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## **Roche's ocrelizumab first investigational medicine to show positive pivotal study results in both relapsing and primary progressive forms of multiple sclerosis**

- **Ocrelizumab showed superiority to interferon beta-1a (Rebif®) in two identical Phase III studies in people with relapsing multiple sclerosis (MS), the most common form of the disease**
- **Ocrelizumab is the first investigational medicine to show efficacy in people with primary progressive MS in a large Phase III study**
- **Ocrelizumab Phase III data will be presented at the 31st congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) from 7th to 10th October in Barcelona, Spain**

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced data from three positive, pivotal Phase III studies of ocrelizumab in people with relapsing multiple sclerosis (MS) and primary progressive multiple sclerosis (PPMS). Data from two identical studies (called OPERA I and OPERA II) in people with relapsing MS, which affects approximately 85 percent of people with MS at the time of diagnosis, showed ocrelizumab was superior to interferon beta-1a (Rebif®), a well-established MS therapy, in reducing the three major markers of disease activity over the two-year controlled treatment period.

In a separate study (called ORATORIO) in people with PPMS, a form of the disease marked by steadily worsening symptoms and typically without distinct relapses or periods of remission, ocrelizumab significantly reduced the progression of clinical disability sustained for at least 12 weeks (the primary endpoint) and 24 weeks (a secondary endpoint) compared with placebo. Additionally, the study met other secondary endpoints of reducing the time required to walk 25 feet, the volume of chronic inflammatory brain lesions, and brain volume loss.

“The results of these three pivotal trials have the potential to transform the treatment of MS,” said Sandra Horning, M.D., Roche's Chief Medical Officer and Head of Global Product Development. “Ocrelizumab is the first investigational medicine to significantly reduce disability progression in people with relapsing MS and people with primary progressive MS – a form of MS with no approved treatments. We are eager to work with

regulatory authorities to bring this investigational medicine to the MS community as soon as possible.”

“These results redefine our understanding of MS by highlighting the central role of the B cell,” said Stephen Hauser, M.D., Chair of the Scientific Steering Committee of the OPERA studies and Chair of the Department of Neurology at the University of California San Francisco School of Medicine. “The findings may also encourage the MS community to look more closely at earlier treatment of the disease. Currently, many doctors reserve what are considered highly effective MS medicines until a patient’s disease becomes more advanced. Patients and their doctors need new treatment options that offer the potential for greater efficacy than a standard-of-care interferon with a similar safety profile.”

“This is an important moment for the MS community,” said Xavier Montalban, M.D., Ph.D., Chair of the Scientific Steering Committee of the ORATORIO study and Professor of Neurology and Neuroimmunology at Vall d’Hebron University Hospital and Research Institute, Barcelona, Spain. “For decades, trial after trial has failed to show the benefit of any medicine for people with primary progressive MS. Now, for the first time, we have a positive Phase III study result for people with this debilitating form of the disease.”

Roche plans to pursue marketing authorisation for ocrelizumab in relapsing MS and in PPMS. Data from the ocrelizumab OPERA I and OPERA II studies and from the ORATORIO study will be submitted to global regulatory authorities in early 2016.

### **About the OPERA I and OPERA II studies in relapsing MS**

Results from the OPERA I and OPERA II studies will be presented by Dr. Hauser on Friday, 9th October (Abstract #246, 14:40 - 14:52 CET). OPERA I and OPERA II are Phase III, randomised, double-blind, double-dummy, global multi-centre studies evaluating the efficacy and safety of ocrelizumab (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 (i.e., relapsing-remitting MS and secondary-progressive MS with relapses).<sup>1</sup>

In the OPERA I and OPERA II studies, ocrelizumab significantly reduced the annualised relapse rate (ARR) – the primary endpoint of both studies – by nearly 50 percent compared with interferon beta-1a over the two-year period. Additionally, ocrelizumab met secondary endpoints of the study, significantly delaying confirmed

disability progression (CDP; loss of physical abilities, measured by the Expanded Disability Status Scale, or EDSS) by approximately 40 percent sustained for both 12 and 24 weeks compared with interferon beta-1a in pre-specified, pooled analyses of the two studies ( $p=0.0006$  and  $p=0.0025$ , respectively). Ocrelizumab also significantly reduced acute MS-related inflammation and brain injury (total number of T1-gadolinium-enhancing lesions measured by magnetic resonance imaging, or MRI) at 24, 48 and 96 weeks by more than 90 percent and the emergence of more chronic or growing areas of MS-related brain injury (T2 hyperintense lesions) at 24, 48 and 96 weeks by around 80 percent compared with interferon beta-1a.

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

- A 46-percent and 47-percent reduction in the ARR compared with interferon beta-1a over the two-year period in OPERA I and OPERA II, respectively ( $p<0.0001$  and  $p<0.0001$ ).
- A 43-percent and 37-percent risk reduction in CDP sustained for 12 weeks compared with interferon beta-1a in OPERA I and OPERA II, respectively ( $p=0.0139$  and  $p=0.0169$ ).
- A 43-percent and 37-percent risk reduction in CDP sustained for 24 weeks compared with interferon beta-1a in OPERA I and OPERA II, respectively ( $p=0.0278$  and  $p=0.0370$ ).
- A 94-percent and 95-percent 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 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 ( $p<0.0001$  and  $p<0.0001$ ).

