Media Release

Roche's Hemlibra provided sustained bleed control in the largest pivotal study to date of children with haemophilia A with factor VIII inhibitors

- **Nearly 77% of children receiving Hemlibra once weekly experienced zero treated bleeds**
- **Hemlibra once weekly reduced treated bleeds by 99% compared to prior bypassing agents in a prospective intra-patient comparison**
- **Hemlibra every two weeks and every four weeks also showed clinically meaningful control of bleeding**

Basel, 3 December 2018 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced data from the primary analysis of the phase III HAVEN 2 study evaluating Hemlibra® (emicizumab) prophylaxis in children younger than 12 years of age with haemophilia A with factor VIII inhibitors, including longer follow-up for once-weekly dosing and new data for less frequent dosing schedules (every two weeks or every four weeks). These data from the largest pivotal study in children with haemophilia A with factor VIII inhibitors were presented at the 60th American Society of Hematology (ASH) Annual Meeting.

"Children with inhibitors are at increased risk of life-threatening bleeds and may experience frequent, repeated bleeding into joints," said Guy Young, MD, Director of Hemostasis and Thrombosis Center, Children's Hospital Los Angeles, and Professor of Pediatrics, University of Southern California Keck School of Medicine, Los Angeles, California. "These updated data from HAVEN 2 showed that the majority of children with haemophilia A with factor VIII inhibitors treated with emicizumab had zero treated bleeds across three different dosing schedules, reinforcing the ability of this medicine to provide sustained, effective bleed control."

In updated results from the HAVEN 2 study with a median of 11 additional months of data, 76.9% (95% CI: 64.8; 86.5) of children with haemophilia A with factor VIII inhibitors treated with Hemlibra once weekly (n=65) experienced zero treated bleeds. Importantly, once-weekly Hemlibra showed a 99% (95% CI: 97.7; 99.4) reduction in treated bleeds compared to prior treatment with bypassing agents (BPAs) as prophylaxis (n=15) or on-demand (n=3) in a prospective intra-patient comparison. New data also showed that 90% (95% CI: 55.5; 99.7) of children with factor VIII inhibitors receiving Hemlibra every two weeks (n=10) and 60% (95% CI: 26.2; 87.8) of children receiving Hemlibra every four weeks (n=10) experienced zero treated bleeds, demonstrating clinically meaningful bleed control at both dosing schedules. No cases of thrombotic microangiopathy (TMA) or thrombotic events occurred. The most common adverse events (AEs) in the HAVEN 2 study primary analysis were consistent with those previously observed in the interim analyses.

"The updated analysis from the HAVEN 2 study supports the potential of Hemlibra to control bleeds at less frequent subcutaneous dosing, providing parents and their children more flexibility to choose a treatment schedule that is right for them," said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "Many children with haemophilia A with factor VIII inhibitors have already experienced the benefits of Hemlibra, and with these new positive data, we are confident that this treatment will continue to make a meaningful difference in their lives."

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Hemlibra is approved in over 50 countries worldwide, including the US, EU member states and Japan, to treat people of all ages with haemophilia A with factor VIII inhibitors based on pivotal data that included interim results from the HAVEN 2 study. In October 2018, the FDA also approved Hemlibra to treat people of all ages with haemophilia A without factor VIII inhibitors. Hemlibra is the only FDA-approved treatment for people with haemophilia A with and without factor VIII inhibitors that can be administered subcutaneously (under the skin) and at multiple dosing options (once weekly, every two weeks or every four weeks). The Marketing Authorisation Application variation for haemophilia A without factor VIII inhibitors is currently under review by the European Medicines Agency. Submissions to other regulatory authorities around the world are ongoing.

Hemlibra 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 HAVEN studies (HAVEN 1, HAVEN 2, HAVEN 3 and HAVEN 4).

About HAVEN 2 (NCT02795767)
HAVEN 2 is a multicentre, open-label, clinical study in children younger than 12 years of age with haemophilia A with factor VIII inhibitors. The study is evaluating the efficacy, safety and pharmacokinetics of once-weekly, every two weeks or every four weeks subcutaneous administration of Hemlibra prophylaxis.

The HAVEN 2 primary analysis included 85 children (once-weekly dosing, n=65; every two week dosing, n=10; every four week dosing, n=10) with haemophilia A with factor VIII inhibitors. The median follow-up period for each cohort was 58 (range 17.9–92.6), 21.3 (range 18.6–24.1), and 19.9 (range 8.9–24.1) weeks, respectively. The prospective intra-patient comparison included 18 patients from the once-weekly cohort previously treated with BPAs either as prophylaxis (n=15) or on-demand (n=3) as part of a non-interventional study.

The study met its primary endpoint and key secondary endpoints. Data presented at the 60th ASH Annual Meeting showed:

HAVEN 2 (NCT02795767)		
Hemlibra prophylaxis 1.5 mg/kg QW (Arm A; n=65)*		
	Annualised bleeding rate [ABR] † (95% CI)	**Median ABR (Interquartile range; IQR)**
Treated bleeds (primary endpoint)**	0.3 (0.17; 0.50)	0.0 (0.00; 0.00)
All bleeds	3.2 (1.94; 5.22)	0.6 (0.00; 2.92)
Treated spontaneous bleeds	0.0 (0.01; 0.10)	0.0 (0.00; 0.00)

Treated joint bleeds	0.2 (0.08; 0.29)	0.0 (0.00; 0.00)
Treated target joint bleeds	Not estimable	0.0 (0.00; 0.00)

*Efficacy assessment was conducted only in patients aged <12 years who had spent at least 12 weeks on the study. Excludes three patients aged >12 years.

A loading dose of 3 mg/kg Hemlibra was given for four weeks followed by the maintenance dose listed.

† Estimated using negative binomial regression

**In patients receiving Hemlibra once weekly (Arm A), 76.9% (95% CI, 64.8; 86.5) experienced zero treated bleeds and 23.1% experienced 1–3 treated bleeds.

	Hemlibra prophylaxis 3 mg/kg Q2W (Arm B; n=10)*	**Hemlibra prophylaxis 6 mg/kg Q4W (Arm C; n=10)***
ABR (95% CI) †	**0.2 (0.03–1.72)**	2.2 (0.69–6.81)
Median ABR (IQR)	0.0 (0.00–0.00)	0.0 (0.00–3.26)
% patients with zero treated bleeds (95% CI)	90.0% (55.5; 99.7)	60.0% (26.2; 87.8)
% patients with 1-3 treated bleeds (95% CI)	10.0%	40.0%

*A loading dose of 3 mg/kg Hemlibra was given for four weeks followed by the maintenance dose listed.

† Estimated using negative binomial regression

The most common adverse reactions occurring in 10% or more of children treated with Hemlibra were common cold symptoms (nasopharyngitis; 37.5%), injection site reactions (29.5%), fever (pyrexia; 23.9%), upper respiratory tract infection (23.9%), cough (23.9%), diarrhoea (15.9%), vomiting (15.9%), headache (14.8%), contusion (12.5%), fall (12.5%) and influenza (10.2%). No cases of TMA or thrombotic events occurred. Four patients tested positive for anti-drug antibodies (ADAs) to Hemlibra. Of these patients, two had ADAs with neutralising potential based on reduced Hemlibra levels. As previously reported, the ADA in one of these patients resulted in reduced efficacy of Hemlibra and led to discontinuation of treatment. The other patient had no bleeds as of the clinical cut-off date of the study.

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 Non-proprietary 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 2017 employed about 94,000 people worldwide. In 2017, Roche invested CHF 10.4 billion in R&D and posted sales of CHF 53.3 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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