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## **Roche's emicizumab showed positive results in phase III studies (HAVEN 1 and HAVEN 2) in haemophilia A with inhibitors**

- **Emicizumab showed substantial and clinically meaningful reduction in bleeds across two pivotal studies**
- **Data from HAVEN 1 in adults and adolescents and interim data from HAVEN 2 in children to be presented at the 26<sup>th</sup> International Society on Thrombosis and Haemostasis (ISTH) Meeting**

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced positive data from the primary analysis of the phase III HAVEN 1 study in adults and adolescents and interim analysis of the phase III HAVEN 2 study in children evaluating once-weekly subcutaneous emicizumab prophylaxis (preventative) for the treatment of haemophilia A with inhibitors to factor VIII. Data from both studies will be presented on 10 July at the 26<sup>th</sup> International Society on Thrombosis and Haemostasis (ISTH) Meeting in Berlin, Germany.

The phase III HAVEN 1 study compared emicizumab prophylaxis with on-demand (no prophylaxis; episodic use only) and prophylactic use of bypassing agents (BPAs) in adults and adolescents with haemophilia A with inhibitors. The primary endpoint was treated bleeds, and results showed a statistically significant and clinically meaningful reduction in bleed rate of 87% (risk rate [RR]=0.13,  $p < 0.0001$ ) with emicizumab prophylaxis compared with on-demand treatment with BPAs.

After a median observation time of 31 weeks, 62.9% of patients receiving emicizumab experienced zero treated bleeds compared to 5.6% of those receiving on-demand BPAs. Reduction in bleed rate with emicizumab was consistent across all secondary endpoints, including all bleeds (80%, RR=0.20,  $p < 0.0001$ ), treated spontaneous bleeds (92%, RR=0.08,  $p \leq 0.0001$ ), treated joint bleeds (89%, RR=0.11,  $p = 0.0050$ ) and treated target joint bleeds (95%, RR=0.05,  $p = 0.0002$ ) compared with on-demand BPAs. Results also showed a statistically significant and clinically meaningful improvement in health-related quality of life (HRQoL) measured at 25 weeks, including Haem-A-Qol physical health domain and total score and EQ-5D-5L visual analogue scale and total utility score.

In an additional study arm (Arm C, n=49), patients who had previously received prophylaxis with BPAs received emicizumab prophylaxis. A subset of patients in this arm (n=24) had previously participated in a non-interventional study (NIS), allowing for a first of its kind intra-patient analysis. This analysis showed a 79% (RR=0.21, p=0.0003) reduction in treated bleeds in people receiving emicizumab compared to their prior prophylaxis with BPAs.

Adverse events (AEs) occurring in 5% or more of patients treated with emicizumab, were injection site reactions, headache, fatigue, upper respiratory tract infection and arthralgia. As previously reported, serious adverse events of thromboembolic events (TE) and thrombotic microangiopathy (TMA) occurred in two patients and three patients\*, respectively, while receiving emicizumab prophylaxis. The TE and TMA events were associated with repeated high doses of a BPA, activated prothrombin complex concentrate, when used to treat breakthrough bleeds.

Interim results from the single arm HAVEN 2 study in children younger than 12 years of age with haemophilia A with inhibitors who received emicizumab prophylaxis are consistent with the positive results from the HAVEN 1 study. After a median observation time of 12 weeks, the study showed that only one of 19 children receiving emicizumab reported a treated bleed. There were no reported joint or muscle bleeds. An intra-patient comparison (n=8) in patients who were previously enrolled in the NIS, showed that all patients experienced a 100% reduction in treated bleeds following treatment with emicizumab (previous ABR ranged from 0 to 34.24); this included seven children who had received prior BPA prophylaxis, and one who had received prior on-demand BPA. The data also indicate that the same dose of emicizumab is appropriate for children as for adults and adolescents, based on the levels of emicizumab in the blood (pharmacokinetics) of the children compared with the level of emicizumab in the blood of adults and adolescents. The most common AEs with emicizumab in the HAVEN 2 study were mild injection site reactions and common cold symptoms (nasopharyngitis).

#### **About HAVEN 1 (NCT02622321)**

HAVEN 1 is a randomised, multicentre, open-label, phase III study evaluating the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis compared to on-demand BPA (no prophylaxis; episodic use only) in adults and adolescents with haemophilia A with inhibitors to factor VIII. The study included 109 patients (12 years of age or older) with haemophilia A with inhibitors to factor VIII, who were previously treated with on-demand or prophylactic BPAs.

