Basel, 21 May 2018

Roche's Hemlibra reduced treated bleeds by 96 percent compared to no prophylaxis in phase III HAVEN 3 study in haemophilia A without factor VIII inhibitors

- **In a subset of patients in the HAVEN 3 study who previously received factor VIII prophylaxis, the standard of care, Hemlibra reduced bleeds by 68 percent compared to their prior therapy**
- **Phase III HAVEN 4 results showed Hemlibra every four weeks provides clinically meaningful control of bleeding in people with or without factor VIII inhibitors**

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced full results from the phase III HAVEN 3 study evaluating Hemlibra® (emicizumab) prophylaxis administered every week or every two weeks in people with haemophilia A without factor VIII inhibitors and the phase III HAVEN 4 study evaluating Hemlibra prophylaxis administered every four weeks in people with haemophilia A with or without factor VIII inhibitors. Data from both pivotal studies were presented today as late-breaking abstracts at the World Federation of Hemophilia (WFH) 2018 World Congress in Glasgow, Scotland.

"Hemlibra is the first medicine to show superior efficacy to prior factor VIII prophylaxis, the current standard of care therapy, as demonstrated by a statistically significant reduction in treated bleeds in the HAVEN 3 study intra-patient comparison," said Johnny Mahlangu, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa. "Even with current prophylactic treatments, many people with haemophilia A continue to have bleeds that can lead to long-term joint damage, and there is a need for more treatment options."

In the phase III HAVEN 3 study, adults and adolescents aged 12 years or older without factor VIII inhibitors who received Hemlibra prophylaxis every week or every two weeks showed a 96% ($p<0.0001$) and 97% ($p<0.0001$) reduction in treated bleeds, respectively, compared to those who received no prophylaxis. In addition, 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. Importantly, in an intra-patient comparison, in

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patients who were previously enrolled in a prospective non-interventional study (NIS), once-weekly Hemlibra prophylaxis showed superior efficacy compared to prior factor VIII prophylaxis, the standard of care for people with haemophilia A without factor VIII inhibitors, as demonstrated by a 68% reduction ($p<0.0001$) in treated bleeds. Additionally, 93.7% (n=89/95; 95% CI, 86.8; 97.7) of all participants who completed a treatment preference survey preferred Hemlibra to their previous haemophilia treatment, with 97.8% (n=45/46) of those in the intra-patient comparison preferring Hemlibra to their prior factor VIII prophylaxis. There were no unexpected or serious adverse events (AEs) related to Hemlibra, and the most common AEs were consistent with previous studies. The most common AEs occurring in 5% or more of people in the HAVEN 3 study were injection site reactions, joint pain (arthralgia), common cold symptoms (nasopharyngitis), headache, upper respiratory tract infection and influenza.

“These new pivotal data show that Hemlibra controlled bleeds in people with haemophilia A, while offering the flexibility of less frequent subcutaneous dosing options,” said Sandra Horning, MD, Roche’s Chief Medical Officer and Head of Global Product Development. “With this data, we now have positive results from all four of our phase III trials that reinforce the overall efficacy and safety of Hemlibra and its potential to improve care for all people with haemophilia A.”

In the single-arm phase III HAVEN 4 study, adults and adolescents aged 12 years or older with or without factor VIII inhibitors receiving Hemlibra prophylaxis every four weeks had a median annualised bleeding rate for treated bleeds of 0.0 (IQR: 0.0; 2.1), with 56.1% (95% CI: 39.7; 71.5) of people experiencing zero treated bleeds and 90.2% (95% CI: 76.9; 97.3) experiencing three or fewer treated bleeds. These results demonstrate that Hemlibra administration every four weeks can provide clinically meaningful control of bleeding in people with haemophilia A with or without factor VIII inhibitors. Additionally, all participants (n=41/41; 95% CI, 91.4; 100.0) who responded to a patient preference survey preferred Hemlibra to their previous haemophilia treatment. There were no serious AEs related to Hemlibra, and the most common AEs were consistent with previous studies. Injection site reaction was the most common AE, occurring in nine people in the HAVEN 4 study.

