FDA approves Roche's Evrysdi (risdiplam) for treatment of spinal muscular atrophy (SMA) in adults and children 2 months and older

- **In two clinical trials, Evrysdi improved motor function in people living with SMA over a broad spectrum of ages and levels of disease severity, including Types 1, 2, and 3 SMA**
- **Evrysdi helped infants survive without permanent ventilation and achieve the ability to sit without support, a key motor milestone not normally seen in the natural course of the disease**
- **Evrysdi is the first and only medicine for SMA that can be taken at home**

Basel, 10 August 2020 - Roche (SIX: RO, ROG; OTCQX: RHHBY) Roche announced today that the U.S. Food and Drug Administration (FDA) has approved Evrysdi™ (risdiplam) for the treatment of spinal muscular atrophy (SMA) in adults and children 2 months of age and older. Evrysdi showed clinically-meaningful improvements in motor function across two clinical trials in people with varying ages and levels of disease severity, including Types 1, 2, and 3 SMA. Infants achieved the ability to sit without support for at least 5 seconds, a key motor milestone not normally seen in the natural course of the disease. Evrysdi also improved survival without permanent ventilation at 12 and 23 months, compared to natural history. A liquid medicine, Evrysdi is administered daily at home by mouth or feeding tube.

"Given the majority of people with SMA in the U.S. remain untreated, we believe Evrysdi, with its favorable clinical profile and oral administration, may offer meaningful benefits for many living with this rare neurological disease," said Levi Garraway, M.D., Ph. D., Roche's Chief Medical Officer and Head of Global Product Development. "The strength and resolve of the SMA community has continually inspired us as we developed this first-of-its-kind medicine for SMA, so today we celebrate our collective accomplishment together with them."

Evrysdi is being studied in more than 450 people as part of a large and robust clinical trial program in SMA. The program includes infants aged 2 months to adults aged 60 with varying symptoms and motor function, such as people with scoliosis or joint contractures, and those previously treated for SMA with another medication. The approval is based on data from two clinical studies designed to represent a broad spectrum of people living with SMA: FIREFISH in symptomatic infants aged 2 to 7 months; and SUNFISH in children and adults aged 2 to 25 years. SUNFISH is the first and only placebo-controlled trial to include adults with Types 2 and 3 SMA.

In FIREFISH, 41% (7/17) of infants treated with the therapeutic dose achieved the ability to sit without support for at least 5 seconds as measured by the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III). Additionally, 90% (19/21) of infants were alive without permanent ventilation at 12 months of treatment and reached 15 months of age or older. As described in the natural history of untreated infantile-onset SMA, infants would not be expected to be able to sit independently, and only 25 percent would be expected to survive without permanent ventilation beyond 14 months of age. In SUNFISH, children and adults treated with Evrysdi experienced a clinically-meaningful and statistically significant improvement in motor function at 12 months (1.55 point mean difference; p=0.0156) compared to placebo

(1.36 points [95% CI: 0.61, 2.11]; -0.19 points [95% CI: -1.22, 0.84], respectively), as measured by a change from baseline in the Motor Function Measure-32 (MFM-32) total score.

Evrysdi demonstrated a favorable efficacy and safety profile, with the safety profile established across the FIREFISH and SUNFISH trials. The most common adverse reactions were fever, diarrhea, and rash in later-onset SMA. In infantile-onset SMA, the most common adverse events were similar and also included upper respiratory tract infection, pneumonia, constipation, and vomiting. There were no treatment-related safety findings leading to withdrawal from either study.

"Throughout their lives, many people with SMA may lose their ability to perform critical movements, which can impact the ability to independently participate in aspects of daily life and even be life altering," said Kenneth Hobby, president of Cure SMA. "The approval of Evrysdi is an eagerly awaited milestone for our community. We appreciate Genentech/Roche's commitment to reflecting the full scope of the real-world SMA population in their clinical trial program and developing a treatment that can be administered at home."

Evrysdi is designed to treat SMA by increasing production of the survival of motor neuron (SMN) protein. SMN protein is found throughout the body and is critical for maintaining healthy motor neurons and movement. Roche leads the clinical development of Evrysdi as part of a collaboration with the SMA Foundation and PTC Therapeutics.

Evrysdi will be available in the United States within two weeks for direct delivery to patients' homes through Accredo Health Group Inc., an Express Scripts specialty pharmacy.

About Evrysdi™ (risdiplam)
Evrysdi is a survival of motor neuron 2 (SMN2) splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Evrysdi is administered daily at home in liquid form by mouth or by feeding tube.

Risdiplam was granted PRIME designation by the European Medicines Agency (EMA) in 2018 and Orphan Drug Designation by FDA and EMA in 2017 and 2019, respectively. At this time, risdiplam has been filed in Brazil, Chile, China, Indonesia, Russia, South Korea, and Taiwan. A Marketing Authorization Application (MAA) submission to the EMA for Evrysdi is imminent.

About the Pivotal Studies
FIREFISH (NCT02913482)
FIREFISH, an open-label, two-part pivotal study, was designed to assess Evrysdi safety, tolerability, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) in patients aged 1 to 7 months with Type 1 SMA. Part 1 evaluated several doses of Evrysdi and determined the therapeutic dose of 0.2 mg/kg for Part 2. In Part 1, after 12 months of Evrysdi treatment:

- 41% (7/17) of infants treated with the therapeutic dose achieved the ability to sit without support for at least 5 seconds as measured by the BSID-III gross motor scale.

