15 December 2022
EMA/9454/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hemlibra

International non-proprietary name: emicizumab

Procedure No. EMEA/H/C/004406/II/0027

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ABR	annualized bleeding rate
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AJBR	annualized joint bleeding rate
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMQ	bleed medication questionnaire
BPA	bypassing agent
BU	Bethesda unit
CATCH	Comprehensive Assessment Tool of Challenges in Hemophilia
CCOD	clinical cutoff date
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CSR	Clinical Study Report
CV	coefficient of variation
DSC	daily step count
ELISA	enzyme-linked immunosorbent assay
EmiPref	Emicizumab Preference Survey
EOI	Extension of indication
ERT	eResearch Technology, Inc.
EQ-5D-5L	EuroQol 5-Dimension 5-Level Questionnaire
FDP	fibrinogen degradation product
FIX	factor IX
FIXa	activated factor IX
FVIII	factor VIII
FVIIIa	activated factor VIII
FX	factor X
HA	Hemophilia A

HIPAA	Health Insurance Portability and Accountability Act
HJHS	Hemophilia Joint Health Survey
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
IEC	independent ethics committee
IgG4	immunoglobulin G4
IMP	investigational medicinal product
IQR	interquartile range
IRB	institutional review board
ISR	injection site reaction
ITI	immune tolerance induction
IVD	in-vitro diagnostic
ko	knockout
LLOQ	lower limit of quantitation
MBQ	Menstrual Bleeding Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MD	Menstruation Diary
m/m HA	mild / moderate haemophilia A
MVPA	moderate to vigorous physical activity
nAb	neutralizing antibody
nADA	neutralizing anti-emicizumab antibody
NHP	non-human-primates
NB	negative binomial
PBAC	Pictorial Blood Assessment Chart
PBAC	Pictorial Blood Assessment Chart
NB	negative binomial
PBAC	Pictorial Blood Assessment Chart
PD	pharmacodynamic
PK	pharmacokinetic
PT	Preferred Term
QoL	quality of life
QTL	quality tolerance limit

QW	every week
Q2W	every 2 weeks
Q4W	every 4 weeks
RWD	real world data
RWE	real world evidence
SAE	serious adverse event
SAP	statistical analysis plan
SBP	Summary of Biopharmaceutics
SC	subcutaneous(ly)
SD	standard deviation
SLR	systematic literature review
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
TE	thromboembolic events
TFPI	tissue factor pathway inhibitor
TG	thrombin generation
TGA	thrombin generation assay
TMA	thrombotic microangiopathy
ULN	upper limit of normal
WFH	World Federation of Hemophilia
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 17 September 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult and paediatric patients with haemophilia A without factor VIII (FVIII) inhibitors who have mild or moderate disease for whom prophylaxis is clinically indicated. Consequently, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC and Section 1 of the package leaflet are updated. In addition, Section 4.2 is updated to make it clear that the maintenance dose for Hemlibra applies from week 5 of dosing. The PIL is updated accordingly. Version 4.7 of the RMP has also been submitted.

Information on paediatric requirements

At the time of submission of the application, the PIP (EMEA-001839-PIP01-15) was completed (EMA/145369/2017).

The PDCO issued an opinion on compliance for the PIP (P/0196/2016).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	17 September 2021
Start of procedure:	30 October 2021
CHMP Co-Rapporteur Assessment Report	6 January 2022
CHMP Rapporteur Assessment Report	21 December 2021
PRAC Rapporteur Assessment Report	3 January 2022
CHMP Co-Rapporteur Critique	5 January 2022
PRAC members comments	5 January 2022
Updated PRAC Rapporteur Assessment Report	6 January 2022
PRAC Outcome	13 January 2022
CHMP members comments	19 January 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 January 2022
Request for supplementary information (RSI)	27 January 2022
CHMP Rapporteur Assessment Report	20 April 2022
PRAC Rapporteur Assessment Report	26 April 2022
PRAC Outcome	5 May 2022
CHMP members comments	10 May 2022
Updated CHMP Rapporteur Assessment Report	13 May 2022
Request for supplementary information (RSI)	19 May 2022
CHMP Rapporteur Assessment Report	13 September 2022
PRAC Rapporteur Assessment Report	16 September 2022
Ad hoc expert group meeting	22 September 2022
Updated PRAC Rapporteur Assessment Report	23 September 2022
PRAC Outcome	29 September 2022
CHMP members comments	3 October 2022
Updated CHMP Rapporteur Assessment Report	7 October 2022
Request for supplementary information (RSI)	13 October 2022
CHMP Rapporteur Assessment Report	15 November 2022
PRAC Rapporteur Assessment Report	18 November 2022
PRAC members comments	23 November 2022
Updated PRAC Rapporteur Assessment Report	25 November 2022
PRAC Outcome	1 December 2022
CHMP members comments	5 December 2022
Updated CHMP Rapporteur Assessment Report	8 December 2022
Opinion	15 December 2022
The CHMP adopted a report on similarity of Hemlibra with Roctavian on date (Appendix 1)	15 December 2022

2. Scientific discussion

2.1. Introduction

In 2018, the MAH had already sought an extension of indication for the treatment of HA without inhibitors (EMEA/H/C/004406/II/02). Taking into account an advice of an ad hoc expert group and considering the lack of data and because of the risk of thrombosis in patient with appreciable endogenous FVIII activity when exposed to emicizumab and the risk of TMA, the CHMP concluded that no recommendation can be made to grant the indication in mild and moderate HA patients without inhibitors.

With this application, the MAH is now submitting data from HAVEN 6 clinical study which is a multicentre, open-label study to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients with mild or moderate haemophilia A without FVIII inhibitors.

2.1.1. Problem statement

Disease or condition

Haemophilia A (HA), which accounts for 80% of all cases of haemophilia, is an X-linked recessive bleeding disorder caused by a congenital deficiency of FVIII activity, an essential co-factor for the enzymatic reaction in which FIXa activates FX.

State the claimed therapeutic indication

This application seeks to extend the currently approved indication statement for emicizumab to include adult and paediatric patients with HA without FVIII inhibitors who have mild or moderate disease for whom prophylaxis is clinically indicated.

Epidemiology

The prevalence of HA at birth is approximately 24.6 in 100,000 males and it is estimated that 650,000 people worldwide are living with this condition (WFH 2020). Data on the prevalence of HA (FVIII activity <40%) in female carriers are scarce as women with HA have historically been underdiagnosed and undertreated.

Clinical presentation, diagnosis

In patients with haemophilia, the residual plasma level of clotting factor is considered to be the most critical predictor of spontaneous bleeding. It is on this basis that the severity of the HA patients is phenotypically classified by the residual endogenous level of FVIII activity into severe (<1%), moderate (≥1% and ≤5%) and mild (>5% and <40%) categories. Although classifications based exclusively on residual FVIII levels are often proportionally manifested in clinical presentations of types and numbers of bleeding episodes, phenotypic heterogeneity exists, some moderate patients (FVIII level ≥1%) may exhibit a severe bleeding phenotype and therefore may require regular prophylactic therapy.

Common clinical signs of HA include easy bruising, prolonged bleeding after trauma or surgery, spontaneous bleeding into joints, muscles, or soft tissues and intracranial haemorrhage. Joint bleeding is a hallmark of HA, repeated hemarthrosis causes inflammation and synovial degeneration leading to

chronic arthropathy, a common and major complication in patients with haemophilia. Patients with non-severe HA can experience significant and debilitating bleeding, including homophilic arthropathy in approximately 30% of patients, which affect patient's quality of life (QoL).