Separately, real-world data from the NIS on the impact of haemophilia A on health-related quality of life (HRQoL) and the burden of current treatment (either on-demand or prophylactic bypassing agents or factor VIII replacement therapy, depending on inhibitor status and local clinical guidelines) were also presented. Results from a cohort of the NIS in children with haemophilia A with factor VIII inhibitors showed that living with and managing the condition has a substantially negative impact on physical and emotional health

and results in a significant burden for caregivers. In another cohort of the NIS, adults and adolescents with haemophilia A without factor VIII inhibitors reported higher HRQoL with prophylactic factor VIII treatment compared to episodic factor VIII treatment, based on validated tools including Haem-A-QoL and Haemo-QoL-SF. In addition, prophylactic factor VIII therapy resulted in fewer school and work days missed compared to episodic treatment. This NIS represents one of the largest studies of this type in people with haemophilia A with or without factor VIII inhibitors, and collected prospective real-world data for use as a valid historical control for pivotal studies in patients with haemophilia A.

In April 2018, the US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation to Hemlibra for people with haemophilia A without factor VIII inhibitors, based on data from the HAVEN 3 study. Hemlibra was approved by the FDA in November 2017 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with haemophilia A with factor VIII inhibitors based on results from the HAVEN 1 study and interim results from the HAVEN 2 study. Hemlibra was also recently approved by regulatory authorities in other countries around the world, including by the European Commission in February 2018 for routine prophylaxis of bleeding episodes in people with haemophilia A with factor VIII inhibitors. Data from both the HAVEN 3 and HAVEN 4 studies are being submitted to health authorities around the world for approval consideration.

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 for 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 4 weeks, followed by 1.5 mg/kg/wk until the end of study (Arm A), subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for 4 weeks, followed by 3 mg/kg/2wks for at least 24 weeks (Arm B), or no prophylaxis (Arm C). Patients previously treated with factor VIII prophylaxis received subcutaneous Hemlibra prophylaxis at 3 mg/kg/wk for 4 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.

Study name	**HAVEN 3 (NCT02847637)**		
Study group	No Prophylaxis (Arm C; n=18)	1.5 mg/kg Hemlibra Prophylaxis (Once weekly dosing) (Arm A; n=36)	3 mg/kg Hemlibra Prophylaxis (Dosing every two weeks) (Arm B; n=35)
Treated bleeds annualised bleeding rate (ABR; primary endpoint)			
Median efficacy period, weeks (min–max)	24.0 (14.4–25.0)	29.6 (17.3–49.6)	31.3 (7.3–50.6)
Model-based ABR (95% CI)*	38.2 (22.9; 63.8)	1.5 (0.9; 2.5)	1.3 (0.8; 2.3)
% reduction vs arm C (RR, p-value)	N/A	**96% reduction** (0.04, p <0.0001)	**97% reduction** (0.03, p <0.0001)
Median ABR (Interquartile range; IQR)	40.4 (25.3; 56.7)	0.0 (0.0; 2.5)	0.0 (0.0; 1.9)
% patients with zero bleeds (95% CI)	0.0 (0.0; 18.5)	55.6 (38.1; 72.1)	60 (42.1; 76.1)
% patients with zero to three bleeds (95% CI)	5.6 (0.1; 27.3)	91.7 (77.5; 98.2)	94.3 (80.8; 99.3)
All bleeds (secondary endpoint)			
Model-based ABR* (95% CI)	47.6 (28.5; 79.6)	2.5 (1.6; 3.9)	2.6 (1.6; 4.3)
% reduction RR† (p-value)	N/A	**95% reduction** (p <0.0001)	**94% reduction** (p <0.0001)
% patients with zero bleeds (95% CI)	0.0 (0.0; 18.5)	50.0 (32.9; 67.1)	40.0 (23.9; 57.9)

