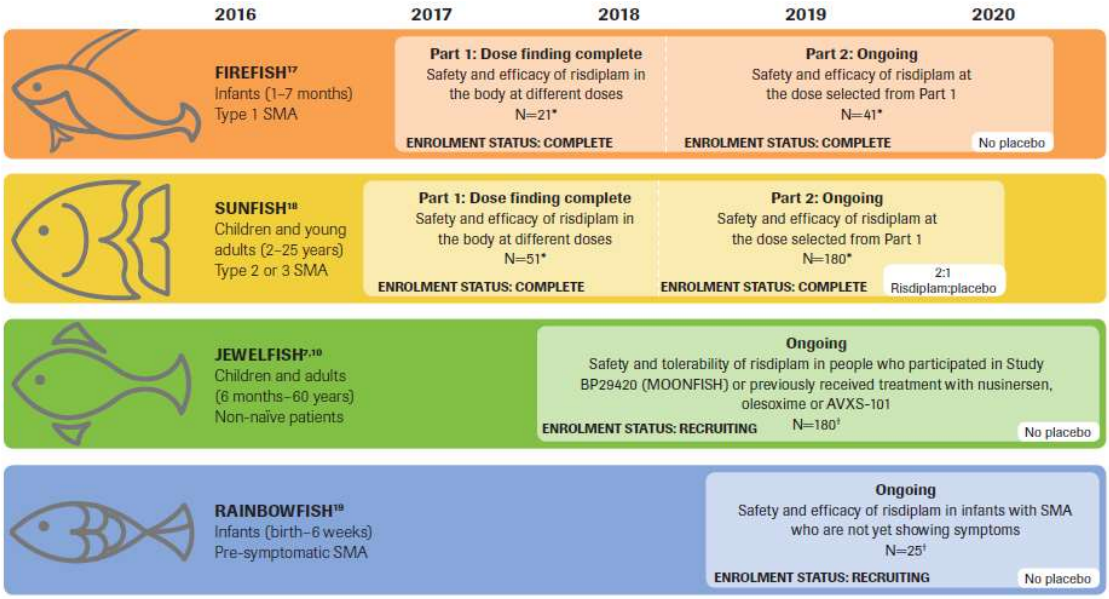
There are two risdiplam trials, JEWELFISH and RAINBOWFISH, where recruitment is currently ongoing. JEWELFISH will be recruiting until the end of 2019 whereas RAINBOWFISH has just started enrollment. The clinicaltrials.gov website lists current and past clinical trials, including the status of the trial and whether it is recruiting patients. If you search for "Spinal Muscular Atrophy", you can find information about all registered SMA clinical trials. Information about the two trials, can be found at:

- JEWELFISH; https://clinicaltrials.gov/ct2/show/NCT03032172?term=Jewelfish&rank=1
- RAINBOWFISH; https://clinicaltrials.gov/ct2/show/NCT03779334?term=Rainbowfish&rank=1

We encourage you to speak to your healthcare provider about what may be the best option for you.

9. About the risdiplam Clinical Development Programme

Roche's clinical development program for risdiplam is centered around four multicentre trials that are designed to provide us with an understanding of how the medicine may impact a broad spectrum of people living with SMA. We are assessing the safety and potential benefit of risdiplam in patients with SMA ranging from pre-symptomatic infants to 60-year old adults, as well as in patients previously treated with other therapies[8-9-10-11]:



*Final participant study numbers; †Number of participants based on planned enrolment.

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