Media Release

European Commission approves Roche's Hemlibra for people with severe haemophilia A without factor VIII inhibitors

- **First medicine to significantly reduce treated bleeds compared to prior factor VIII prophylaxis, in a prospective intra-patient comparison**
- **Only prophylactic medicine that can be given subcutaneously and with multiple dosing options**
- **The efficacy and safety of Hemlibra has been demonstrated in one of the largest pivotal clinical trial programmes in haemophilia A**

Basel, 14 March 2019 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the European Commission has approved Hemlibra® (emicizumab) for routine prophylaxis of bleeding episodes in people with severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors. Hemlibra can be used in all age groups, and can also now be used at multiple dosing options (once weekly, every two weeks, or every four weeks) for all indicated people with haemophilia A, including those with factor VIII inhibitors.

This approval is based on results from the pivotal HAVEN 3 and HAVEN 4 studies. In the HAVEN 3 study in people with haemophilia A without factor VIII inhibitors, Hemlibra prophylaxis led to statistically significant and clinically meaningful reductions in treated bleeds compared to no prophylaxis, and compared to prior treatment with factor VIII prophylaxis in a prospective intra-patient comparison. In the HAVEN 4 study in people with haemophilia A with and without factor VIII inhibitors, Hemlibra showed a clinically meaningful control of bleeding when dosed every four weeks.

"We are delighted that now people with severe haemophilia A without inhibitors in the EU will also have the opportunity to benefit from Hemlibra, which has been shown to significantly reduce bleeds compared to no prophylaxis and compared to prior factor VIII prophylaxis," said Dr Elena Santagostino, Director of the Hemophilia Unit at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre of the Cà Granda Foundation, Maggiore Hospital Policlinico of Milan, Italy. "We are hopeful that the three different dosing options will allow people with haemophilia A and their physicians to choose the option that's right for them, based on their lifestyle and preferences."

"Today's approval is a landmark moment as Hemlibra is the first new class of treatment for people with severe haemophilia A without inhibitors in nearly 20 years," said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "Moreover, Hemlibra can effectively control bleeds while offering subcutaneous dosing once weekly, every two weeks or every four weeks. We will continue to work with EU member states, to bring this important treatment to those in need as quickly as possible."

In the phase III HAVEN 3 study, adults and adolescents aged 12 years or older with haemophilia A without factor VIII inhibitors who received Hemlibra prophylaxis once weekly (n=36) or every two weeks (n=35) experienced a 96% (rate ratio [RR]=0.04; p<0.0001) and 97% (RR= 0.03; p<0.0001) reduction in treated

bleeds, respectively, compared to those who received no prophylaxis (n=18). Hemlibra is the first medicine to significantly reduce treated bleeds compared to prior factor VIII prophylaxis, the standard of care for people with haemophilia A without factor VIII inhibitors, as demonstrated by a statistically significant reduction of 68% (RR=0.32; p<0.0001) in treated bleeds in an intra-patient comparison (n=48) of people who previously received factor VIII prophylaxis in a prospective non-interventional study and switched to Hemlibra prophylaxis.

In the single-arm phase III HAVEN 4 study, Hemlibra prophylaxis every four weeks led to clinically meaningful control of bleeding in adults and adolescents aged 12 years or older with haemophilia A with factor VIII inhibitors (n=5) and without factor VIII inhibitors (n=36).

In pooled data from the phase III HAVEN programme (n=373), the most common adverse reactions occurring in 10% or more of people treated with Hemlibra were injection site reactions (20%), joint pain (arthralgia; 15%) and headache (14%).

On 4 October 2018, Hemlibra was approved by the US Food and Drug Administration (FDA) for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children, ages newborn and older, with haemophilia A without factor VIII inhibitors, following Priority Review. Hemlibra was also previously granted Breakthrough Therapy Designation by the FDA for haemophilia A without factor VIII inhibitors. Priority Review designation is granted to medicines that the FDA has determined to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a serious disease. Breakthrough Therapy Designation is designed to expedite the development and review of medicines intended to treat a serious condition with preliminary evidence that indicates they may demonstrate substantial improvement over existing therapies. Submissions to other regulatory authorities around the world are ongoing.

Hemlibra has been approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in people with haemophilia A with factor VIII inhibitors in over 60 countries worldwide, including the US in November 2017, EU member states in February 2018 and Japan in March 2018. It has been studied in one of the largest pivotal clinical trial programmes in people with haemophilia A with and without factor VIII inhibitors, including four phase III studies (HAVEN 1, HAVEN 2, HAVEN 3 and HAVEN 4).

About HAVEN 3 (NCT02847637)
HAVEN 3 is a randomised, multicentre, open-label, phase III study evaluating the efficacy, safety and pharmacokinetics of Hemlibra prophylaxis versus no prophylaxis (episodic/on-demand factor VIII treatment) in people with haemophilia A without factor VIII inhibitors. The study included 152 patients with haemophilia A (12 years of age or older) who were previously treated with factor VIII therapy either on-demand or as prophylaxis. Patients previously treated with on-demand factor VIII were randomised in a 2:2:1 fashion to receive subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for four weeks, followed by 1.5 mg/kg/wk for at least 24 weeks (Arm A), subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for four weeks, followed by 3 mg/kg/2wks (Arm B) for at least 24 weeks or no prophylaxis (Arm C) for at least 24 weeks.