Management

The standard treatment for HA patients with severe bleeding phenotype is FVIII replacement therapy either episodic or prophylactic which are the same for patients with moderate and severe disease. Prophylactic therapy has been recognised as superior to episodic treatment. However, due to the high treatment burden of FVIII prophylaxis, a substantial fraction of patients is only treated episodically ("on demand") in response to the occurrence of bleeding symptoms.

The FVIII mimetic Hemlibra is currently indicated for routine prophylaxis of bleeding episodes in patients with HA with FVIII inhibitors or severe HA without inhibitors. The key benefits of Hemlibra are its subcutaneous route of administration, long half-life, high efficacy in bleed prevention, and reduction of the frequency of bleeding episodes.

In case of non-severe HA without inhibitor, treatment approaches depend significantly on patient's individual bleeding phenotype:

Desmopressin is approved across Europe for treatment of minor bleeds and to prevent bleedings in connection with surgery for patients with mild HA; however, the individual patient response is variable and needs to be tested at the start of treatment. Repeated administration may result in tachyphylaxis and increased risk of complications, therefore, use for more than 3 consecutive days is not recommended and other therapy is required for patients who require routine prophylaxis, such as patients with a more severe bleeding phenotype.

In addition, tranexamic acid (anti-fibrinolytics) is indicated in adults and children in Europe for prevention and treatment of haemorrhages due to general or local fibrinolysis. It is useful in treatment of superficial soft tissue and mucosal bleed either alone or combined with desmopressin, women and girls with haemophilia experiencing heavy menstrual bleeding are also commonly prescribed tranexamic acid.

Unmet need in patients with moderate and mild HA

Primary prophylaxis with FVIII is beneficial for patients with non-severe HA without inhibitors who present with more severe bleeding patterns and is used by approximately 30% of patients with non-severe HA. However, currently available FVIII replacement therapy often requiring IV administration 2 to 4 times a week constitutes a high treatment burden for patients which results in partial adoption and adherence to prophylaxis. In addition, the need for frequent venous access in turn often requires the use of central venous access device and delay initiation of prophylaxis in young children.

The CHESS (Cost of Haemophilia in Europe: a Socioeconomic Survey) -II and CHESS Paediatrics studies are retrospective, burden-of-illness studies in adults and children respectively, with HA without inhibitors carried out across European countries. These studies show that the daily life of patients is compromised due to their HA, with reduced physical and social activities, fewer opportunities and feelings of frustration.

A systematic literature review (SLR) aimed to determine the unmet medical need in patients on prophylactic treatment (excluding emicizumab) for congenital HA, in a population without inhibitors to FVIII, across all age groups and disease severities. This SLR found six observational studies with data on bleeding frequency in the moderate HA without FVIII inhibitors receiving FVIII prophylaxis. The results of these studies highlight the significant unmet medical need in the moderate HA population, as evidenced by considerable amount of bleeds, despite the heavy treatment burden. Data for mild patients are scarce and not reported separately.

In addition, currently available FVIII replacement therapy carries a high treatment burden and non-adherence continues to be a frequent problem due to it.

2.1.2. About the product

Emicizumab (also known as ACE910, RO5534262, and Hemlibra) is a recombinant, humanised, bispecific immunoglobulin G4 monoclonal antibody that bridges with moderate affinity activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of FVIII. In patients with HA, haemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of SC administration, removing the need for venous access. Finally, because of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of this antibody, use of emicizumab enables a dosing interval of once a week (QW), every 2 weeks (Q2W), or every 4 weeks (Q4W).

As of 23 July 2021, emicizumab is approved in 105 countries worldwide for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and paediatric patients with HA (congenital FVIII deficiency) with FVIII inhibitors. A total of 92 countries also have an approval in patients without FVIII inhibitors, including the United States, Canada, and Japan. In the European Union, the approval in patients without FVIII inhibitors is restricted to individuals with severe disease only.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

In 2018, the MAH had already sought an extension of indication for the treatment of HA without inhibitors (EMEA/H/C/004406/II/02). The advice of the ad hoc expert group convened on 25 January 2019 was the following:

- In principle, there would be a clinical need for safe and effective medicines for a subgroup of patients with moderate haemophilia for whom prophylaxis is considered appropriate (e.g., patients with FVIII levels less than 5%), particularly if easy to administer compared to frequent intravenous administration of existing options.

- However, in the case of Hemlibra, due to lack of exhaustive pre-clinical data, and lack of clinical data, it is not possible to conclude that the product has relevant efficacy in this population. It is indeed possible, that the efficacy observed in severe haemophilia cannot be easily extrapolated to patients with higher levels of FVIII. Furthermore, the submitted in vitro data are too limited to predict the complexity of the coagulation system in vivo and justify any extrapolation from severe to moderate haemophilia. More importantly, there are safety concerns from a pharmacodynamic point of view (long half-life; irreversibility of the effect) and the risk of acute or chronic thrombosis given the observation of thrombotic microangiopathy (TMA) and thromboembolic events in 5 patients who received emicizumab as routine prophylaxis in the clinical programme. Clinical and extensive non-clinical data should be available before the benefits and risks can be properly assessed in non-severe haemophilia.

- The company's laboratory and non-clinical data submitted are not sufficient to address the safety concerns (mainly the risk of thrombosis and TMA) and do not predict its clinical effects. There was also concern regarding how effective Hemlibra would be with measurable levels of circulating FVIII given the PK data. Clinical data (and extensive non-clinical data) should be available before the benefits and risks can be sufficiently assessed in patients with non-severe haemophilia.

- The experts agreed that a clinical trial in the relevant population is warranted to demonstrate efficacy. Concerning safety, extensive non-clinical studies and laboratory markers (such as markers of thrombosis and of thrombotic microangiopathy, thrombin, AT, D-Dimer, TGA with a suitable triggering agent, FVIII

central assessment) in this clinical study would provide useful information about the risk of thrombosis and TMA. A post-authorisation safety study would likely also be needed considering that a clinical trial may not be adequately powered to fully address safety concerns.

- In addition, the lack of data in children less than 1 year and the need to generate data in this group given that not only PK but also the coagulation system is likely to be different in the newborn children was also raised.

Taking into account the above advice of SAG and considering the lack of data and because of the risk of thrombosis in patient with appreciable endogenous FVIII activity when exposed to emicizumab and the risk of TMA, the CHMP concluded that no recommendation can be made to grant the indication in mild and moderate HA patients without inhibitors. Therefore, the approval in patients without inhibitors was restricted to subjects with severe HA at that time.

2.1.4. General comments on compliance with GCP

The MAH states that all Sponsor studies included in this submission were conducted in accordance with the principles of GCP, the principles of the Declaration of Helsinki and the local laws and regulations of the countries in which the studies were conducted. Ethics Committees and Institutional Review Boards reviewed and approved the studies as appropriate.

2.2. Non-clinical aspects

An addendum to the 2.4 Nonclinical Overview is submitted:

- To provide a rationale for why studies in mild to moderate hemophilia A animal models are not feasible and/or appropriate;
- To explain why the *in vitro* and *in vivo* data provide the best available basis for nonclinical risk assessment in this indication;
- To further support the low potential of procoagulant emicizumab – FVIII interactions.