Treated spontaneous bleeds (secondary endpoint)			
Model-based ABR* (95% CI)	15.6 (7.6; 31.9)	1.0 (0.5; 1.9)	0.3 (0.1; 0.8)
% reduction RR† (p-value)	N/A	**94% reduction** p <0.0001	**98% reduction** p <0.0001
% patients with 0 bleeds (95% CI)	22.2 (6.4; 47.6)	66.7 (49.0; 81.4)	88.6 (73.3; 96.8)
Treated joint bleeds (secondary endpoint)			
Model-based ABR* (95% CI)	26.5 (14.7; 47.8)	1.1 (0.6; 1.9)	0.9 (0.4; 1.7)
% reduction RR† (p-value)	N/A	**96% reduction** (p <0.0001)	**97% reduction** (p <0.0001)
% patients with 0 bleeds (95% CI)	0.0 (0.0; 18.5)	58.3 (40.8; 74.5)	74.3 (56.7; 87.5)
Treated target joint bleeds (secondary endpoint)			
Model-based ABR* (95% CI)	13.0 (5.2; 32.3)	0.6 (0.3; 1.4)	0.7 (0.3; 1.6)
% reduction RR† (p-value)	N/A	**95% reduction** p <0.0001	**95% reduction** p <0.0001
% patients with 0 bleeds (95% CI)	27.8 (9.7; 53.5)	69.4 (51.9; 83.7)	77.1 (59.9; 89.6)
Treated bleeds intra-patient comparison (Arm D patients who participated in NIS n=48; secondary endpoint)			
Study group	Prior factor VIII prophylaxis (Arm C; n=48)	1.5 mg/kg Hemlibra Prophylaxis (Once weekly dosing) (Arm D; n=48)	
Duration of efficacy period, median (min-max), weeks	30.1 (5.0–45.1)	33.7 (20.1–48.6)	
Model-based ABR* (95% CI)	4.8 (3.2; 7.1)	1.5 (1.0; 2.3)	

% reduction vs NIS Factor VIII (RR, p-value)	**68% reduction (0.32, p<0.0001)**	
Median ABR (IQR)	1.8 (0.0; 7.6)	0.0 (0.0; 2.1)
% patients with 0 bleeds (95% CI)	39.6 (25.8; 54.7)	54.2 (39.2; 68.6)
% patients with 0-3 bleeds (95% CI)	72.9 (58.2; 84.7)	91.7 (80.0; 97.7)

*Negative binomial regression model

†Compared with Arm C

- Intra-patient comparison includes data from 48 patients in Arm D who participated in the NIS shown
- All arm D (n=63) ABR 1.6 (95% CI, 1.1; 2.4); % zero bleeds 55.6 (95% CI, 42.5; 68.1)

Haem-A-QoL Physical Health domain score			
Study group	No Prophylaxis (Arm C; n=17)	1.5 mg/kg Hemlibra Prophylaxis (Once weekly dosing) (Arm A; n=36)	3 mg/kg Hemlibra Prophylaxis (Dosing every two weeks) (Arm B; n=35)
Physical Health domain score at Week 25			
Patients, n	13	34	29
Adjusted mean difference (95% CI) vs Arm C	N/A	12.5 (–2.0; 27.0)	16.0 (1.2; 30.8)
P-value	N/A	0.089	0.035

- Hemlibra resulted in numerical improvement
- Since the comparison of Haem-A-QoL between Arms A and C is not statistically significant, the comparison of Arms B and C is not considered statistically significant due to the order of endpoints in the hierarchical testing framework

Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults.

HAVEN 3 Safety Summary: all Hemlibra participants Hemlibra prophylaxis (N=150)					
n (%) unless otherwise stated	**Arm A: 1.5 mg/kg QW (n = 36)**	**Arm B: 3 mg/kg Q2W (n = 35)**	**Arm C: 3 mg/kg Q2W (n = 16)***	**Arm D: 1.5 mg/kg QW (n = 63)**	**Total (N=150)**
Total number of AEs	143	145	19	236	543
Number of serious AEs	1	3	0	10	14
Hemlibra-related serious AEs	0	0	0	0	0
Selected AEs occurring in 5% or more of all patients, n (%)‡					
ISR†	9 (25.0)	7 (20.0)	2 (12.5)	20 (31.7)	38 (25.3)
Upper respiratory tract infection	4 (11.1)	4 (11.4)	0	8 (12.7)	16 (10.7)
Patients with AE leading to withdrawal, n (%)	0	1 (2.9)	0	0	1 (0.7)

* Data represent period of Hemlibra prophylaxis only; at the clinical cutoff date, 1 patient was lost to follow-up and another was waiting to start Hemlibra

† Grades 1–2 AE. 1 additional patient in Arm D (and total column) reported an "injection site erythema" not "injection site reaction" as the Preferred Term

‡ Other AEs occurring in 5% or more of patients were arthralgia (19%), nasopharyngitis (12%), headache (11%), and influenza (6%)

- 1 patient in Arm B discontinued due to multiple mild AEs (insomnia, hair loss, nightmare, lethargy, depressed mood, headache and pruritus); 2 patients were lost to follow-up (Arms A and C, 1 patient each)
- Of 215 events of co-exposure to factor VIII and Hemlibra in 64 patients, 43 included an average factor VIII dose ≥50 IU/kg/24 hours, of which 8 events lasted >24 hours; co-exposure to Hemlibra and factor VIII was not related to serious AEs, TMA or TEs
- No serious AE was associated with Hemlibra per investigator assessment
- No patients on Hemlibra developed de novo factor VIII inhibitors

- No ADAs detected

ADA, anti-drug antibodies; AE, adverse event; ISR, injection site reaction; NIS, non-interventional study; TE, thromboembolic event; TMA, thrombotic microangiopathy

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) 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.