Patients previously treated with factor VIII prophylaxis received subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for four weeks, followed by 1.5 mg/kg/wk until the end of study (Arm D). Episodic treatment of breakthrough bleeds with factor VIII therapy was allowed per protocol.

HAVEN 3 met its primary endpoint and key secondary endpoints. Data from the study showed:

- Hemlibra prophylaxis every week or every two weeks resulted in a 96% (RR=0.04; p<0.0001,) and 97% (RR= 0.03; p<0.0001) reduction in treated bleeds, respectively, compared to no prophylaxis.
- 55.6% (95% CI: 38.1, 72.1) of people treated with Hemlibra every week and 60% (95% CI: 42.1, 76.1) of people treated with Hemlibra every two weeks experienced zero treated bleeds, compared to 0% (95% CI: 0.0; 18.5) of people treated with no prophylaxis.
- Hemlibra prophylaxis every week or every two weeks resulted in a 95% (RR=0.05; p<0.0001) and 95% (RR=0.05; p<0.0001) reduction in treated target joint bleeds, respectively, compared to no prophylaxis.
- Hemlibra prophylaxis every week or every two weeks resulted in a 95% (RR=0.05; p<0.0001) and 94% (RR=0.06; p<0.0001) reduction in all bleeds, respectively, compared to no prophylaxis.
- Hemlibra prophylaxis every week demonstrated a statistically significant reduction of 68% (RR=0.32; p<0.0001) in treated bleeds compared to prior factor VIII prophylaxis based on an intra-patient comparison of people who were previously enrolled in a prospective non-interventional study.
- In pooled data from the phase III HAVEN programme (n=373), the most common adverse reactions occurring in 10% or more of people treated with Hemlibra were injection site reactions (20%), joint pain (arthralgia; 15%) and headache (14%).

About HAVEN 4 (NCT03020160)

HAVEN 4 is a single-arm, multicentre, open-label, phase III study evaluating the efficacy, safety and pharmacokinetics (PK) of subcutaneous administration of Hemlibra dosed every four weeks. The study included 48 patients (12 years of age or older) with haemophilia A with or without factor VIII inhibitors who were previously treated with either factor VIII or bypassing agents, on-demand or as prophylaxis. The study was conducted in two parts: a PK run-in and an expansion cohort. All patients in the PK run-in (n=7) were previously treated on-demand and received subcutaneous Hemlibra at 6 mg/kg to fully characterise the PK profile after a single dose during four weeks, followed by 6 mg/kg every four weeks for at least 24 weeks. Patients in the expansion cohort (n=41), patients with haemophilia A with factor VIII inhibitors (n=5) and without factor VIII inhibitors (n=36), received subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for four weeks, followed by 6 mg/kg every four weeks for at least 24 weeks. Episodic treatment of breakthrough bleeds with factor VIII therapy or bypassing agents, depending on a patient's factor VIII inhibitor status, was allowed per study protocol. In the HAVEN 4 study, 56.1% (95% CI: 39.7; 71.5) of people with or without factor VIII inhibitors treated with Hemlibra prophylaxis every four weeks experienced zero treated bleeds.

About Hemlibra® (emicizumab)

Hemlibra is a bispecific factor IXa- and factor X-directed antibody. It is designed to bring together factor IXa and factor X, proteins required to activate the natural coagulation cascade and restore the blood clotting process for people with haemophilia A. Hemlibra is a prophylactic (preventative) treatment that can be administered by an injection of a ready-to-use solution under the skin (subcutaneously) once-weekly, every two weeks or every four weeks. Hemlibra was created by Chugai Pharmaceutical Co., Ltd. and is being co-

developed globally by Chugai, Roche and Genentech. It is marketed in the United States by Genentech as Hemlibra (emicizumab-kxwh), with kxwh as the suffix designated in accordance with Nonproprietary Naming of Biological Products Guidance for Industry issued by the US Food and Drug Administration.

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 disorder. [3] 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. Depending on the severity of their disorder, people with haemophilia A can bleed frequently, especially into their joints or muscles. [1] These bleeds can present a significant health concern as they often cause pain and can lead to chronic swelling, deformity, reduced mobility, and long-term joint damage. [4] A serious complication of treatment is the development of inhibitors to factor VIII replacement therapies. [5] Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII, [6] 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 Venclexta®/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 Hemlibra® (emicizumab), a bispecific monoclonal antibody for the treatment of haemophilia A.

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. 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 tenth consecutive year, Roche has been recognised as

the most sustainable company 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 2018 employed about 94,000 people worldwide. In 2018, Roche invested CHF 11 billion in R&D and posted sales of CHF 56.8 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.

References

[1] WFH. Guidelines for the management of haemophilia. 2012 [Internet; cited 2019 February]. Available from: 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. Milwakee, Wisconsin. Lippincott Williams and Wilkin.
[4] Franchini M, Mannucci PM. Haemophilia A in the third millennium. Blood Rev 2013; 179-84.
[5] Gomez K, et al. Key issues in inhibitor management in patients with haemophilia. Blood Transfus. 2014; 12: s319-s329.
[6] Whelan, SF, et al. Distinct characteristics of antibody responses against factor VIII in healthy individuals and in different cohorts of haemophilia A patients. Blood 2013; 121:1039-48.

Roche Group Media Relations

Phone: +41 61 688 8888 / e-mail: media.relations@roche.com
- Nicolas Dunant (Head)
- Patrick Barth
- Ulrike Engels-Lange
- Simone Oeschger
- Anja von Treskow