Thrombotic events in patients with single factor coagulation deficits including hemophilia A are generally rare. The procoagulant interaction potential of emicizumab with FVIII has been addressed in a series of *in vitro* and *in vivo* nonclinical studies to identify risks for patients with low residual FVIII activity present in mild-to-moderate human hemophilia A or for patients receiving direct co-medication with FVIII.
Overall, FVIIIa cofactor activity and physiology is consistent with a relatively low prothrombotic liability. This is supported by the clinical experience of the therapeutic use of factor FVIII concentrates, which are generally associated with a relatively low risk of thrombotic adverse events, even at high doses [Coppola *et al.* 2012]. A prothrombotic risk has been described in patients with abnormally high plasma levels of FVIII [Kyrle *et al.* 2000].
The repeat-dose toxicity studies in *Cynomolgus* monkeys showed no indication of prothrombotic effects at high steady state emicizumab exposure on top of the normal endogenous FVIII activity. In particular, no thrombus-related histopathological changes were seen in any organs or tissues at emicizumab doses of up to 100 mg/kg/week in the 4-week IV toxicity study in *Cynomolgus* monkeys.
Similarly, no thrombus-associated gross or histopathological changes in any organs or tissues were seen in the pathology examinations at subcutaneous (SC) emicizumab doses of up to 30 mg/kg/week for 26 weeks. Clinically relevant markers of increased fibrinolysis (D-dimers, fibrinogen degradation product-FDP) typically observed when thrombi are formed were not elevated in these studies.
Because emicizumab is a humanised antibody, which is a foreign protein for *Cynomolgus* monkeys, anti-drug antibodies (ADAs) developed in animals in the repeated dose toxicology studies. However, neutralising antibodies were only observed in a minority of the animals.

As the majority of animals had relevant exposure levels to emicizumab during the entire dosing phases, these studies represent clinically relevant *in vivo* models and readouts to assess potential prothrombotic FVIII emicizumab interactions at chronic long term exposure conditions.
The effect of emicizumab on thrombus formation was also compared with the effect of FVIII treatment in an acute model of venous stasis in normo-coagulative *Cynomolgus* monkeys. In this study, provoked thrombus formation of emicizumab was equal to the thrombus formation induced by additive FVIII activity, indicating that the risk of FVIII-emicizumab interactions causing thrombosis is similar to the risk of high FVIII concentrations.
Although emicizumab facilitates the intrinsic tenase reaction, its affinity for FIXa or FX is however at least 10-fold lower than that of FVIIIa and accordingly, the FIXa-catalyzed FX activation rate is about 1/44 of the reaction rate induced by FVIIIa. Therefore, a low potential of synergistic interaction of emicizumab with FVIII was demonstrated *in-vitro* in a thrombin generation assay in this dossier. A small additive effect was noted at low dose emicizumab FVIII combinations. At FVIII concentrations of 1 IU/mL (corresponding to 100 IU/dL normocoagulative FVIII levels) emicizumab showed only marginal or no effect on thrombin generation (TG), indicating that FVIII effectively competes with emicizumab on FIXa-FX binding. The potency for a low additive procoagulant emicizumab FVIII interaction and the loss of emicizumab activity at increasing FVIII concentrations has also recently been reported by others in thrombin generation assays [Bravo et al. 2020], FXa generation assays [Minami et al. 2018] or in assays using modified clot waveform analysis [Nogami et al. 2018; Nakajima et al. 2020].
Emicizumab does not affect the inhibitory pathways of the clotting system. Emicizumab did not interfere with antithrombotic regulation of antithrombin or Tissue Factor Pathway Inhibitor (TFPI) activity *in vitro* [Noguchi-Sasaki *et al.* 2018].
Although unlike FVIIIa, emicizumab is not inactivated by APC (Activated Protein C)-mediated proteolysis, APC-catalyzed FVa proteolysis could however still downregulate emicizumab-driven hemostasis [Yada et *al.* 2018].
Further *in vivo* studies in particular studies mimicking the more complex mild to moderate hemophilia hemostatic and potential pro-thrombotic disease pathology of low FVIII levels have not been conducted because predictive models with a human translatable mild-to-moderate phenotype do not exist.
Although the severity of hemophilia A is generally associated with the grade of FVIII coagulant deficiency, the clinical severity does not always fully correlate with the FVIII *in vitro* clotting activity.
The World Federation of Hemophilia (WFH) has therefore defined the three major stages of hemophilia A as a relationship of bleeding severity to clotting factor levels [Srivastava *et al.* 2020]. Severe hemophilia A is defined as FVIII <1% of normal with spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge. The moderate form has typically FVIII of 1- 5% of normal with occasional spontaneous bleeding and prolonged bleeding with minor trauma or surgery, while mild hemophilia A with FVIII 5 to <40% of normal show severe bleeding with major trauma or surgery but only rare spontaneous bleeding.
Nonclinical research in hemophilia A has been focused on models of severe hemophilia A. Such models have been established via targeted ablation of the FVIII gene in mice and alternatively, strains of rats, dogs and sheep with a congenital FVIII deficiency have been selected and bred in colonies. These well-characterised disease models have mostly replaced experimentally induced acquired hemophilia conditions where FVIII is depleted with anti FVIII monoclonal antibodies. A natural hemophilia A disease to establish a primate hemophilia A colony has not been discovered in the *Cynomolgus* monkey.
For the nonclinical characterisation of emicizumab in *Cynomolgus* monkeys, a FVIII depleting procedure was therefore used as the method of choice to establish a relevant model of hemophilia A.
Defined by their complete FVIII functional deficiency, all these models mimic the severe form of hemophilia A in humans. Their bleeding phenotype is however variable and differs quite significantly between species and strains. There is consensus that these models do not fully and accurately recapitulate the bleeding phenotype of the human disease described above. Hemophilia A mice, unlike in man, in general, show no spontaneous bleeding. Spontaneous bleeding is one of the criteria important for

differentiation of the 3 gradings of the human disease, while in hemophilia A mice as in the human disease provoked injuries e.g., skin cuts are prone to severe and sometimes life-threatening bleeding complications. Despite such phenotypic differences, the experimental work done in severe hemophilia A models, have immensely helped to advance our understanding of hemostatic complications of factor VIII deficiency.
Experimentally induced provoked bleeding methods are, as in the studies with emicizumab, often applied to simulate more closely human spontaneous hemorrhagic pathologies.
Options to run studies with emicizumab in milder forms of hemophilia A than the originally submitted efficacy study of an acquired severe hemophilia A *Cynomolgus* monkey model are therefore not available in the NHP. Targeted partial FVIII depletion is not feasible and persistent long term low level steady-state FVIII substitution with porcine FVIII, which lacks cross-reactivity to the depleting monoclonal antibody, is also not an option due to the fast clearance of FVIII.
Recently, a modified FVIII deficient hemophilia A mouse model has been published as an opportunity to investigate emicizumab effects in an alternative species to the *Cynomolgus* monkey [Ferriere *et al.* 2020]. In this model, FVIII knock-out (ko) mice were rendered humanised by infusions of human FIX and FX prior to functional *in vivo* hemostasis tests. Of interest, the model has also been used to investigate the interaction of emicizumab with FVIII on hemostasis tests under such experimental short-term conditions. Consistent with *in vitro* results, the interaction data showed that emicizumab provides additional procoagulant activity at low but not at high concentrations of FVIII. While this is a valuable model for acute hemostasis readouts, it cannot be adapted to a functional stable steady-state *in vivo* mild to moderate long-term model due to the rapid clearance of FVIII, FIX and FX. This dilemma can theoretically be minimised by crossbreeding of FVIII ko mice with human factor IX and X (hFIX & X) knock-in mice as previously presented [Li et al. 2018]. The hFIX&X knock-in mice carry however already a mild hemophilic phenotype which limits the human translatability of such data. Furthermore, the need and problems with stable low steady-state FVIII substitution infusions remain, however, unsolved in this model.

