

Roche's risdiplam shows significant improvement in survival and motor milestones in infants with Type 1 spinal muscular atrophy (SMA)

- **FIREFISH Part 2 study met its primary endpoint by demonstrating a significant increase in motor milestones in infants aged 1-7 months after 12 months of treatment**
- **Large, pivotal global study confirms clinically meaningful efficacy seen in the dose-finding Part 1 of the trial**
- **Safety was consistent with the safety profile observed to date and no new safety signals were identified**

Basel, 28 April 2020 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today presented 1-year data from FIREFISH Part 2, a pivotal global study evaluating risdiplam in infants aged 1 – 7 months old with symptomatic Type 1 spinal muscular atrophy (SMA). The study met its primary endpoint with 29% of infants (12/41; $p < 0.0001$) sitting without support for five seconds by month 12, as assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III). No infants achieve this milestone in the natural history of Type 1 SMA. 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). Safety for risdiplam in the FIREFISH study was consistent with its known safety profile.

“These results confirm the clinically meaningful efficacy of risdiplam in infants with an advanced and difficult-to-treat disease,” said Levi Garraway, M.D., Ph. D., Roche’s Chief Medical Officer and Head of Global Product Development. “We thank the SMA community for their partnership and especially the 62 families from around the world who participated in Parts 1 and 2 of the FIREFISH study.”

The data were selected for the 72nd American Academy of Neurology (AAN) Annual Meeting and will be made available online via virtual presentation in the coming weeks (in lieu of an in-person event). Roche leads the clinical development of risdiplam, an investigational, orally administered survival motor neuron-2 (SMN2) splicing modifier for SMA, as part of a collaboration with the SMA Foundation and PTC Therapeutics.

At the time of analysis, the median duration of treatment was 15.2 months and the median age was 20.7 months. 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 these has been attributed by the investigator as related to risdiplam. Ninety per cent (37/41) had a CHOP-INTEND* score increase of at least 4 points, with 56% (23/41) achieving a score above 40; the median increase was 20 points. Without treatment, infants with Type 1 SMA show a decrease in CHOP-INTEND scores over time.

In an exploratory endpoint, 95% of infants who were alive at 12 months (36/38) maintained the ability to swallow and 89% (34/38) were able to feed orally. In contrast, in a natural history cohort, all infants with Type 1 SMA older than 12 months required feeding support.

“These results are particularly encouraging given the median age at enrolment was 5.3 months, so these infants already had progressed disease,” said Professor Laurent Servais, FIREFISH investigator and Professor of Paediatric Neuromuscular Diseases at the MDUK Oxford Neuromuscular Centre. “Maintaining the ability to swallow is particularly important as it helps infants to feed and suggests risdiplam has a major effect on bulbar function.”

Safety for risdiplam in the FIREFISH study was consistent with its previously reported safety profile and no new safety signals were identified. The most common adverse events (AE) 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%).

Risdiplam is being studied in a broad clinical trial programme in SMA, with patients ranging from birth to 60 years old, and includes pre-symptomatic patients and those previously treated with other SMA-targeting therapies. The clinical trial programme was designed to represent the broad, real-world spectrum of people living with this disease with the aim of ensuring access for all appropriate patients.

In November 2019, the U.S Food and Drug Administration granted Priority Review for risdiplam with an expected decision on approval by August 24, 2020.

About SMA

Spinal muscular atrophy (SMA) is a severe, inherited, progressive neuromuscular disease that causes devastating muscle atrophy and disease-related complications. It is the most common genetic cause of infant mortality and one of the most common rare diseases, affecting approximately one in 11,000 babies. SMA leads to the progressive loss of nerve cells in the spinal cord that control muscle movement. Depending on the type of SMA, an individual’s physical strength and their ability to walk, eat or breathe can be significantly diminished or lost.

SMA is caused by a mutation in the survival motor neuron 1 (SMN1) gene that results in a deficiency of SMN protein. SMN protein is found throughout the body and increasing evidence suggests SMA is a multi-system disorder and the loss of SMN protein may affect many tissues and cells, which can stop the body from functioning.

About risdiplam

Risdiplam is an investigational survival motor neuron-2 (SMN2) splicing modifier for SMA and is an orally administered liquid. It is designed to durably increase and sustain SMN protein levels both throughout the central nervous system and in peripheral tissues of the body. It is being evaluated for its potential ability to help the SMN2 gene produce more functional SMN protein throughout the body.

Risdiplam was granted PRIME designation by the European Medicines Agency (EMA) in 2018 and Orphan Drug Designation by the U.S Food and Drug Administration in 2017. At this time, we have filed in Brazil, Chile, China, Indonesia, Russia, South Korea, and Taiwan.

Risdiplam is currently being evaluated in four multicentre trials in people with SMA:

- FIREFISH (NCT02913482) – an open-label, two-part pivotal clinical trial in infants with Type 1 SMA. Part 1 was a dose-escalation study in 21 infants. The primary objective of Part 1 was to assess the safety profile of risdiplam in infants and determine the dose for Part 2. Part 2 is a pivotal, single-arm study of risdiplam in 41 infants with Type 1 SMA treated for 24 months, followed by an open-label extension. Enrolment for Part 2 was completed in November 2018. The primary objective of Part 2 is to assess efficacy as measured by the proportion of infants sitting without support after 12 months of treatment, as assessed in the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) (defined as sitting without support for 5 seconds).
- SUNFISH (NCT02908685) – SUNFISH is a two part, double-blind, placebo controlled pivotal study in people aged 2-25 years with Types 2 or 3 SMA. Part 1 (n=51) determined the dose for the confirmatory Part 2. Part 2 (n=180) evaluated 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. The study met its primary endpoint.
- JEWELFISH (NCT03032172) – an open-label exploratory trial in people with SMA aged 6 months–60 years who have been previously treated with SMA-directed therapies. The study has completed recruitment (n=174).
- RAINBOWFISH (NCT03779334) – an open-label, single-arm, multicentre study, investigating the efficacy, safety, pharmacokinetics and pharmacodynamics of risdiplam in babies (~n=25), from birth to six weeks of age (at first dose) with genetically diagnosed SMA who are not yet presenting with symptoms. The study is currently recruiting.

About Roche in neuroscience

Neuroscience is a major focus of research and development at Roche. The company's goal is to develop treatment options based on the biology of the nervous system to help improve the lives of people with chronic and potentially devastating diseases.

Roche has more than a dozen investigational medicines in clinical development for diseases that include multiple sclerosis, spinal muscular atrophy, neuromyelitis optica spectrum disorder, Alzheimer's disease, Huntington's disease, Parkinson's disease, Duchenne muscular dystrophy and autism.

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management.

Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. More than thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Moreover, for the eleventh consecutive year, Roche has been recognised as one of the most sustainable companies in the Pharmaceuticals Industry by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2019 employed about 98,000 people worldwide. In 2019, Roche invested CHF 11.7 billion in R&D and posted sales of CHF 61.5 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit www.roche.com.

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References

[1] *Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

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