Overall, the proportion of patients in the ocrelizumab group with adverse events was similar to interferon beta-1a in a pooled analysis of both studies (83.3 percent in each treatment group); the most common adverse event associated with ocrelizumab was infusion-related reactions (34.3 percent of patients who received ocrelizumab experienced at least one infusion-related reaction vs. 9.7 percent for interferon beta-1a). The proportion of patients in the ocrelizumab group with serious adverse events, including serious infections, was also similar to interferon beta-1a (6.9 percent vs. 8.7 percent, respectively).

### **About the ORATORIO study in PPMS**

Results from the ORATORIO study will be presented as a late-breaking abstract by Professor Montalban on Saturday, 10th October (Abstract #2368, 8:52-9:03 CET). ORATORIO is a Phase III, randomised, double-blind,

global multi-centre study evaluating the efficacy and safety of ocrelizumab (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.<sup>2</sup> 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 ocrelizumab or placebo and a predefined number of CDP events was reached overall in the study.

The ORATORIO study met its primary endpoint, showing treatment with ocrelizumab significantly reduced the risk of progression of clinical disability sustained for at least 12 weeks by 24 percent compared with placebo, as measured by the EDSS ( $p=0.0321$ ). Additionally, ocrelizumab was superior to placebo in significantly reducing the risk of progression of clinical disability for at least 24 weeks by 25 percent ( $p=0.0365$ ) and the time required to walk 25 feet (Timed 25-Foot Walk, or T25-FW) over 120 weeks by 29 percent ( $p=0.0404$ ). Ocrelizumab decreased the volume of hyperintense T2 lesions by 3.4 percent over 120 weeks, compared to placebo which increased T2 volume by 7.4 percent ( $p<0.0001$ ). Ocrelizumab reduced the rate of whole brain volume loss over 120 weeks by 17.5 percent compared to placebo ( $p=0.0206$ ).

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

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### **About ocrelizumab**

Ocrelizumab is an investigational, humanised monoclonal antibody designed to selectively target CD20-positive B cells. CD20-positive B cells are a specific type of immune cell thought to be a key contributor to myelin (nerve cell insulation and support) and axonal (nerve cell) damage, which can result in disability in people with MS. Based on preclinical studies, ocrelizumab 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.

The Phase III clinical development programme for ocrelizumab includes three studies: OPERA I, OPERA II and ORATORIO.

### **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.<sup>3,4</sup> 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. Damage to these nerves can cause a wide range of symptoms, including muscle weakness, fatigue and difficulty seeing, and may eventually lead to disability.<sup>5,6,7</sup> 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.<sup>8</sup>

Relapsing MS is the most common form of the disease. 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.<sup>9</sup> Approximately one in 10 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, Down syndrome and autism.

### **About Roche**

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and neuroscience. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. Roche's personalised

healthcare strategy aims at providing medicines and diagnostics that enable tangible improvements in the health, quality of life and survival of patients. Founded in 1896, Roche has been making important contributions to global health for more than a century. 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 chemotherapy.

In 2014, the Roche Group employed 88,500 people worldwide, invested 8.9 billion Swiss francs in R&D and posted sales of 47.5 billion Swiss francs. 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 [roche.com](http://roche.com).

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### **References**

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<sup>1</sup> F. Hoffmann-La Roche. ClinicalTrials.gov NCT01247324 and NCT01412333. National Library of Medicine. Available at: <https://clinicaltrials.gov/ct2/show/NCT01247324> and <https://clinicaltrials.gov/ct2/show/NCT01412333>.

<sup>2</sup> F. Hoffmann-La Roche. ClinicalTrials.gov NCT01194570. National Library of Medicine. Available at: <https://clinicaltrials.gov/ct2/show/NCT01194570>.

<sup>3</sup> Multiple Sclerosis International Federation. (2013). Atlas of MS 2013. Available at: <http://www.msif.org/about-us/advocacy/atlas/>.

<sup>4</sup> National Institutes of Health-National Institute of Neurological Disorders and Stroke. (2015). Multiple Sclerosis: Hope Through Research. Available at: [http://www.ninds.nih.gov/disorders/multiple\\_sclerosis/detail\\_multiple\\_sclerosis.htm#280373215](http://www.ninds.nih.gov/disorders/multiple_sclerosis/detail_multiple_sclerosis.htm#280373215).

<sup>5</sup> Ziemssen T. (2005). Modulating processes within the central nervous system is central to therapeutic control of multiple sclerosis. *J Neurol*, 252(Suppl 5), v38-v45.

<sup>6</sup> Hauser S.L. et al. (2012). Multiple sclerosis and other demyelinating diseases. In *Harrison's Principles of Internal Medicine* (pp.3395-3409). New York, NY: McGraw Hill Medical.

<sup>7</sup> Hadjimichael O. et al. (2007). Persistent pain and uncomfortable sensations in persons with multiple sclerosis. *Pain*, 127(1-2), 35-41.

<sup>8</sup> Multiple Sclerosis International Federation. What is MS? Available at <http://www.msif.org/about-ms/what-is-ms/>. Last accessed January 2015.

<sup>9</sup> MS International Federation. Types of MS. Available at: <http://www.msif.org/about-ms/types-of-ms/>.