2.2.1. Ecotoxicity/environmental risk assessment

Emicizumab is a recombinant bispecific monoclonal antibody. Emicizumab is a large protein with a molecular mass of approximately 146 kDa. Like all monoclonal antibodies, Emicizumab is not bioavailable by oral pathway but is extensively degraded in the patient's body by regular proteolytic mechanisms before excretion; hence, it is unlikely to result in a significant risk to the environment.
In support of this statement, a Manometric Respirometry Test showed that formulated Emicizumab (including excipients) is readily biodegradable. The mineralisation for the active substance Emicizumab (deducting the BOD for the excipients, which were shown to be readily biodegradable themselves) corresponded to 99% by day 28 and 90% at the end of the 10-day window. Therefore, while Emicizumab may normally be expected to be degraded by regular human protein metabolism in the patient, based on the attained ready biodegradability any Emicizumab that might escape human metabolic degradation may be safely expected to be biodegraded in sewage works and surface waters.
Ecotoxicity limit tests with green algae (*Desmodesmus subspicatus*), daphnids (*Daphnia magna*) and fish were performed with emicizumab formulated solution under GLP. All three limit tests consistently showed no adverse effects at the only tested concentration of 100 mg/l nominal concentration relating to the active substance emicizumab. These tests underpin a low risk for unexpected aquatic ecotoxicity of emicizumab, particularly considering the rapid, far-reaching removal expected through biodegradation in sewage treatment.
As supporting evidence, several monoclonal antibodies and other protein active pharmaceutical substances were tested for biodegradability and acute ecotoxicity. All unaltered monoclonal antibodies, without exception, proved to be readily biodegradable, resulting in very low predicted environmental concentrations in receiving waters. In addition, acute ecotoxicity was not remarkable for any of the monoclonal antibodies (Kümmerer and Hempel, 2010).

2.2.2. Discussion on non-clinical aspects

No non-clinical studies have been carried out to support the extension of indication of emicizumab (Hemlibra) for routine prophylaxis of bleeding episodes in patients with mild or moderate disease.

Instead, the MAH has provided a rationale for why studies in mild to moderate hemophilia A animal models are not feasible and/or appropriate, an explanation why the *in vitro* and *in vivo* data provide the best available basis for nonclinical risk assessment in this indication, and information to further support the low potential of procoagulant emicizumab – FVIII interactions.

Based on the considerations and data outlined above, it is concluded that none of the nonclinical *in vivo* models of hemophilia A would provide relevant information on the thrombosis risk at therapeutically relevant emicizumab exposure translatable to humans.
A human risk extrapolation for using emicizumab in mild-to-moderate hemophilia A patients can however be done using available *in vitro* and *in vivo* data. Due to its significantly lower affinity for FIXa or FX compared with FVIIIa, FVIIIa competes with increasing concentrations with emicizumab for FIXa-FX binding and activation, leading to a gradual loss of emicizumab activity indicated by a low additive procoagulant potential.

The data provided in this application demonstrated this overall low additive procoagulant and prothrombotic interaction potential of FVIII with emicizumab in various *in vitro* clotting assays. Further *in vivo* studies in a provoked thrombosis model in the *Cynomolgus* monkey and in particular long term toxicity studies in *Cynomolgus* monkey combining the two risk factors of normocoagulative endogenous FVIII activity with high plasma exposure of emicizumab showed no evidence for prothrombotic complications, using sensitive measurements like histopathology and serum markers of fibrinolysis.

2.2.3. Conclusion on the non-clinical aspects

None of the nonclinical *in vivo* models of haemophilia A would provide relevant information on the translatable to humans thrombosis risk to therapeutically relevant emicizumab exposure. Thus, new non clinical studies were not carried out, which is acceptable. Justifications taking into account available *in vitro* and *in vivo* data can be considered to support this application.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of emicizumab.

- Considering the above data, emicizumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

Table 1: Clinical development program for emicizumab in patients with HA:

Studies	Population	Design	Maintenance Dose / Regimen	Status / Efficacy Data Presented [a]
Phase III Studies				
BO41423 (HAVEN 6)	Patients of all ages with mild (FVIII level >5% and <40%) or moderate (FVIII level ≥1% and ≤5%) hemophilia A without inhibitors against FVIII	Open-label, multicenter, global, single-arm	Patient preference of: 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W	Ongoing / Interim analysis CCOD: 16 Apr 2021
BH29884 (HAVEN 1)	Patients ≥12 years of age with hemophilia A with inhibitors to FVIII	Open-label, multicenter, global, randomized	1.5 mg/kg QW	Completed / Primary analysis CCOD 25 Oct 2016
BH29992 (HAVEN 2)	Pediatric patients from birth to <12 years of age with hemophilia A with inhibitors to FVIII, with allowance of patients 12–17 years of age who weighed <40 kg	Open-label, multicenter, global, non-randomized	1.5 mg/kg QW 3 mg/kg Q2W 6 mg/kg Q4W	Completed / Primary analysis CCOD 30 Apr 2018
BH30071 (HAVEN 3)	Patients ≥12 years of age with severe hemophilia A (intrinsic FVIII level <1%) without inhibitors against FVIII who have been treated with FVIII agents to control or prevent bleeds	Open-label, multicenter, global, randomized	1.5 mg/kg QW 3 mg/kg Q2W	Ongoing / Primary analysis CCOD 15 Sep 2017
BO39182 (HAVEN 4)	Patients ≥12 years of age with hemophilia A with or without inhibitors to FVIII	Open-label, multicenter, global, non-randomized	6 mg/kg Q4W	Ongoing / Primary analysis CCOD 15 Dec 2017
JO39881 (HOHOEMI)	Japanese pediatric patients (<12 years old) with hemophilia A without inhibitors to FVIII	Open-label, multicenter, non-randomized	3 mg/kg Q2W 6 mg/kg Q4W	Completed
Phase I and Phase I/II Studies				
ACE001JP	Healthy Japanese (Part A) and Caucasian (Part B) adult male volunteers ≥20 and <45 years of age Part C: Japanese patients ≥12 and <60 years of age with or without FVIII inhibitors	Parts A and B: Placebo-controlled, randomized, double-blind, single ascending dose Part C: Open-label, inter-individual, multiple-ascending dose	Parts A/B: up to 1 mg/kg (single dose) Cohort C1: 0.3 mg/kg QW Cohort C2: 1 mg/kg QW Cohort C3: 3 mg/kg QW	Completed
ACE002JP	Eligible patients from ACE001JP Part C	Open-label extension of ACE001JP Part C	0.3 mg/kg QW 1 mg/kg QW 3 mg/kg QW	Completed
JP29574	Healthy adult male volunteers ≥20 and <45 years of age	Randomized, open-label, SC and IV single doses. Site of administration and absolute/relative bioavailability	Single doses: 1 mg/kg SC (different administration sites and formulations) or 0.25 mg/kg IV	Completed
Non-interventional Study				
BH29768	Cohort A: patients with FVIII inhibitors ≥12 years of age Cohort B: patients with FVIII inhibitors <12 years of age Cohort C: patients without FVIII inhibitors ≥12 years of age	Multi-cohort, multicenter, non-interventional	Not applicable	Completed

