Media Release

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Roche's Hemlibra continued to substantially reduce bleeds in people with haemophilia A with inhibitors

- **Newly approved Hemlibra demonstrated superior efficacy compared to prior treatment with bypassing agents as prophylaxis or on-demand**
- **Nearly 95% of children who received Hemlibra experienced zero treated bleeds**

Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that new data from the ongoing Hemlibra® (emicizumab) clinical development programme were presented at the 59th American Society of Hematology (ASH) Annual Meeting. These data include longer-term results from the pivotal HAVEN 1 and HAVEN 2 studies in people with haemophilia A with inhibitors to factor VIII, showing once-weekly subcutaneous Hemlibra prophylaxis demonstrated superior efficacy compared to prior treatment with bypassing agents (BPAs) as prophylaxis or on-demand. These new data from the largest pivotal studies in people with haemophilia A with inhibitors further support Hemlibra as an important new treatment option for these adults, adolescents and children.

In updated results from the HAVEN 2 study with six additional months of data and 40 more children (younger than 12 years of age), 94.7% (95% CI: 85.4; 98.9) of children with haemophilia A with inhibitors who received Hemlibra prophylaxis had zero treated bleeds (n=57). The intra-patient analysis comparing the effects of different therapies in the same child (n=13) showed a 99% reduction in treated bleeds with Hemlibra prophylaxis compared to prior treatment with a BPA, either as prophylaxis (n=12) or on-demand (n=1). Substantial improvements in health-related quality of life and aspects of caregiver burden, measured by the haemophilia-specific quality of life short form (Haemo-QoL-SF) and adapted health-related quality of life in haemophilia patients with inhibitors (Inhib-QoL) questionnaires, were also observed with Hemlibra prophylaxis compared to prior BPA prophylaxis. These data were featured today in the official press programme of the ASH Annual Meeting.

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With nearly ten additional months of follow-up, updated results from the HAVEN 1 intra-patient analysis of adults and adolescents showed an 88% (risk rate [RR]=0.12, 95% CI: 0.05; 0.28) reduction in treated bleeds with Hemlibra prophylaxis compared to prior BPA prophylaxis (n=24). The results also showed a 95% (RR=0.05, 95% CI: 0.02; 0.12) reduction in treated bleeds in patients who received Hemlibra prophylaxis compared to prior on-demand BPA treatment (n=24). After more than one year, substantially more patients continued to experience zero bleeds with Hemlibra prophylaxis compared to their prior prophylaxis or on-demand BPA treatment across bleed endpoints, including treated bleeds and all bleeds. The previously reported improvement in health status after 24 weeks, measured by the haemophilia-specific quality of life (Haem-A-QoL) and EuroQol 5-Dimensions 5-level (EQ-5D-5L) questionnaires, was also maintained with longer follow-up.

“These data demonstrate the continued reduction in bleeds over time with Hemlibra prophylaxis and reinforce the potential of this medicine, recently approved by the FDA for haemophilia A with inhibitors, to redefine the standard of care,” said Sandra Horning, MD, Roche’s Chief Medical Officer and Head of Global Product Development. “We are continuing to study Hemlibra in a robust clinical development programme to help advance care for all people with haemophilia A, regardless of age or inhibitor status, and provide even less frequent dosing options.”

Data from the run-in cohort of the ongoing phase III HAVEN 4 study showed that Hemlibra prophylaxis dosed once every four weeks in people 12 years of age or older with haemophilia A, with or without inhibitors, resulted in levels of Hemlibra in the blood (pharmacokinetics) that were consistent with predictions. These data supported opening the expansion cohort of the study to further evaluate this dosing regimen. After a median observation time of eight weeks, 85.7% of patients (six out of seven) had zero bleeds while receiving Hemlibra prophylaxis once every four weeks. These data follow the recent announcement that an interim analysis of the phase III HAVEN 4 study showed a clinically meaningful control of bleeding in people 12 years of age or older with haemophilia A who received Hemlibra prophylaxis once every four weeks.

The most common adverse events (AEs) in the HAVEN 1 and HAVEN 2 studies at the time of these follow-up data were consistent with those observed previously in the studies. No unexpected safety findings were observed in the run-in cohort of the HAVEN 4 study. No new cases of thrombotic microangiopathy (TMA) or thrombotic events were observed in HAVEN 1, and no cases occurred in HAVEN 2 or HAVEN 4.