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\* One event occurred after the clinical cut-off date for the primary analysis

Patients previously treated with on-demand BPAs were randomised in a 2:1 fashion to receive emicizumab prophylaxis (Arm A) or no prophylaxis (Arm B). Patients previously treated with prophylactic BPAs received emicizumab prophylaxis (Arm C). Additional patients previously on BPA (on-demand or prophylaxis) 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 primary endpoint of the study is the number of treated bleeds over time with emicizumab prophylaxis (Arm A) compared with 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 BPAs (Arm C) or no prophylaxis (Arm A). The study also evaluated safety and pharmacokinetics.

A summary of the HAVEN 1 study results to be presented at ISTH are included below.

<b>Study Name</b>	<b>HAVEN 1 (NCT02622321)</b>	
<b>Study Description</b>	Phase III randomised, multicentre, open-label study evaluating the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis versus no prophylaxis in people with haemophilia A with inhibitors to factor VIII	
<b>Patients</b>	Patients with haemophilia A with inhibitors aged $\geq 12$ years on episodic or prophylactic treatment with bypassing agent(s) (N=109).	
<b>Study group</b>	No prophylaxis (prior episodic BPAs) (Arm B; n=18)	Emicizumab prophylaxis (prior episodic BPAs) (Arm A; n=35)
<b>Treated bleeds ABR (primary endpoint)</b>		
<b>Annualised bleeding rate [ABR]* (95% CI)</b>	23.3 (12.33; 43.89)	2.9 (1.69; 5.02)
<b>% reduction (RR, p-value)</b>	87% reduction (RR= 0.13, p<0.0001)	
<b>Median ABR (Interquartile range; IQR)</b>	18.8 (12.97; 35.08)	0.0 (0.00; 3.73)
<b>% patients with zero bleeds (95% CI)</b>	5.6 (0.1; 27.3)	62.9 (44.9; 78.5)

Treated bleeds ABR intra-patient comparison (Arm C patients who participated in NIS n=24; secondary endpoint)		
Study group	Prior prophylaxis with a BPA	Emicizumab prophylaxis
ABR* (95% CI)	15.7 (11.08; 22.29)	3.3 (1.33; 8.08)
% reduction (RR, p-value)	79% reduction (RR= 0.21, p=0.0003)	
Median ABR (IQR)	12.0 [5.73; 24.22]	0.0 [0.00; 2.23]
% patients with zero bleeds	12.5 (2.7; 32.4)	70.8 (48.9; 87.4)

\*Negative binomial regression model

### About HAVEN 2 (NCT02795767)

HAVEN 2 is a single-arm, multicentre, open-label, phase III study evaluating the efficacy, safety, and pharmacokinetics of once-weekly subcutaneous administration of emicizumab. The interim analysis after a median of 12 weeks of treatment included 19 children younger than 12 years of age with haemophilia A with inhibitors to factor VIII, who require treatment with BPAs. The objectives of the study are to evaluate the number of treated bleeds over time with emicizumab prophylaxis, safety, pharmacokinetics, health-related quality of life (HRQoL) and proxy HRQoL with aspects of caregiver burden. The study will enrol a total of 60 children for its final analysis planned after 52 weeks of treatment with emicizumab.

### 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. Additional trials are exploring less frequent dosing schedules. The clinical development programme is assessing the safety and efficacy of emicizumab 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. 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,<sup>1,2</sup> approximately 50-60% of whom have a severe form of the disorder.<sup>3</sup> 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.<sup>1</sup> 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.<sup>4</sup> In addition to impacting a person's quality of life,<sup>5</sup> these bleeds can be life threatening if they go into vital organs, such as the brain.<sup>6,7</sup> A serious complication of treatment is the development of inhibitors to factor VIII replacement therapies.<sup>8</sup> Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII<sup>9</sup>, making it difficult, if not impossible to obtain a level of factor VIII sufficient to control bleeding. Most people with haemophilia A who develop inhibitors will infuse BPA therapies, either on-demand (episodic) or as prophylaxis, to control bleeding. This approach is known to be less effective and less predictable than factor VIII replacement therapy in people with haemophilia A without inhibitors.<sup>10</sup>

## **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 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. 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 eight 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](http://www.roche.com).

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