CCOD=clinical cutoff date; CSR: Clinical Study Report; QW: every week; Q2W: every 2 weeks; Q4W: every 4 weeks.

a In this clinical overview, the following data are presented: Efficacy data based on the primary CSRs (covering up to 24 weeks of treatment) for Studies BH29884 (HAVEN 1, CCOD: 25 Oct 2016), BH29992 (HAVEN 2, CCOD: 30 Apr 2018), BH30071 (HAVEN 3, CCOD: 15 Sep 2017), and BO39182 (HAVEN 4, CCOD: 15 Dec 2017), as well as BO41423 (HAVEN 6) data from the interim analysis with CCOD 16 Apr 2021.

In addition to the studies mentioned above, and as of 12 August 2021, emicizumab clinical program includes the following studies (Phase III and above):

• YO39309 (HAVEN 5): An ongoing Phase III study in Chinese patients with HA regardless of FVIII inhibitor status

• MO41787 (HAVEN 7): An ongoing global Phase IIIb study in infants (0-12 months old) with HA without inhibitors

• MO39129 (STASEY): A completed Phase IIIb global safety study in adult and adolescent (≥12 years old) patients with HA with inhibitors

• MO42245 (HemiNorth 2): A planned Phase IV study in adult and adolescent patients (12-51 years old) with severe HA without inhibitors in the Nordic countries

• MO42623 (BEYOND ABR): A planned global Phase IV study in adult and adolescent (≥12 years old) patients with severe or moderate hemophilia A without inhibitors

The original MAA, which resulted in approval for the indication in adult and paediatric patients with HA with inhibitors to FVIII in EU, comprised results from the pivotal Phase III Study HAVEN 1 in patients ≥12 years of age and interim results from the pivotal Study HAVEN 2 in children <12 years of age (along with supporting data from three Phase I and Phase I/II studies: ACE001JP, ACE002JP, and JP29574).

The 2018 Variation EMEA/H/C/004406/II/02 submission that granted the EOI to non-inhibitor patients with severe HA (FVIII level <1%) included clinical data from the pivotal Phase III Studies HAVEN 3 and HAVEN 4, and updated results from pivotal Study HAVEN 2 (along with supporting data from HAVEN 1 and ACE002JP).

The current application includes data from the new Phase III Study BO41423 (HAVEN 6), which was designed to provide clinical safety and efficacy evidence to support the EOI to include adult and paediatric patients of all ages with mild and moderate HA without inhibitors to FVIII that warrant prophylactic treatment.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol Number	Study Name	EU Countries	Non-EU Countries
BO41423	HAVEN 6	Belgium, France, Germany, Spain, Poland, The Netherlands	Canada, South Africa, United Kingdom, United States

2.3.2. Pharmacokinetics

The PK discussion for this variation comes from PK data of study BO41423 (HAVEN 6) and population PK analysis.

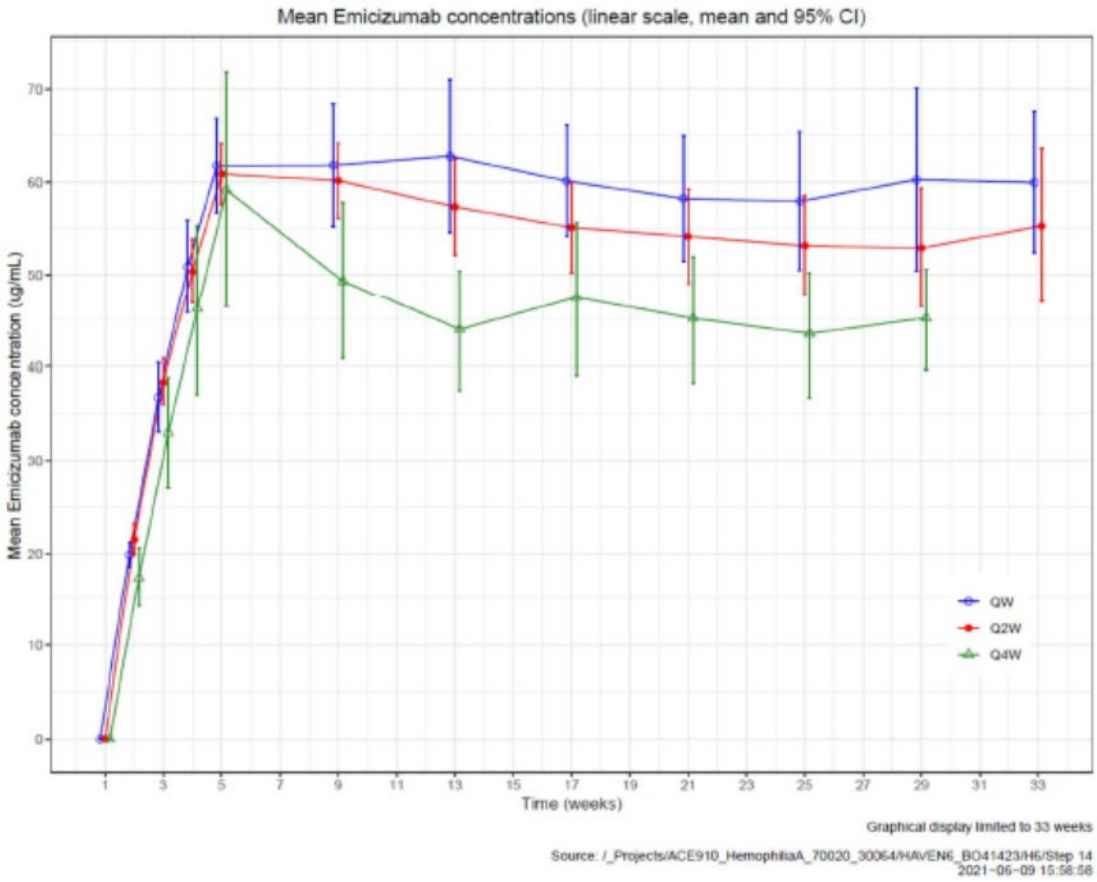
Study BO41423 (HAVEN 6)

In patients who received the emicizumab QW regimen, mean trough plasma concentrations of emicizumab increased with loading doses of 3 mg/kg QW to achieve 61.8 microg/mL at Week 5. Mean trough concentrations of approximately 60 microg/mL were maintained from Week 9 to Week 25 with maintenance doses of 1.5 mg/kg QW.

In patients who received the emicizumab Q2W regimen, mean trough plasma, concentrations of emicizumab increased with loading doses of 3 mg/kg QW to achieve 60.2 microg/mL at Week 5. Mean trough concentrations of approximately 53 microg/mL were maintained from Week 9 to Week 25 with maintenance doses of 3 mg/kg Q2W.