Based on earlier results from the HAVEN 1 and HAVEN 2 studies, 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 with haemophilia A with inhibitors. Data from HAVEN 1 and HAVEN 2 are also being reviewed under accelerated assessment by the European Medicines Agency (EMA) and submissions to health authorities around the world are ongoing. The clinical development programme also includes the ongoing phase III HAVEN 4 study and the phase III HAVEN 3 study, which showed a statistically significant and clinically meaningful reduction in the number of treated bleeds over time in people aged 12 years or older with haemophilia A without inhibitors who received Hemlibra prophylaxis every week or every other week, compared to those receiving no prophylaxis.

About HAVEN 1 (NCT02622321)

HAVEN 1 is a randomised, multicentre, open-label, phase III study evaluating the efficacy, safety and pharmacokinetics of once-weekly subcutaneous administration of Hemlibra prophylaxis compared to no prophylaxis in adults and adolescents with haemophilia A with inhibitors to factor VIII. The study included 113 patients (12 years of age and older) with haemophilia A with inhibitors to factor VIII, who were previously treated with BPAs on-demand or as prophylaxis. Patients previously treated with on-demand BPAs were randomised in a 2:1 ratio to receive Hemlibra prophylaxis (Arm A) or no prophylaxis (Arm B). Patients previously treated with BPAs as prophylaxis received Hemlibra prophylaxis (Arm C). Additional patients previously treated with on-demand BPAs were also enrolled in a separate arm (Arm D). On-demand treatment of breakthrough bleeds with BPAs was allowed per protocol in all arms.

The updated HAVEN 1 intra-patient analysis data presented at ASH comparing treatment with Hemlibra prophylaxis to prior BPAs as prophylaxis or on-demand showed:

HAVEN 1 (NCT02622321)				
Phase III randomised, multicentre, open-label study evaluating the efficacy, safety and pharmacokinetics of Hemlibra prophylaxis versus no prophylaxis in patients with haemophilia A with inhibitors to factor VIII				
Patients with haemophilia A with inhibitors aged ≥12 years on bypassing agent(s) on-demand (episodic) or as prophylaxis				
Endpoint	**Arm A (n=24)**		**Arm C (n=24)**	
	Hemlibra prophylaxis	**Prior episodic BPAs**	**Hemlibra prophylaxis**	**Prior prophylactic BPAs**
Median (range) duration of efficacy period (weeks)	76.3 (0.1-94.3)	21.1 (10.6-33.9)	75.6 (24.1-90.7)	32.1 (8.1-49.3)
Treated bleeds				
ABR (95% CI)	1.0 (0.4; 2.4)	21.4 (15.2; 30.1)	1.8 (0.7; 4.6)	15.7 (11.2; 22.0)
% reduction (RR [95% CI]), p-value	95% (0.05 [0.02; 0.12]), p<0.0001		88% (0.12 [0.05; 0.28]), p<0.0001	
% patients with 0 bleeds (95% CI)	62.5 (40.6; 81.2)	8.3 (1.0; 27.0)	58.3 (36.6; 77.9)	12.5 (2.7; 32.4)
% patients with 1-3 bleeds (95% CI)	33.3 (15.6; 55.3)	25.0 (9.8; 46.7)	25.0 (9.8; 46.7)	16.7 (4.7; 37.4)
% of patients with ≥4 bleeds (95% CI)	4.2 (0.1; 21.1)	66.7 (44.7; 84.4)	16.7 (4.7; 37.4)	70.8 (48.9; 87.4)
All bleeds				
ABR (95% CI)	3.1 (1.6; 6.2)	37.8 (28.6; 50.1)	3.6 (1.9; 6.7)	24.6 (18.4; 32.9)
% reduction (RR [95% CI]), p-value	92% (0.08 [0.04; 0.17]), p<0.0001		85% (0.15 [0.08; 0.28]), p<0.0001	
% patients with 0 bleeds (95% CI)	45.8 (25.6; 67.2)	0 (0.0; 14.2)	33.3 (15.6; 55.3)	0 (0.0; 14.2)
% patients with 1-3 bleeds (95% CI)	25.0 (9.8; 46.7)	4.2 (0.1; 21.1)	29.2 (12.6; 51.1)	16.7 (4.7; 37.4)
% of patients with ≥4 bleeds (95% CI)	29.2 (12.6; 51.1)	95.8 (78.9; 99.9)	37.5 (18.8; 59.4)	83.3 (62.6; 95.3)

ABR, annualised bleeding rate; BPA, bypassing agent; NIS, non-interventional study; RR, risk ratio

No new AEs resulted in treatment discontinuation. No new cases of TMA or thrombotic events were observed. As previously reported, three people experienced TMA events and two people experienced serious thrombotic events in the HAVEN 1 study when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving Hemlibra prophylaxis.

