# *Media Release*

## Roche presents data from the risdiplam pivotal FIREFISH and SUNFISH studies in spinal muscular atrophy at the 2019 AAN Annual Meeting

- **In the dose-finding Part 1 of FIREFISH, infants with Type 1 spinal muscular atrophy survive and achieve key milestones beyond those expected in the natural history of the disease**
- **New data from the dose-finding Part 1 of SUNFISH reinforce risdiplam as a promising investigational therapy for people with Type 2 or 3 spinal muscular atrophy**
- **No treatment-related safety findings leading to withdrawal seen to date in risdiplam trials**

Basel, 7 May 2019 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced new data from the dose-finding Part 1 of the pivotal FIREFISH trial showing infants with Type 1 spinal muscular atrophy (SMA) achieved key motor milestones after one year of treatment with investigational risdiplam.[1] Among the infants who received the dose selected for the confirmatory Part 2 of the study (n=17), 7 (41.2%) were able to sit without support for at least 5 seconds, assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III). In addition, 11 (64.7%) infants were able to sit (with or without support) while 9 (52.9%) achieved upright head control after 12 months of treatment as assessed by the Hammersmith Infant Neurological Examination Module 2 (HINE-2).  Finally, 1 infant (5.9%) achieved the milestone of standing (supports weight) by this 12-month time point.

The data were presented at the 71st American Academy of Neurology (AAN) Annual Meeting from 4-10 May in Philadelphia, Pennsylvania. 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.

"The continued improvements in motor milestones and function in the FIREFISH study to date are meaningful for this typical SMA Type 1 population where the majority of babies started treatment at nearly seven months old," said FIREFISH study lead investigator Giovanni Baranello, MD, Carlo Besta Neurological Research Institute Foundation, Developmental Neurology Unit, Milan, Italy.* "These encouraging findings further validate a treatment approach that increases survival motor neuron protein in both the central nervous system and throughout the body."

Part 1 of FIREFISH also assessed motor function with the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), a scale used for infants with Type 1 SMA.[1] Results showed that 10 out of 17 infants (58.8%) in the therapeutically dosed group achieved a CHOP-INTEND total score of 40 points or more.[1] Median change from baseline to month 12 in CHOP-INTEND was 17.5 points.  The maximum CHOP-INTEND score was 57 points after 12 months treatment, increasing from a maximum of 49 points after 8 months.[1]

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Among all 21 infants enrolled in Part 1 of the FIREFISH study, the median duration of treatment is 14.8 months, with 19 infants treated for more than 12 months.[2] Three infants experienced fatal complications of their disease after approximately 1, 8, and 13 months of treatment. None of these has been attributed by the investigator as related to risdiplam. No infant has lost the ability to swallow during the study, and no infant has required tracheostomy or permanent ventilation. [2] The event-free survival was 18 out of 21 (85.7%) overall and 15 out of 17 (88.2%) in the therapeutically dosed group. The most common adverse events included fever (pyrexia; 52.4%), upper respiratory tract infections (42.9%), diarrhea (28.6%), vomiting (23.8%), cough (23.8%) pneumonia (19.0%) and constipation (19.0%).[2]

"We are highly encouraged by our latest findings for risdiplam, which take us one step closer to potentially bringing the first oral treatment option to the SMA community," said Sandra Horning, MD, Roche's Chief Medical Officer and head of Global Product Development. "While SMA has seen important advances over the past few years, significant medical need remains for people living with all types of SMA across multiple age groups. We look forward to sharing additional data from our broad development programme for risdiplam as it emerges."

Roche also presented new data from Part 1 of its pivotal SUNFISH trial in people aged 2 -25 years with Type 2 or 3 SMA. The dose-finding SUNFISH Part 1 includes a particularly broad patient population. Baseline functional status ranged from individuals unable to sit to those capable of walking. Scoliosis ranged from none to severe. As previously reported, a sustained median increase from baseline in SMN protein of greater than two-fold, as measured in blood, was seen after 12 months of treatment with risdiplam.