In patients who received the emicizumab Q4W regimen, mean trough plasma concentrations of emicizumab increased with loading doses of 3 mg/kg QW to achieve 59.2 microg/mL at Week 5. Mean trough concentrations of approximately 45 microg/mL were maintained from Week 9 to Week 25 with maintenance doses of 6 mg/kg Q4W.

Overall, the variability was moderate (coefficient of variations usually below 35%), with range of individual trough plasma concentrations after Week 5 between 19.1 and 128 microg/mL after QW doses of 1.5 mg/kg, between 14.0 and 110 microg/mL after Q2W doses of 3 mg/kg, and between 30.1 and 65.4 microg/mL after Q4W doses of 6 mg/kg.



QW=once weekly; Q2W=every 2 weeks; Q4W=every 4 weeks.
Data Source: CSR BO41423, Report 1107300, Figure 6.

Figure 1: Mean trough plasma emicizumab concentrations vs time profiles by dosing regimen

The PK data were generally similar for patients with mild haemophilia A and moderate haemophilia A.

However, trough concentrations were on average 15% higher than those reported with corresponding dosing regimens in HAVEN 1 to 4 studies, with inconsistent overlap of the 95% confidence intervals.

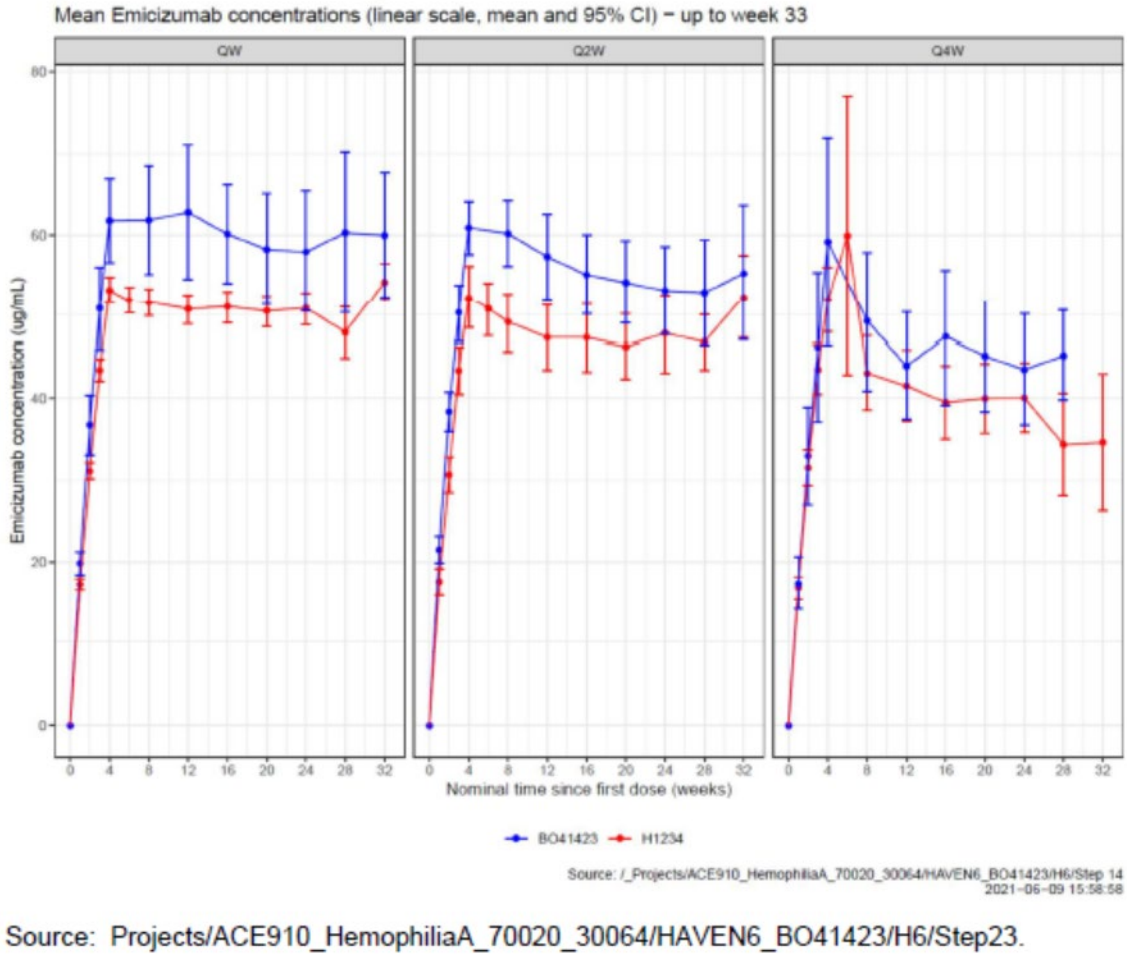


Figure 2: Mean emicizumab trough plasma concentrations in HAVEN 6 study and pooled HAVEN 1 to 4 studies

2.3.3. PK/PD modelling

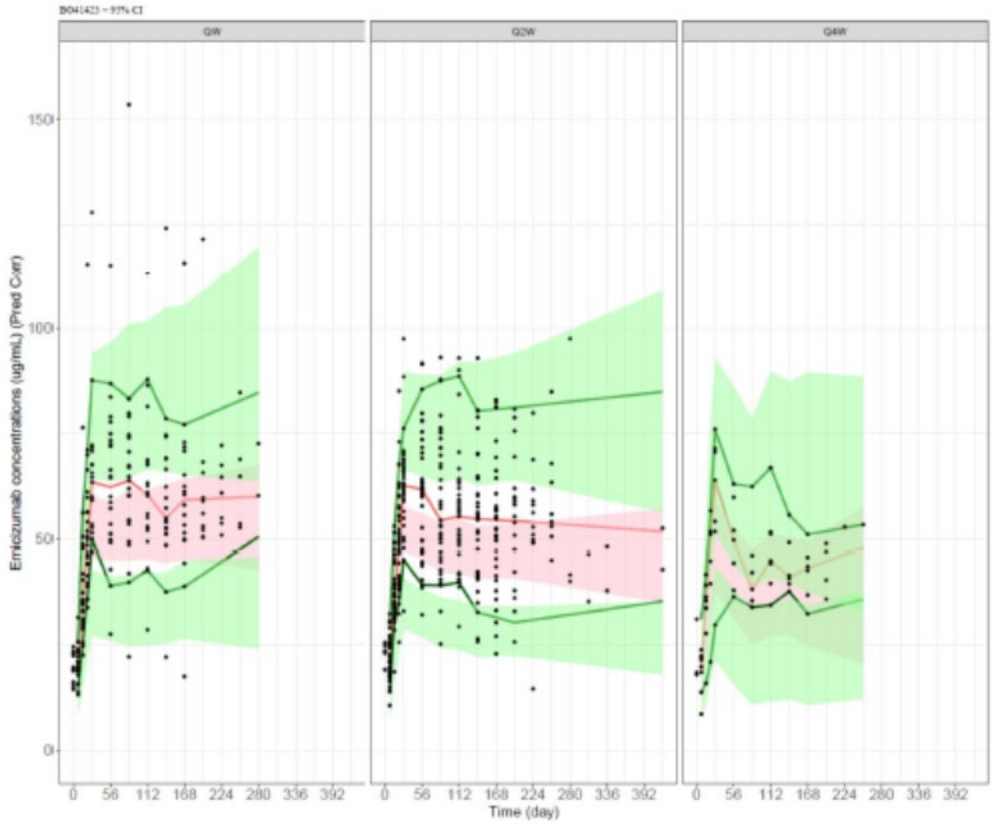
Population PK modelling

The population PK model developed in severe haemophilia A patients was able to properly predict the PK profiles in mild and moderate haemophilia A patients. For the QW and Q2W dosing regimen, the observed 5th percentiles and median are slightly above the 95% confidence interval for the initial part of the PK time course. Those small differences between observations and predictions are likely to be due to the limited sample size.

