FDA approves Roche’s OCREVUS™ (ocrelizumab) for relapsing and primary progressive forms of multiple sclerosis

- First and only approved disease-modifying therapy for primary progressive form of multiple sclerosis (PPMS) – one of the most disabling forms of multiple sclerosis (MS)
- An important new treatment option for people with relapsing forms of MS (RMS) demonstrating superior efficacy on the three major markers of disease activity compared with Rebif®
- A favourable benefit-risk profile demonstrated in three large Phase III studies with a diverse patient population, including those early in the disease

Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that the US Food and Drug Administration (FDA) approved OCREVUS™ (ocrelizumab) as the first and only medicine for both relapsing and primary progressive forms of multiple sclerosis. The majority of people with MS have a relapsing form or primary progressive MS at diagnosis.¹

“The FDA’s approval of OCREVUS is the beginning of a new era for the MS community and represents a significant scientific advance with this first-in-class B-cell targeted therapy”, said Sandra Horning, MD, Roche’s Chief Medical Officer and Head of Global Product Development. “Until now, no FDA-approved treatment has been available to the primary progressive MS community, and some people with relapsing forms of MS continue to experience disease activity and disability progression despite available therapies. We believe OCREVUS, given every six months, has the potential to change the disease course for people with MS, and we are committed to helping those who can benefit gain access to our medicine.”

In two identical RMS Phase III studies (OPERA I & OPERA II), OCREVUS demonstrated superior efficacy on the three major markers of disease activity by reducing relapses per year by nearly half, slowing the worsening of disability and significantly reducing MRI lesions compared with Rebif® (high-dose interferon beta-1a) over the two-year controlled treatment period. A similar proportion of patients in the OCREVUS group experienced serious adverse events and serious infections compared with patients in the high-dose interferon beta-1a group in the RMS studies.
In a separate PPMS Phase III study (ORATORIO), OCREVUS was the first and only treatment to significantly slow disability progression and reduce signs of disease activity in the brain (MRI lesions) compared with placebo with a median follow-up of three years. A similar proportion of patients in the OCREVUS group experienced adverse events and serious adverse events compared with patients in the placebo group in the PPMS study.

The most common side effects associated with OCREVUS in all Phase III studies were infusion reactions and upper respiratory tract infections, which were mostly mild to moderate in severity. Results from these three Phase III studies were recently published in the 19 January 2017 issue of the *New England Journal of Medicine* (NEJM).²

“This is an exciting day for everyone touched by MS, a disease that strikes in the prime of a person’s life when she or he may be starting a career or family”, said June Halper, MSN, APN-C, MSCN, FAAN, Chief Executive Officer at the Consortium for MS Centers. “We have eagerly awaited the FDA approval of OCREVUS because it not only offers a new, highly efficacious treatment option for people with relapsing multiple sclerosis, but it is also the first disease-modifying therapy indicated for primary progressive multiple sclerosis, a highly disabling type of this chronic disease. For many people living with MS, this FDA approval is a source of hope.”

The OCREVUS Marketing Authorisation Application (MAA) has also been validated by the European Medicines Agency (EMA) and is currently under review.

**About OCREVUS (ocrelizumab)**

OCREVUS is a 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.

OCREVUS is administered by intravenous infusion every six months. The first dose is given as two 300 mg
infusions given two weeks apart. Subsequent doses are given as single 600 mg infusions.

**About the OPERA I and OPERA II studies in relapsing forms of 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.

**About the ORATORIO study in primary progressive MS**

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. The blinded treatment period of the ORATORIO study continued 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.

A summary of the data from the OPERA I, OPERA II and ORATORIO studies that support this approval is below.

**Key data in RMS patients treated with OCREVUS 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<0.0001).
- A 40 percent relative risk reduction in confirmed disability progression (CDP) sustained for 12 weeks compared with interferon beta-1a in a pooled analysis of OPERA I and OPERA II, as measured by the Expanded Disability Status Scale (EDSS) (p=0.0006).
- 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<0.0001 and p<0.0001).
- A 77 percent and 83 percent relative reduction in the total number of new and/or enlarging T2 lesions compared with interferon beta-1a in OPERA I and OPERA II, respectively (p<0.0001 and p<0.0001).

**Key data in PPMS patients treated with OCREVUS showed:**

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• A 24 percent relative risk reduction in CDP sustained for at least 12 weeks compared with placebo, as measured by the EDSS (p=0.0321).
• A -0.39 cm³ mean change in volume of brain hyperintense T2 lesions compared with a 0.79 cm³ mean change in volume of placebo-treated patients over 120 weeks (p<0.0001).
• A 25 percent relative risk reduction in the proportion of patients with 20 percent worsening of the timed 25-foot walk confirmed at 12 weeks.

The most common side effects associated with OCREVUS in all Phase III studies were infusion reactions and upper respiratory tract infections, which were mostly mild to moderate in severity. Potential serious side effects may include infusion reactions, infections and malignancies where only routine screening is required based on age and medical history.

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{8}

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.\textsuperscript{9,10} Approximately 85 percent of people with MS are initially diagnosed with RRMS.\textsuperscript{11} The majority of people who are diagnosed with RRMS will eventually transition to secondary progressive MS (SPMS), in which they experience steadily worsening disability over time.\textsuperscript{11} Relapsing forms of MS (RMS) include people with RRMS and people with SPMS who continue to experience relapses. 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.\textsuperscript{1} Approximately 15 percent of people with MS are diagnosed with the primary progressive form of the disease.\textsuperscript{11} Until now, there have been no FDA approved treatments for PPMS.

People with all forms of MS experience disease activity – inflammation in the nervous system and permanent
loss of nerve cells in the brain – even when their clinical symptoms aren’t apparent or don’t appear to be getting worse.\textsuperscript{12} An important goal of treating MS is to reduce disease activity as soon as possible to slow how quickly a person’s disability progresses.\textsuperscript{13} Despite available disease-modifying treatments (DMTs), some people with RMS continue to experience disease activity and disability progression.

\textbf{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.

\textbf{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 \textit{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 for improving patient access to medical innovations by working with all relevant stakeholders. 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 (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2016 employed more than 94,000 people worldwide. In 2016, Roche invested CHF 9.9 billion in R&D and posted sales of CHF 50.6 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 \textit{www.roche.com}. 
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