- 90% (19/21) of all infants were alive without permanent ventilation* and reached 15 months of age or older
- 81% (17/21) of all patients were alive without permanent ventilation* after a minimum of 23 months of treatment and reached an age of 28 months or older (median 32 months; range 28 to 45 months)

*Permanent ventilation defined as tracheostomy or ≥16 hours of noninvasive ventilation per day or intubation for ≥21 consecutive days in the absence of, or following the resolution of, an acute reversible event.

SUNFISH (NCT02908685)

SUNFISH, a two-part placebo-controlled multicenter pivotal trial, was designed to assess Evrysdi safety, tolerability, efficacy, PK and PD in people with Type 2 or 3 SMA aged 2 to 25, including those with scoliosis (67% in Part 2) and joint contractures at baseline. In Part 2, after 12 months, Evrysdi treatment led to:

- A clinically-meaningful and statistically significant improvement in motor function among children and adults, as measured by a change from baseline in the MFM-32 total score (1.55 point mean difference; p=0.0156), at 12 months as compared to placebo (1.36 points [95% CI: 0.61, 2.11]; -0.19 points [95% CI: 1.22, 0.84], respectively). MFM-32 assesses 32 different motor functions across a wide range of people with SMA.
- Improved upper limb motor function compared to baseline, as measured by the Revised Upper Limb Module (RULM), a secondary independent motor function endpoint of the study (1.59 point difference; p=0.0028).

Pivotal Trial Safety Data

The safety profile of Evrysdi was established across the FIREFISH and SUNFISH pivotal trials. The most common adverse reactions in later-onset SMA (incidence of at least 10% of patients treated with Evrysdi and more frequently than control) were fever, diarrhea, and rash. The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, the most common adverse reactions (incidence of at least 10%) were upper respiratory tract infection, pneumonia, constipation, and vomiting.

About the Evrysdi Clinical Trial Program

In addition to FIREFISH and SUNFISH, Evrysdi is being evaluated in a broad range of people with SMA, including in:

- JEWELFISH (NCT03032172): an open-label exploratory trial designed to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in people with SMA aged 6 months to 60 years who received other investigational or approved SMA therapies for at least 90 days prior to receiving Evrysdi. Recruitment for this study is complete with 174 people enrolled.
- RAINBOWFISH (NCT03779334): an open-label, single-arm, multicenter study investigating the efficacy, safety, pharmacokinetics and pharmacodynamics of Evrysdi in infants (~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 SMA
SMA is a severe, progressive neuromuscular disease that can be fatal. It affects approximately one in 10,000 babies and is the leading genetic cause of infant mortality. SMA is caused by a mutation of the survival motor neuron 1 (SMN1) gene, which leads to a deficiency of SMN protein. This protein is found throughout the body and is essential to the function of nerves that control muscles and movement. Without it, nerve cells cannot function correctly, leading to muscle weakness over time. 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.

About Roche in Neuroscience
Neuroscience is a major focus of research and development at Roche. Our goal is to pursue groundbreaking science to develop new treatments that help improve the lives of people with chronic and potentially devastating diseases.

Roche is investigating more than a dozen medicines for neurological disorders, including multiple sclerosis, neuromyelitis optica spectrum disorder, Alzheimer's disease, Huntington's disease, Parkinson's disease, Duchenne muscular dystrophy and autism spectrum disorder. Together with our partners, we are committed to pushing the boundaries of scientific understanding to solve some of the most difficult challenges in neuroscience today.

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.

Roche Group Media Relations
Phone: +41 61 688 8888 / e-mail: media.relations@roche.com

Dr. Nicolas Dunant
Phone: +41 61 687 05 17

Patrick Barth
Phone: +41 61 688 44 86

Daniel Grotzky
Phone: +41 61 688 31 10

Karsten Kleine
Phone: +41 61 682 28 31

Nina Mählitz
Phone: +41 79 327 54 74

Nathalie Meetz
Phone: +41 61 687 43 05

Barbara von Schnurbein
Phone: +41 61 687 89 67

Roche Investor Relations

Dr. Karl Mahler
Phone: +41 61 68-78503
e-mail: karl.mahler@roche.com

Jon Kaspar Bayard
Phone: +41 61 68-83894
e-mail: jon_kaspar.bayard@roche.com

Dr. Sabine Borngräber
Phone: +41 61 68-88027
e-mail: sabine.borngraeber@roche.com

Dr. Bruno Eschli
Phone: +41 61 68-75284
e-mail: bruno.eschli@roche.com

Dr. Birgit Masjost
Phone: +41 61 68-84814
e-mail: birgit.masjost@roche.com

Dr. Gerard Tobin
Phone: +41 61 68-72942
e-mail: gerard.tobin@roche.com

Investor Relations North America

Loren Kalm
Phone: +1 650 225 3217
e-mail: kalm.loren@gene.com

Dr. Lisa Tuomi
Phone: +1 650 467 8737
e-mail: tuomi.lisa@gene.com