The principal difference between the previous HAVEN studies and Study BO41423 resides in the severity of the disease, with mild and moderate patients enrolled only in Study BO41423 while the vast majority of patients in the previous HAVEN studies had severe haemophilia (a few patients with inhibitors against FVIII had mild or moderate haemophilia). Of note, the presence of residual endogenous FVIII in patients with mild or moderate haemophilia A is not expected to interfere with the ELISA used to measure

emicizumab concentration. Furthermore, the pharmacokinetic data were generally similar between patients with mild haemophilia A (n=20) and with moderate haemophilia A (n=51) in Study BO41423, indicating that the difference in residual FVIII activity is not the reason behind the higher exposure observed in Study BO41423.

Of note, the increase of emicizumab concentrations in Study BO41423 remains overall limited, and the safety observed in Study BO41423 was comparable with other clinical studies of emicizumab. Altogether, this supports the use of emicizumab in patients with mild or moderate haemophilia A.



Points: Observed value; lines correspond to the median, 5th and 95th percentiles of the simulated values; shaded areas represent the 95% prediction intervals of the median, 5th and 95th percentiles of the simulated values.
Source: vpc_8_33_BO41423_2021-05-31

Figure 3: Visual predictive checks

2.3.4. Pharmacodynamics

FVIII activity

Chromogenic FVIII Activity Assay with Human Factors: FVIII activity between 1 U/dL (LLOQ of the assay) and 65 U/dL at baseline was observed in most patients reflecting their residual endogenous FVIII activity and the use of FVIII prior to study entry in some patients. Following initiation of treatment with emicizumab, mean reported FVIII activity increased to achieve approximately 38 U/dL (mean range across the three dosing regimens: 34.50-38.46 U/dL) at Week 5 and remained stable thereafter, while patients were treated with emicizumab. Sporadic elevated reported FVIII values observed in patients throughout the study duration are a consequence of FVIII use during the study. Declining reported FVIII

activity was observed in one patient from week 13 reaching a minimum of 4 U/dL at Week 25 with concomitant decrease in PK to ~20 ug/mL at Week 25. The patient tested negative for ADA.

Chromogenic FVIII Activity Assay with Bovine Factors: This assay is insensitive to emicizumab (no activity measured) and was used to monitor endogenous or infused FVIII activity. FVIII activity between 6 U/dL (LLOQ of the assay) and 55 U/dL was observed in 30 patients at baseline reflecting their endogenous FVIII activity or the use of FVIII prior to study entry in some patients. 39 patients had baseline FVIII activity <6 U/dL. 15 of the patients with detectable baseline FVIII activity had the diagnosis of mild HA. FVIII activity levels were maintained at 6-21 U/dL throughout the observation period in 14 patients reflecting their endogenous FVIII activity. 11 of these patients had the diagnosis of mild HA. The other patients with detectable baseline FVIII activity had FVIII activity below LLOQ at subsequent timepoints. The LLOQ of this assay is 6 U/dL, thus the endogenous FVIII activity was not detectable in the majority of the moderate patients, where activity levels between 1 U/dL and 5 U/dL are expected. Sporadic elevated FVIII values observed in patients throughout the study duration are a consequence of FVIII use during the study.

Factor VIII Protein

FVIII protein levels for most patients were between 2 U/dL (LLOQ of the assay) and 92 U/dL at baseline, reflecting endogenous and infused FVIII protein levels. FVIII protein levels were generally stable over the study period. One patient had a high FVIII protein level from baseline to week 5 (92-143 U/dL), which then decreased at week 9 and stayed lower (27-56 U/dL) for the rest of the study. FVIII activity measured using the chromogenic assay with bovine proteins, in this patient, was <6 U/dL throughout the study period. The patient remained negative for FVIII inhibitors throughout the study. Two patients had baseline FVIII protein levels of 55 U/dL and 63 U/dL, which doubled to week 2 and were maintained thereafter. Other biomarker measurements in these two patients at baseline failed due to questionable sample integrity, which may have also affected the FVIII protein level baseline measurements.

Thrombin Generation

Thrombin generation was detected at baseline in most patients reflecting endogenous FVIII activity or the use of FVIII by these patients prior to study entry and during the first week after initial emicizumab administration. Sporadic elevated peak height values observed in patients throughout the study duration across treatment arms are also a consequence of FVIII use during the study. Despite the effects of endogenous FVIII and concomitant FVIII usage on the time course of individual patients, the mean peak height can be seen to increase during emicizumab loading doses and stabilize at approximately 150 nM and 90 nM from Week 5 onward by Thrombin Generation Assay Triggered by Factor XIa or by Tissue Factor respectively. The observed trend in the mean values over time is similar between FXIa and TF triggered thrombin generation.

Activated Partial Thromboplastin Time (aPTT)

For most patients, aPTT was elevated at baseline as expected due to the deficiency of FVIII; aPTT values in the normal range at baseline in a number of patients likely reflects the use of FVIII therapy by these patients prior to study entry. After the 1st dose of emicizumab, aPTT was normalized at Week 2 in all but one patient, in whom aPTT was normalized at Week 3. This is likely a local lab data issue as the patients reported FVIII activity (measured with the chromogenic assay containing human proteins) increased from 2 U/dL at baseline to 13 U/dL at Week 2. aPTT remained largely within normal limits for the entire duration of treatment. Several patients had values consistently under the lower limit of normal, which is an expected pharmacodynamic effect of emicizumab.

2.3.5. Discussion on clinical pharmacology

Pharmacodynamic Results

Following initiation of treatment with emicizumab, mean reported FVIII activity increased to achieve approximately 38 U/dL (mean range across the three dosing regimens: 34.50-38.46 U/dL) at Week 5 and remained stable thereafter. Sporadic elevated reported FVIII values observed in patients throughout the study duration are a consequence of FVIII use during the study.

Endogenous FVIII activity and protein levels were generally stable over the study period.

Thrombin generation was detected at baseline in most patients. Sporadic elevated peak height values observed in patients throughout the study duration are also a consequence of FVIII use during the study. Despite the effects of endogenous FVIII and concomitant FVIII usage on the time course of individual patients, the mean peak height can be seen to increase during emicizumab loading doses and stabilise at approximately 150 nM (FXIa-triggered TG) or 90 nM (low TF-triggered TG) from Week 5 onward.

For most patients, aPTT was elevated at baseline as expected due to the deficiency of FVIII. After the first dose of emicizumab, aPTT was normalised at Week 2 in all but one patient, in whom aPTT was normalised at Week 3. aPTT remained within or below normal limits (reference ranges defined by local laboratories) for the entire duration of treatment.

2.3.6. Conclusions on clinical pharmacology

The analyses of biomarkers such as FVIII activity, FVIII protein, TGA triggered by FXIa/ TF and aPTT show consistent pharmacodynamics effects with emicizumab mechanism of action as well as with prior HAVEN studies.