The most common adverse events in Part 1 of the SUNFISH study were fever (pyrexia; 41%), cough (33%), vomiting (29%), upper respiratory tract infections (26%), persistent sore throat (oropharyngeal pain; 22%) and cold (nasopharyngitis; 20%).[3] The most common serious adverse event that occurred in two of the 51 patients exposed to risdiplam was pneumonia.[3] To date there have been no treatment-related safety findings leading to withdrawal from any study.[2],[3]

An exploratory efficacy analysis of Part 1 (n=51) of the SUNFISH study assessed motor function, using the Motor Function Measure-32 (MFM32) scale. This scale is designed to detect motor function changes in a broad range of patients, from weak Type 2 to strong Type 3 SMA, and is therefore more appropriate for the SUNFISH population. One patient withdrew from the trial during the open-label extension.[3] Among the patients for which the MFM32 scale has been completed at all visits up to month 12 (n=43), 58% saw an improvement of at least 3 points on the scale from baseline, including 71% among patients 2-11 years old and 42% aged 12-25 years.[3] While Part 1 of the SUNFISH study was not designed or powered to detect efficacy, the change from baseline in total MFM32 score is the primary efficacy endpoint in the ongoing Part 2 (n=180) of the trial.

The confirmatory Part 2 portions of the SUNFISH and FIREFISH studies have completed enrollment and will conduct their primary efficacy analyses in Q4 2019 and Q1 2020, respectively.

Roche is planning to include the new data presented at the AAN Annual Meeting in regulatory filings with

the U.S. Food and Drug Administration and European Medicines Agency during the second half of 2019.

**About SMA**

Spinal muscular atrophy (SMA) is a severe, inherited, progressive neuromuscular disease that causes devastating muscle atrophy and disease-related complications.[4] 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.[5] SMA leads to the progressive loss of nerve cells in the spinal cord that control muscle movement.[6] 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.[7]

SMA is caused by a mutation in the survival motor neuron 1 (SMN1) gene that results in a deficiency of SMN protein.[6] 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.[8]

**About risdiplam**

Risdiplam is an investigational orally-administered medicine 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 SMN protein 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.[9]

Roche leads the clinical development of risdiplam as part of a collaboration with the SMA Foundation and PTC Therapeutics. Risdiplam is currently being evaluated in four multicentre trials in people with SMA:

- FIREFISH (NCT02913482) – an open-label, two-part seamless 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.  Per protocol, four infants enrolled ("Cohort A") were required to remain at their low dose for over 12 months in order to evaluate longer term safety at multiple doses. The remaining patients ("Cohort B"; n=17) were allowed by the protocol to more quickly escalate to the expected therapeutic dose selected in Part 2. Part 2 is a pivotal, single-arm study of risdiplam in 41 infants with Type 1 SMA 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). Part 2 is ongoing.
- SUNFISH (NCT02908685) – a two-part, double-blind, placebo-controlled pivotal clinical trial in children and young adults (2–25 years old) with Type 2 and 3 SMA. Part 1 determined the dose for the confirmatory Part 2. The primary objective of Part 2 is to evaluate motor function using total score of Motor Function Measure 32 (MFM-32) at 12 months. Enrolment for Part 2 was completed in September 2018 with 180 patients randomised and the study is ongoing.

- JEWELFISH (NCT03032172) – an open-label exploratory trial in people with all types of SMA aged 6 months–60 years who have been previously treated with SMN-targeting therapy or olesoxime. The study is currently recruiting.
- RAINBOWFISH (NCT03779334) – a new trial in pre-symptomatic SMA initiated earlier this year.

**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. 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 tenth consecutive year, Roche has been recognised as the most sustainable company 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 2018 employed about 94,000 people worldwide. In 2018, Roche invested CHF 11 billion in R&D and posted sales of CHF 56.8 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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