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Positive Phase III results for Roche's investigational medicine OCREVUS® (ocrelizumab) published in New England Journal of Medicine

- **OCREVUS is the first and only investigational medicine to show superior efficacy versus comparators in both relapsing and primary progressive multiple sclerosis in clinical studies**
- **OCREVUS demonstrated a favourable safety profile in three large Phase III studies**

Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that data from three Phase III studies of its investigational medicine OCREVUS® (ocrelizumab)– the OPERA I and OPERA II studies in relapsing multiple sclerosis (RMS) and the ORATORIO study in primary progressive multiple sclerosis (PPMS) – were published in the 21 December 2016 online issue of the *New England Journal of Medicine* (NEJM).

Data from the OCREVUS Phase III studies showed consistent and clinically meaningful reductions in major markers of disease activity and progression compared with Rebif® (interferon beta-1a) in RMS and with placebo in PPMS. The primary endpoint was met in all three studies, which includes relative reduction of annualised relapse rate in the RMS studies and relative reduction in the progression of clinical disability sustained for at least 12 weeks in the PPMS study. Key secondary endpoints in all three studies were also met, including multiple measures of disability progression and brain lesion activity.

“These publications that indicate that B cells play a central role in MS are the result of a longstanding collaboration between the scientific community and industry for the benefit of people with MS,” said Stephen Hauser, MD, Chair of the Scientific Steering Committee of the OPERA studies, Director of the Weill Institute for Neurosciences and Chair of the Department of Neurology at the University of California, San Francisco.

“In the OPERA I and OPERA II RMS studies, OCREVUS consistently and significantly reduced disease activity and disability progression compared with a standard-of-care high-dose interferon while demonstrating a favourable safety profile. The consistency of these pioneering data, the effect seen in these

clinical studies, and the favourable safety profile may support treating MS earlier with a high-efficacy disease-modifying medicine.”

Data from two identical studies (OPERA I and OPERA II) in RMS showed OCREVUS was superior to high-dose Rebif (interferon beta-1a), a well-established MS therapy, in reducing three major markers of disease activity: relapses (primary endpoint), disability progression, brain lesion activity over the two-year controlled treatment period.

In a separate PPMS study (ORATORIO), OCREVUS significantly reduced the risk of confirmed disability progression sustained for at least 12 weeks (primary endpoint) and 24 weeks (a key secondary endpoint) compared with placebo. OCREVUS treatment was also superior to placebo on other key measures of disease progression in PPMS patients including the time required to walk 25 feet, the volume of chronic brain lesions, and brain volume loss.

“OCREVUS is the first and only investigational medicine to significantly reduce the progression of physical disability in primary progressive MS in a large Phase III study,” said Xavier Montalban, MD, PhD, Chair of the Scientific Steering Committee of the ORATORIO study and Professor of Neurology and Neuroimmunology at Vall d’Hebron University Hospital, Research Institute and Cemcat, Barcelona, Spain. Over the last decade, other molecules have tried and failed to demonstrate efficacy for PPMS, so the positive results for OCREVUS mark an important step in our understanding of this highly disabling form of the disease.”

The OCREVUS safety profile was evaluated in the three Phase III studies. In the RMS studies, the proportion of patients with serious adverse events and serious infections was similar between the OCREVUS and interferon beta-1a treatment groups. In the PPMS study, the proportion of patients with adverse events and serious adverse events was similar between the OCREVUS and placebo treatment groups. Safety analyses continue in the open-label extension studies in both RMS and PPMS.

Marketing applications for OCREVUS, submitted for RMS and PPMS, have been validated and are currently under review by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). As previously announced, OCREVUS was granted Priority Review Designation by the FDA with a targeted

action date of 28 March 2017.

OCREVUS® is the proprietary name submitted to global regulatory authorities for the investigational medicine ocrelizumab.

About the OPERA I and OPERA II studies in relapsing MS

OPERA I and OPERA II are Phase III, randomised, double-blind, double-dummy, global multi-centre studies evaluating the efficacy and safety of OCREVUS (600 mg administered by intravenous infusion every six months) compared with interferon beta-1a (44 mcg administered by subcutaneous injection three times per week) in 1,656 people with relapsing forms of MS. In these studies, relapsing MS (RMS) was defined as relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) with relapses.¹ The primary and key secondary endpoints were previously presented at the 2015 congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

Data from the Phase III OPERA studies in patients with relapsing MS showed:

- A 46-percent and 47-percent relative reduction in the annualised relapse rate (ARR) compared with interferon beta-1a over the two-year period in OPERA I and OPERA II, respectively ($p < 0.001$ and $p < 0.001$).
- A 43-percent and 37-percent relative risk reduction in confirmed disability progress (CDP) sustained for 12 weeks compared with interferon beta-1a in OPERA I and OPERA II, respectively, as measured by the Expanded Disability Status Scale (EDSS) ($p = 0.01$ and $p = 0.02$).
- A 43-percent and 37-percent relative risk reduction in CDP sustained for 24 weeks compared with interferon beta-1a in OPERA I and OPERA II, respectively ($p = 0.03$ and $p = 0.04$).
- A 94-percent and 95-percent relative reduction in the total number of T1 gadolinium-enhancing lesions compared with interferon beta-1a in OPERA I and OPERA II, respectively ($p < 0.001$ and $p < 0.001$).
- A 77-percent and 83-percent relative reduction in the total number of new and/or enlarging hyperintense T2 lesions compared with interferon beta-1a in OPERA I and OPERA II, respectively ($p < 0.001$ and $p < 0.001$).

