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Roche's emicizumab for haemophilia A meets primary endpoint in phase III study

- **Emicizumab prophylaxis reduced the number of bleeds over time compared to no prophylaxis in people with haemophilia A and inhibitors to factor VIII**

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the primary endpoint has been met for the phase III HAVEN 1 study evaluating emicizumab prophylaxis in people 12 years of age or older with haemophilia A and inhibitors to factor VIII. The study showed a statistically significant reduction in the number of bleeds over time in people treated with emicizumab prophylaxis compared to those receiving no prophylactic treatment. The study also met all secondary endpoints, including a statistically significant reduction in the number of bleeds over time with emicizumab prophylaxis treatment in an intra-patient comparison in people who had received prior bypassing agent prophylaxis treatment. The most common adverse events with emicizumab were injection site reactions, consistent with prior studies.

“The development of inhibitors that render factor VIII replacement less effective, or ineffective, is one of the greatest challenges in the treatment of haemophilia A today, putting patients at high risk for life-threatening bleeds and repeated bleeds that may cause long-term joint damage,” said Sandra Horning, MD, Chief Medical Officer and Head of Global Product Development. “We are pleased to see that, in our first pivotal trial, emicizumab prophylaxis significantly reduced the number of bleeds over time in people in this difficult-to-treat setting. We look forward to working with health authorities to bring this treatment to the haemophilia community as soon as possible.”

“Since the mid-1990’s, there have been incremental improvements in the treatment of haemophilia A with inhibitors,” said Alain Baumann, Chief Executive Officer of the World Federation of Hemophilia. “The current burden of treatment is significant. WFH is supportive of research that could yield new therapeutic agents and offer a new treatment option for inhibitor patients. Filling this need would be a significant advance in our quest to achieve Treatment for All including those living with inhibitors.”

As previously reported, two patients had thromboembolic events and two patients developed thrombotic microangiopathy (TMA). The common aspect between all cases of thromboembolic events and TMA is that they occurred in patients who were on emicizumab prophylaxis and in addition received activated prothrombin complex concentrate to treat breakthrough bleeds. Neither thromboembolic event required anti-coagulation therapy and one patient restarted emicizumab. Both cases of TMA have completely resolved, and one patient restarted emicizumab.

HAVEN 1 is the first phase III study in the emicizumab clinical development programme to report results. Data from the study will be presented at an upcoming medical meeting and submitted to health authorities around the world for approval consideration.

About HAVEN 1 (NCT02622321)

HAVEN 1 is a randomised, multicenter, open-label, phase III study evaluating the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis versus no prophylaxis in people with haemophilia A and inhibitors to factor VIII. The study included 109 patients with haemophilia A (12 years of age or older) with inhibitors to factor VIII, who were previously treated with episodic or prophylactic bypassing agents. Patients previously treated with episodic bypassing agents were randomised in a 2:1 fashion to receive emicizumab prophylaxis (Arm A) or no prophylaxis (Arm B). Patients previously treated prophylactically with bypassing agents received emicizumab prophylaxis (Arm C). Episodic treatment of breakthrough bleeds with bypassing agents was allowed per protocol. The primary endpoint of the study is the number of bleeds over time with emicizumab prophylaxis (Arm A) versus no prophylaxis (Arm B). Secondary endpoints include all bleed rate, joint bleed rate, spontaneous bleed rate, target joint bleed rate, health-related quality of life (HRQoL)/ health status, intra-patient comparison to bleed rate on their prior prophylaxis regimen with bypassing agents (Arm C) and safety.

About emicizumab (ACE910)

Emicizumab is an investigational bispecific monoclonal antibody designed to bring together factors IXa and X, proteins required to activate the natural coagulation cascade and restore the blood clotting process. Emicizumab can be administered by an injection of a ready-to-use solution under the skin (subcutaneously) once weekly. Emicizumab is being evaluated in pivotal phase III studies in people 12 years of age and older, both with and without inhibitors to factor VIII, and in children under 12 years of age with factor VIII inhibitors. Future trials will seek to explore less frequent dosing schedules. The emicizumab development programme is assessing its potential to help overcome current clinical challenges, such as the short-lasting

effects of existing treatments, the development of factor VIII inhibitors and the need for frequent venous access. Emicizumab was created by Chugai Pharmaceutical Co., Ltd. and is being co-developed by Chugai, Roche and Genentech.

About haemophilia A

Haemophilia A is an inherited, serious disorder in which a person's blood does not clot properly, leading to uncontrolled and often spontaneous bleeding. Haemophilia A affects around 320,000 people worldwide^{1,2}, approximately 50-60% of whom have a severe form of the disorder³. People with haemophilia A either lack or do not have enough of a clotting protein called factor VIII. In a healthy person, when a bleed occurs, factor VIII brings together the clotting factors IXa and X, which is a critical step in the formation of a blood clot to help stop bleeding. A serious complication of treatment is the development of inhibitors to factor VIII replacement therapies⁴. Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII⁵, making it difficult, if not impossible to obtain a level of factor VIII sufficient to control bleeding.

About Roche in haematology

For more than 20 years, Roche has been developing medicines that redefine treatment in haematology. Today, we are investing more than ever in our effort to bring innovative treatment options to people with diseases of the blood. In addition to approved medicines MabThera®/Rituxan® (rituximab), Gazyva®/Gazyvaro® (obinutuzumab), and Venclexxa™/Venclyxto™ (venetoclax) in collaboration with AbbVie, Roche's pipeline of investigational haematology medicines includes Tecentriq® (atezolizumab), an anti-CD79b antibody drug conjugate (polatuzumab vedotin/RG7596) and a small molecule antagonist of MDM2 (idasanutlin/RG7388). Roche's dedication to developing novel molecules in haematology expands beyond malignancy, with the development of the investigational haemophilia A treatment emicizumab (ACE910).

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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<http://www1.wfh.org/publications/files/pdf-1472.pdf>.

² Berntorp E, Shapiro AD. Modern haemophilia care. *The Lancet* 2012; 370:1447-1456.

³ Marder VJ, et al. *Hemostasis and Thrombosis. Basic Principles and Clinical Practice*. 6th Edition, 2013. Milwaukee, Wisconsin. Lippincott Williams and Wilkin.

⁴ Gomez K, et al. Key issues in inhibitor management in patients with haemophilia. *Blood Transfus*. 2014; 12:s319–s329.

⁵ Whelan SF, et al. Distinct characteristics of antibody responses against factor VIII in healthy individuals and in different cohorts of hemophilia A patients. *Blood* 2013; 121:1039–48.