Media Release

Roche announces 2-year risdiplam data from SUNFISH and new data from JEWELFISH in infants, children and adults with spinal muscular atrophy (SMA)

- **SUNFISH Part 1 showed risdiplam significantly improved motor function after 24 months of treatment in people aged 2-25 years with Types 2 or 3 SMA**
- **JEWELFISH study preliminary 12 month data in previously treated patients showed rapid and sustained increases in SMN protein levels**
- **Safety in SUNFISH and JEWELFISH was consistent with the safety profile observed to date and no new safety signals were identified**

Basel, 12 June 2020 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today presented two-year data from Part 1 of its pivotal SUNFISH trial in people aged 2-25 years with Type 2 or 3 spinal muscular atrophy (SMA) at the virtual Cure SMA Annual Conference, 8-12 June, 2020. The results of an exploratory efficacy analysis show risdiplam significantly improved motor function after 24 months of treatment compared to natural history data. In addition, preliminary 12 month data from JEWELFISH, a trial in people with all types of SMA aged 6 months to 60 years previously treated with other SMA therapies, showed that treatment with risdiplam led to rapid and sustained increases in SMN protein levels. No new safety signals were observed and the overall adverse event profile was consistent with that of treatment-naive patients.

"These 24 month exploratory data are important as they are consistent with the medically meaningful results we saw after one year in Part 2 of the SUNFISH study, designed to represent a broad, real-world SMA population," said Levi Garraway, M.D., Ph. D., Roche's Chief Medical Officer and Head of Global Product Development. "We are also encouraged to see an increase in SMN protein levels across both the Sunfish Part 1 and Jewelfish studies. These data reinforce the potential of risdiplam to make a real difference in the lives of the many people living with SMA."

SUNFISH is a large (n=231) global two-part study in children and adults. The dose-finding SUNFISH Part 1 (n=51) includes a broad patient population ranging from individuals unable to sit to those capable of walking, as well as people with scoliosis or joint contractures.

The exploratory efficacy analysis of Part 1 of the SUNFISH study assessed motor function, using the Motor Function Measure (MFM) scale. MFM is a validated scale used to evaluate fine and gross motor function in people with neurological disorders, including SMA. It assesses different motor functions from standing and walking through to use of hands and fingers. In a weighted analysis comparing the data with a robust natural history comparator cohort, MFM total change from baseline at Month 24 was greater in patients receiving risdiplam (3.99 point difference (95% CI: 2.34, 5.65) $p< 0.0001$). Even small changes in motor function can result in meaningful differences to daily living.

Results also showed that treatment with risdiplam led to a median two-fold increase in blood SMN protein levels after four weeks, which was sustained for at least 24 months. This is consistent with previously reported

results through 12 months of treatment. SMN protein is found throughout the body and is critical for maintaining healthy motor neurons, which transmit movement signals from the central nervous system to the muscles.

These results are consistent with the results of the pivotal Part 2 of the trial at 12 months in non-ambulatory patients which demonstrated that change from baseline in total MFM32 score was significantly greater in people treated with risdiplam, compared to placebo (1.55 point mean difference; p=0.0156).

The most common adverse events in Part 1 of the SUNFISH study were fever (pyrexia; 55%), cough (35%), vomiting (33%), upper respiratory tract infections (31%), cold (nasopharyngitis; 24%) and sore throat (oropharyngeal pain; 22%). The most common serious adverse event that occurred in three of the 51 patients exposed to risdiplam was pneumonia. To date there have been no treatment-related safety findings leading to withdrawal.

Enrolment for the JEWELFISH study, assessing safety and pharmacodynamic data in previously treated patients with SMA, who are now receiving risdiplam, is complete (n=174). Among the patients who completed 12 months of treatment with risdiplam, a median two-fold increase in SMN protein versus baseline was observed (n=18). An early assessment of safety showed a consistent safety profile compared to treatment-naive patients.

Of the 174 patients enrolled, 76 were previously treated with nusinersen and 14 with onasemnogene abeparvovec. The remaining 83 patients had been treated with compounds then being developed by Roche.

The most common adverse events were upper respiratory tract infections (13%), headache (12%), fever (8%), diarrhea (8%), nasopharyngitis (7%) and nausea (7%). To date there have been no drug-related safety findings leading to withdrawal from the JEWELFISH trial and the overall adverse event profile is similar to that observed in risdiplam trials of patients not previously treated with a SMA-targeting therapy.

Risdiplam's comprehensive clinical trial programme (birth to 60 years old) 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. 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.

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 orally administered daily in liquid form by mouth or via feeding tube. 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, Roche has 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 with the primary objective of assessing the safety profile of risdiplam in infants and determining 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 was 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). The study met its primary endpoint.
- 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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