Study name	**HAVEN 4 (NCT03020160)**
Study group	Hemlibra prophylaxis (n=48 total; n=41 included in efficacy analyses)
Treated bleeds	
Annualised bleeding rate (ABR)*, model based (95% CI)	2.4 (1.4; 4.3)
Median ABR, calculated (IQR)	0.0 (0.0; 2.1)
% patients with zero bleeds (95% CI)	**56.1** (39.7; 71.5)
% patients with zero to three bleeds (95% CI)	**90.2** (76.9; 97.3)
All bleeds	
ABR, model based (95% CI)	4.5 (3.1; 6.6)

Median ABR, calculated (IQR)	2.1 (0.0; 5.9)
% patients with zero bleeds (95% CI)	**29.3** (16.1; 45.5)
% patients with zero to three bleeds (95% CI)	**80.5** (65.1; 91.2)
Treated spontaneous bleeds	
ABR, model based (95% CI)	0.6 (0.3; 1.5)
Median ABR, calculated (IQR)	0.0 (0.0; 0.0)
% patients with zero bleeds (95% CI)	**82.9** (67.9; 92.8)
% patients with zero to three bleeds (95% CI)	**97.6** (87.1; 99.9)
Treated joint bleeds	
ABR, model based (95% CI)	1.7 (0.8; 3.7)
Median ABR, calculated (IQR)	0.0 (0.0; 1.9)
% patients with zero bleeds (95% CI)	**70.7** (54.5; 83.9)
% patients with zero to three bleeds (95% CI)	95.1 (83.5; 99.4)
Treated target joint bleeds	
ABR, model based (95% CI)	1.0 (0.3; 3.3)
Median ABR, Calculated (IQR)	0.0 (0.0; 0.0)

% patients with zero bleeds (95% CI)	**85.4** (70.8; 94.4)
% patients with zero to three bleeds (95% CI)	**97.6** (87.1; 99.9)

*Negative binomial regression model

- Median (range) efficacy period, 25.6 (24.1–29.4) weeks
- Majority (38/51 [74.5%]) of treated bleeds were traumatic

Haem-A-QoL Physical Health domain score		
	Hemlibra 6 mg/kg Q4W n=38*	
	Baseline	Week 25
Patients	38	37
Physical Health domain score, mean (SD)	47.0 (25.1)	32.4 (25.4)
Change from baseline, mean (95% CI)	N/A	–15.1 (–22.4; –7.8)

- Hemlibra resulted in a numerical improvement
- Change from baseline in the Physical Health domain score for meaningful improvements: ≥10 points (responder threshold)
- *Analysis excludes adolescents (n=3)

HAVEN 4 Safety Summary	
Total Number of AEs	148
Participants with ≥ 1 AE, n (%)	30 (73.2)
Serious AE, n (%) *	1 (2.4)
Grade ≥ 3 AE, n (%)	1 (2.4)
Related AE, n (%)	12 (29.3)
Local injection site reaction (ISR), n (%)	9 (22.0)
AESI	
Hypersensitivity	0
TE/TMA	0

* 1 serious AE in the PK run-in cohort: grade 3 hypertension in patient with medical history of hypertension; unrelated to Hemlibra treatment.

- 73.2% of patients experienced ≥1 AE
- Only 1 serious (Grade ≥3) AE of rhabdomyolysis unrelated to Hemlibra
- Injection-site reaction was the most common Hemlibra-related AE (22.0%)
- No AEs led to Hemlibra discontinuation or withdrawal
- No TEs, TMAs or hypersensitivity reactions

PK, pharmacokinetics; SI, special interest

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. 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 people with haemophilia A with factor VIII inhibitors, 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,[i,ii] approximately 50-60% of whom have a severe form of the disorder.[iii] 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.[i] 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.[iv] A serious complication of treatment is the development of inhibitors to factor VIII replacement therapies.[v] Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII,[vi] 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 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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