

Roche's risdiplam showed significant improvement in motor function in people aged 2-25 with type 2 or 3 spinal muscular atrophy

- **First placebo-controlled trial to include adults with SMA demonstrates risdiplam improved or stabilised motor function**
- **Medically meaningful and statistically significant results in primary and key secondary endpoints**
- **Pivotal SUNFISH Part 2 study population represents broad, real-world spectrum of people living with SMA**

Basel, 06 February 2020 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today presented 1-year data from the pivotal Part 2 of SUNFISH, a global placebo-controlled study evaluating risdiplam in people aged 2-25 years with Type 2 or 3 spinal muscular atrophy (SMA). The study showed that change from baseline in the primary endpoint of the Motor Function Measure scale (MFM-32)* was significantly greater in people treated with risdiplam, compared to placebo (1.55 point mean difference; $p=0.0156$). The Revised Upper Limb Module (RULM),** a key secondary endpoint, also showed an improvement (1.59 point difference; $p=0.0028$). Safety for risdiplam in the SUNFISH study was consistent with its known safety profile. Data were presented at the 2nd International Scientific and Clinical Congress on Spinal Muscular Atrophy from 5-7 February in Evry, France.

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.

“Risdiplam is the first potential treatment to have pivotal placebo-controlled data in a broad population of patients, including children, teenagers and adults,” said SUNFISH principal investigator Eugenio Mercuri, M.D., Ph.D., Department of Paediatric Neurology, Catholic University, Rome, Italy. “The data suggest that risdiplam can preserve and potentially enable greater independence through improved motor function in people with Type 2 or non-ambulant Type 3 SMA.”

Safety for risdiplam in the SUNFISH study was consistent with its known safety profile and no new safety signals were identified. The adverse event profile was similar to placebo. 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 (RIS 19%, PLB 20%), serious lower respiratory tract infections occurred in more patients in the risdiplam group (RIS 10% PLB 2%) but were reported as unrelated and resolved without change to study treatment. To date, more than 400 patients have been treated with risdiplam across all studies, with no treatment related safety findings leading to study withdrawal in any risdiplam trial.

“We are very encouraged by the positive results in this broad group of SMA patients, many of whom are under-served and under-represented in clinical trials,” said Levi Garraway, M.D., Ph.

D., Roche's Chief Medical Officer and Head of Global Product Development. "This study has helped us understand which measurement scales are the most relevant for patients, as well as the importance of stabilisation in people with more established disease."

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. Risdiplam is being studied in a broad clinical trial programme in SMA, with patients ranging from birth to 60 years old, and includes patients previously treated with SMA-targeting therapies. The clinical trial population represents 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 a decision for approval by May 24, 2020.

**MFM-32 is a validated scale used to evaluate fine and gross motor function in people with neurological disorders, including SMA. It assesses 32 different motor functions from standing and walking through to use of hands and fingers.*

***RULM is a scale designed to assess upper limb movement in people with SMA. It can capture progressive muscle weakness across the spectrum of the disease, reflective of the SUNFISH Part 2 study population.*

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

- 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 and the first two secondary endpoints. The total change from baseline in Hammersmith Functional Motor Scale Expanded (HF MSE) was numerically greater for risdiplam but did not reach significance relative to placebo.
- 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).
- 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.
- 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.

Media Release



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 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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