As previously reported at the 2016 American Academy of Neurology Annual Meeting (AAN), OCREVUS increased the proportion of patients who achieved no evidence of disease activity (NEDA) by 64 percent and 89 percent compared with interferon beta-1a at 96 weeks in OPERA I and OPERA II, respectively ($p < 0.001$ and $p < 0.001$). The exploratory endpoint is based on a combination of three major markers of disease activity (relapses, disability progression and inflammatory and chronic MRI activity) and provides a more comprehensive measurement of disease activity and the effect of treatment than any single endpoint. Overall, the proportion of patients in the OCREVUS group with adverse events was similar to interferon beta-1a in both studies (80.1 percent in the OCREVUS group vs. 80.9 percent in the interferon beta-1a group in OPERA I and 86.3 percent in the OCREVUS group vs. 85.6 percent in the interferon beta-1a group in OPERA II); the most common adverse event associated with OCREVUS was infusion-related reactions (34.3 percent of patients who received OCREVUS experienced at least one infusion-related reaction vs. 9.9 percent for interferon beta-1a). The proportion of patients in the OCREVUS group with serious adverse events, including serious infections, was also similar to interferon beta-1a (6.9 percent in the OCREVUS group vs. 7.8 percent in the interferon beta-1a group in OPERA I and 7.0 percent in the OCREVUS group vs. 9.6 percent in the interferon beta-1a group in OPERA II).

About the ORATORIO study in PPMS

ORATORIO is a Phase III, randomised, double-blind, global multi-centre study evaluating the efficacy and safety of OCREVUS (600 mg administered by intravenous infusion every six months; given as two 300 mg infusions two weeks apart) compared with placebo in 732 people with PPMS.² In contrast to the OPERA I and OPERA II studies, where the blinded treatment period was two years, the blinded treatment period of the ORATORIO study continued beyond that until all patients had received at least 120 weeks of either OCREVUS or placebo and a predefined number of confirmed disability progression (CDP) events was reached overall in the study. The primary and key secondary endpoints were previously presented at the 2015 congress of ECTRIMS.

Data from the Phase III ORATORIO study in patients with primary progressive MS showed:

- A 24-percent relative risk reduction in CDP sustained for at least 12 weeks compared with placebo, as measured by the EDSS ($p = 0.03$).
- A 25-percent relative risk reduction in CDP sustained for at least 24 weeks compared with placebo ($p = 0.04$).

- A 29-percent relative reduction in the time required to walk 25 feet (Timed 25-Foot Walk, or T25-FW) compared with placebo over 120 weeks (p=0.04).
- A 3.4-percent reduction in the total volume of brain hyperintense T2 lesions compared with a 7.4-percent increase in placebo-treated patients over 120 weeks (p<0.001).
- A 17.5 percent relative reduction in the rate of whole brain volume loss compared with placebo from week 24 to week 120 (p=0.02).

Overall, the proportion of patients in the OCREVUS group with adverse events was similar to placebo (95.1 percent vs. 90.0 percent, respectively); the most common adverse event associated with OCREVUS was infusion-related reactions (39.9 percent vs. 25.5 percent for placebo). The proportion of patients in the OCREVUS group with serious adverse events, including serious infections, was also similar to placebo (20.4 percent vs. 22.2 percent, respectively).

About OCREVUS® (ocrelizumab)

OCREVUS is an investigational, humanised monoclonal antibody designed to selectively target CD20-positive B cells, a specific type of immune cell thought to be a key contributor to myelin (nerve cell insulation and support) and axonal (nerve cell) damage. This nerve cell damage can lead to disability in people with MS. Based on preclinical studies, OCREVUS binds to CD20 cell surface proteins expressed on certain B cells, but not on stem cells or plasma cells, and therefore important functions of the immune system may be preserved.

About multiple sclerosis

Multiple sclerosis (MS) is a chronic disease that affects an estimated 2.3 million people around the world, for which there is currently no cure.^{3,4} MS occurs when the immune system abnormally attacks the insulation and support around nerve cells (myelin sheath) in the brain, spinal cord and optic nerves, causing inflammation and consequent damage. This damage can cause a wide range of symptoms, including muscle weakness, fatigue and difficulty seeing, and may eventually lead to disability.^{5,6,7} Most people with MS experience their first symptom between 20 and 40 years of age, making the disease the leading cause of non-traumatic disability in younger adults.⁸

Approximately 95 percent of people with MS have a relapsing form or primary progressive MS at diagnosis.⁹ Relapsing-remitting MS (RRMS) is the most common form of the disease and is characterised by episodes of

new or worsening signs or symptoms (relapses) followed by periods of recovery.^{10,11} Over time, some people with RRMS experience steadily worsening symptoms and transition to secondary progressive MS (SPMS), with or without relapses.¹² Disease activity and progression can occur even when people do not show signs or symptoms of MS, despite available relapsing MS treatments. Primary progressive MS (PPMS) is a debilitating form of the disease marked by steadily worsening symptoms but typically without distinct relapses or periods of remission.¹³ Approximately 10-15 percent of people with MS are diagnosed with the primary progressive form of the disease. There are no approved treatments for PPMS.

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, Alzheimer's disease, spinal muscular atrophy, Parkinson's disease and autism.

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives.

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. 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.

Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. Twenty-nine 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. Roche has been recognised as the Group Leader in sustainability within the Pharmaceuticals, Biotechnology & Life Sciences Industry eight years in a row by the Dow Jones Sustainability Indices.

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2015 employed more than 91,700 people worldwide. In 2015, Roche invested CHF 9.3 billion in R&D and posted sales of CHF 48.1 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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