About HAVEN 2 (NCT02795767)

HAVEN 2 is a single-arm, multicentre, open-label, clinical study in children younger than 12 years of age with haemophilia A with inhibitors to factor VIII. The study is evaluating the efficacy, safety and pharmacokinetics of once-weekly subcutaneous administration of Hemlibra prophylaxis.

The updated HAVEN 2 analysis after a median of nine weeks of treatment (range 1.6-41.6 weeks) included 60 children with haemophilia A with inhibitors to factor VIII. The updated data presented at ASH showed:

HAVEN 2 (NCT02795767)				
Pivotal, single-arm, multicentre, open-label, study evaluating the efficacy, safety and pharmacokinetics of once-weekly subcutaneous administration of Hemlibra				
Patients with haemophilia A with inhibitors aged <12 years old (or 12-17 if <40 kg) previously treated with BPAs				
Endpoint	**% zero bleeds (95% CI) N=57**	**% zero bleeds (95% CI) n=23**	**ABR* (95% CI) n=23†**	**Median ABR (IQR) n=23†**
Treated bleeds	94.7 (85.4; 98.9)	87.0 (66.4; 97.2)	0.2 (0.06; 0.62)	0.0 (0.00; 0.00)
All bleeds	64.9 (51.1; 77.1)	34.8 (16.4; 57.3)	2.9 (1.75; 4.94)	1.5 (0.00; 4.53)
Treated spontaneous bleeds	98.2 (90.6; 100.0)	95.7 (78.1; 99.9)	0.1 (0.01; 0.47)	0.0 (0.00; 0.00)
Treated joint bleeds	98.2 (90.6; 100.0)	95.7 (78.1; 99.9)	0.1 (0.01; 0.47)	0.0 (0.00; 0.00)
Treated target joint bleeds	100 (93.7; 100.0)	100 (85.2; 100.0)	Not estimable	0.0 (0.00; 0.00)

*Negative binomial regression model. †Primary efficacy results (ABR analysis) based only on patients aged <12 years on study for ≥12 weeks. ABR, annualised bleeding rate; IQR, interquartile range

The most common AEs related to Hemlibra were injection-site reactions. Six patients experienced serious AEs, including bleeding in the muscles (muscle haemorrhage), eye pain, catheter site infection, device-related infection, bleeding of the mouth or gums (mouth haemorrhage) and appendicitis. No cases of TMA or thrombotic events occurred in the study.

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 inhibitors to factor VIII 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) 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 inhibitor status, was allowed per study protocol.

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 haemophilia A patients. Hemlibra is a prophylactic (preventative) treatment that can be administered by an injection of a ready-to-use solution under the skin (subcutaneously). The clinical development programme is assessing the safety and efficacy of Hemlibra and its potential to help overcome current clinical challenges: the short-lasting effects of existing treatments, the development of factor VIII inhibitors and the need for frequent venous access. Hemlibra was created by Chugai Pharmaceutical Co., Ltd. and is being co-developed by Chugai, Roche and Genentech. It is marketed in the United States as Hemlibra (emicizumab-kxwh) for patients with factor VIII inhibitors, with kxwh as the suffix designated in compliance 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] In addition to impacting a person's quality of life,[5] these bleeds can be life threatening if they go into vital organs, such as the brain.[6,7] A serious complication of treatment is the development of inhibitors to factor VIII replacement therapies.[8] Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII,[9] 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. Roche has been recognised as the Group Leader in sustainability within the Pharmaceuticals, Biotechnology & Life Sciences Industry nine 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 www.roche.com.

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References

[1] WFH. Guidelines for the management of hemophilia. [Internet; cited 2012]. 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. Hemophilia A in the third millennium. Blood Rev 2013; 179-84.

[5] Flood, E et al. Illustrating the impact of mild/moderate and severe haemophilia on health-related quality of life: hypothesised conceptual models. European Journal of Haematology 2014; 93: Suppl. 75, 9–18.

[6] Young G. New challenges in hemophilia: long-term outcomes and complications. Hematology Am Soc Hematol Educ Program 2012. 2012; 362–8.

[7] Zanon E, Iorio A, Rocino A, et al. Intracranial haemorrhage in the Italian population of haemophilia patients with and without inhibitors. Haemophilia 2012; 18: 39–45.

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

[9] 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