5 July 2018

Dear SMA community members,

As requested, we are very pleased to share with you an update of the RG7916 programme, which has reached a number of milestones.

We would also like to extend special thanks to study participants and their families for their incredible commitment to advancing the progress of research in SMA. We acknowledge the tremendous support and collaboration with Patient Organisations around the world. With your partnership, we are able to continue to progress risdiplam as a potential therapeutic option for people with SMA.

RG7916 is now known as risdiplam and you will see risdiplam in all of our communications, starting with this update. During the recent Annual Cure SMA Researcher meeting in Dallas, Texas, we shared the progress of the risdiplam programme. You can read more about this in the sections below.

We are also very happy to introduce our newest study, RAINBOWFISH. This study will evaluate risdiplam in pre-symptomatic babies. We will provide more details about this study soon.

Risdiplam is an SMN2 splicing modifier which is given daily by mouth or by g-tube as a liquid and distributes widely throughout the body. Risdiplam has been designed to help the SMN2 gene produce more SMN protein, as people with SMA have reduced level of SMN protein. Risdiplam is an investigational molecule being developed in collaboration with PTC Therapeutics and the SMA Foundation.

FIREFISH update

What is FIREFISH?
FIREFISH is a two-part study in babies aged 1 to 7 months with Type 1 SMA. It is an open label study, which means that all babies receive risdiplam and there is no placebo. The objective of Part 1 was to assess the safety and concentration of risdiplam in plasma at several different dose levels.

What did FIREFISH show?
Preliminary Part 1 results from FIREFISH were shared at the Annual CureSMA Researcher conference . Part 1 of FIREFISH included 21 babies. The average age at which babies received their first dose of risdiplam was 6.7 months and some babies have been receiving risdiplam for more than one year. Risdiplam has been well tolerated at all dose levels and no babies dropped out of the study due to side effects caused by risdiplam, although two babies passed away as a result of SMA-related causes. The most common side effects were related to the underlying SMA and were fever, diarrhoea, chest infection and vomiting.

The preliminary results of Part 1 of FIREFISH showed an increase in SMN protein and in motor milestone development compared with the beginning of the study. The amount of SMN protein in blood increased by approximately 3.2 times on average compared with the level at the beginning of the study.

CHOP-INTEND was used to measure motor milestone development of babies with SMA Type 1. An increase in the CHOP-INTEND score represents an improvement in motor function, which depending on the baby can mean improved head control or movement of arms or legs. The findings of Part 1 showed an average increase of 5.5 points (based on 20 babies) at 8 weeks of treatment and 12.5 points (based on 16 babies) at 17 weeks of treatment. An increase in score of 4 or more points compared with the start of the study was seen in 75% of babies at 8 weeks (based on 20 babies) and 94% of babies at 17 weeks (based on 16 babies). No babies have lost the ability to swallow, or have needed a tracheostomy or permanent ventilation.

Next steps for FIREFISH
Part 1 has been completed. Information from Part 1 has allowed us to confirm the dose of risdiplam to be investigated in Part 2, which will assess the safety and effiacy of risdiplam. Participants of Part 1 are receiving risdiplam and are still enrolled in FIREFISH as part of an open-label extension phase.

Part 2 is underway and will assess the safety and efficacy of risdiplam, including an additional 40 babies between the ages of 1 and 7 months. The main analysis of efficacy and safety of risdiplam will occur after all babies have completed one year of treatment, and efficacy will be determined by the number of babies that can sit without assistance after one year of treatment.

SUNFISH update

What is SUNFISH?
SUNFISH is a two-part study evaluating risdiplam in people with Type 2 and 3 SMA between 2 and 25 years of age. The objective of Part 1 was to assess the safety profile and concentration of risdiplam at several different dose levels as well as the level of SMN protein in blood in this population. Participants were randomised so that 2 out of every 3 people receive risdiplam and one receives placebo.

What did SUNFISH show?
Part 1 has been completed and enrolled 51 participants. Participants from Part 1 of SUNFISH are continuing to receive risdiplam and are still enrolled in SUNFISH as part of an open-label extension phase.
Some participants have been receiving risdiplam for over one year and, to date, risdiplam has been well tolerated at all doses. Side effects have been mostly mild, they have resolved despite ongoing treatment and were reflective of the underlying SMA. The most common side effect was fever. No-one has left the study due to side effects caused by risdiplam.

The amount of SMN protein measured in blood doubled on average compared with levels at the beginning of the study.

Next steps for SUNFISH
Information from Part 1 has allowed us to confirm the dose of risdiplam to be investigated in Part 2. Part 2 will assess the efficacy and safety of risdiplam. Enrolment into Part 2 of SUNFISH is almost complete, approximately 168 participants will be included. The main analysis of the efficacy and safety of risdiplam will take place after all participants receive one year of treatment.

JEWELFISH update

What is JEWELFISH?
JEWELFISH is an exploratory study investigating the safety of risdiplam in people who have Type 2 or 3 SMA, are between 12 and 60 years old and who have previously taken part in a clinical study with another SMN2 targeting therapy.

What did JEWELFISH show?
Information from the first 10 patients is available, and shows that risdiplam has been well tolerated. Side effects have been mild, the most common being nasopharyngitis (a cold), fever and headache. No-one has left the study to due side effects caused by risdiplam. SMN protein levels doubled on average after taking

risdiplam, compared to the levels before risdiplam was started. The safety observations and the SMN protein level increase in the JEWELFISH study are so far similar to those in the SUNFISH study.

Next steps for JEWELFISH
The JEWELFISH study is currently ongoing in people aged 12 to 60 years and who have previously received an SMN2 targeting therapy as part of a clinical study. We will broaden the inclusion criteria and increase the number of participants in JEWELFISH to include those who

- received nusinersen as part of their regular medical care for SMA
- have SMA Type 1
- are 6 months of age or older.

Further plans for JEWELFISH include eligibility for people who are still actively taking part in the OLEOS study (Olesoxime long term safety and effiacacy study).

These updates to JEWELFISH will be made subject to approval by Health Authorities and Ethics Committees.

You can read more about all of these studies on www.clinicaltrials.gov, www.clinicaltrials.register.eu, and www.roche-sma-clinicaltrials.com

Our journey to develop safe and effective treatment for people with SMA continues to be inspired by you. We are working with urgency, care and in partnership with the SMA community to advance our clinical studies.

We look forward to providing you with more updates on the risdiplam programme.

Kind regards

Sangeeta Jethwa, MD, on behalf of the Roche SMA team

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