2.4. Clinical efficacy

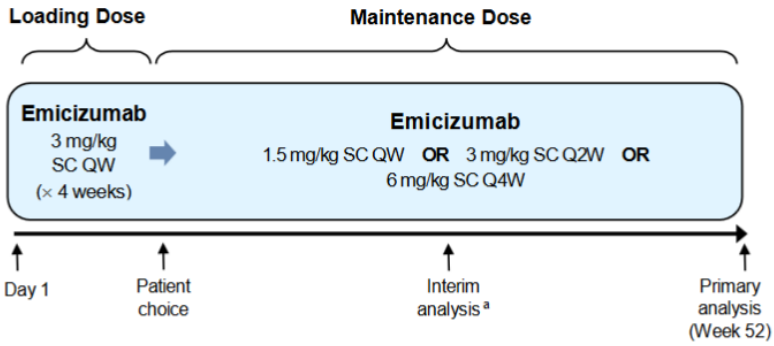
2.4.1. Main study

BO41423 (Haven 6): A multicentre, open-label study to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients with mild or moderate haemophilia A without FVIII inhibitors.

Methods

This is a multicentre, open-label, single-arm phase III study. Approximately 70 patients of all age groups were planned to be enrolled, including approximately 20 patients with mild HA and 50 patients with moderate HA that warrant prophylaxis. The interim analysis presented in this CSR was performed after 50 patients with moderate HA had completed 24 weeks of emicizumab treatment or had withdrawn from treatment.

Figure 1 Study Schema



QW = once a week; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: Patients who discontinue study drug prior to end of study will return to the clinic for a safety follow-up visit 24 weeks after the final dose of study drug.
[a] Interim data reviews may be performed at various timepoints.

During the study, individual bleeds were captured by the patient as the bleeds occur using a Bleed and Medication Questionnaire (BMQ) on a weekly basis to record whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a bleed (e.g., prior to surgery or short-term prophylaxis prior to increased activity) has been given. Breakthrough bleeds should be treated with FVIII at the lowest dose expected to achieve haemostasis. When a bleed has occurred, patients were required to report bleed information details (e.g., site, type, day, time) and medication details including reason for the use of FVIII (e.g., treatment of a bleed, preventative dose before activity), agent, start time, dose, route of administration, and number of infusions needed to treat the bleed via the BMQ.

Study participants

Key inclusion criteria

- Diagnosis of mild (FVIII level between >5% and<40%) or moderate (FVIII level between ≥1% and ≤5%) congenital Hemophilia A without FVIII inhibitors

- Weight ≥3 kg

- Need for prophylaxis based on investigator assessment

- A negative test for inhibitor (i.e., <0.6 BU/mL) within 8 weeks prior to enrollment

- No documented inhibitor (i.e., <0.6 BU/mL), FVIII half-life <6 hours, or FVIII recovery <66% in the last 5 years. Patients who completed successful immune tolerance induction (ITI) at least 5 years before screening are eligible, provided they have had no evidence of inhibitor recurrence (permanent or temporary) as may be indicated by a detection of an inhibitor, FVIII half-life <6 hours or FVIII recovery <66% since completing ITI.

- Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks prior to enrolment

- Adequate hematologic function, defined as platelet count ≥100,000 cells/μL and hemoglobin ≥8 g/dL (4.97 mmol/L) at the time of screening

- Adequate hepatic function defined as total bilirubin ≤1.5×age-adapted ULN (excluding Gilbert syndrome) and both AST and ALT ≤3×age-adapted ULN at the time of screening, and no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis

- Adequate renal function, defined as serum creatinine ≤2.5×age-adapted ULN and creatinine clearance ≥30 mL/min by Cockroft-Gault formula

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use effective contraception.

Key exclusion criteria

- Inherited or acquired bleeding disorder other than mild (FVIII level between >5% and<40%) or moderate (FVIII level between ≥1% and ≤5%) congenital haemophilia A

- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgement

- Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease

- Other conditions (e.g., certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis

- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection

- Planned surgery during the emicizumab loading dose phase. Surgeries in patients on emicizumab from Week 5 onwards are allowed.

- Known HIV infection with CD4 counts <200 cells/μL

- Concomitant disease, condition, significant abnormality on screening evaluation or laboratory tests, or treatment that could interfere with the conduct of the study, or that would in the opinion of the investigator, pose an additional unacceptable risk in administering study drug to the patient

- Receipt of any of the following: a/ An investigational drug to treat or reduce the risk of haemophilic bleeds within 5 half-lives of last drug administration with the exception of prior emicizumab prophylaxis (prior investigational or commercial emicizumab use is not an exclusion criterion); b/ a non-haemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter c/ any other investigational drug currently being administered or planned to be administered

- Pregnant or breastfeeding or intending to become pregnant during the study.

Treatments

The emicizumab dosing regimen was 4 loading doses of emicizumab 3 mg/kg SC QW for 4 weeks followed by a maintenance dose of either 1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W based on patient preference in this single-arm study. The chosen regimen needed to be maintained throughout the study until completion of at least 52W.

Dose-up titration

After 24W on prophylactic emicizumab, all patients with suboptimal bleed control (defined as ≥2 qualifying bleeds within 24W while on prophylactic emicizumab) could be offered the option to increase their dose to 3 mg/kg QW. A qualifying bleed was defined as spontaneous, verified by investigator (e.g., by imaging or physical examination), and occurring while on prophylactic emicizumab at steady state (after W5).

Permitted Therapy

- Regular FVIII prophylaxis may continue until the 2nd emicizumab loading dose to avoid bleeds before adequate emicizumab levels are reached. Concomitant routine FVIII prophylaxis is otherwise not permissible during the study.

- For the treatment of breakthrough bleeds, FVIII should be used at the lowest dose expected to achieve haemostasis. Given that circulating emicizumab may increase patients' coagulation potential, the doses required to achieve haemostasis may be lower than FVIII doses used prior to the study.

- Other drugs intended to control bleeds (e.g., bypassing agents, DDAVP, or antifibrinolytics).

- Drugs and therapies to treat AEs and use of topical antiseptics, anaesthetics, eye drops, etc.

- Drugs to treat an existing medical condition ongoing at study entry that does not violate the eligibility criteria (e.g., anti-retroviral therapy for HIV infections)

Prohibited Therapy

- Drugs that would affect haemostasis (e.g., aspirin, non-steroidal anti-inflammatory drugs that are not selective or preferential COX-2 inhibitors, or anticoagulants [other than to flush, dwell, or declot a venous access device]). However, drugs intended to control bleeding episodes or used in the context of surgeries or injuries (e.g., concussion) to prevent deterioration are allowed.

- Systemic immunomodulators (e.g., rituximab, interferon) other than anti-retroviral therapy

- Elective surgery during the emicizumab loading phase (prior to W5)

- Use of concomitant prophylactic regimen with FVIII or bypassing agents

Objectives

The objectives of this study were to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients of all ages with mild (FVIII level between >5% and<40%) or moderate HA (FVIII level between ≥1% and ≤5%) without inhibitors against FVIII whose bleeding phenotype warrants prophylactic treatment.

Outcomes/endpoints

Safety endpoints

- Incidence and severity of AE, with severity determined according to WHO Toxicity Grading Scale

- Incidence of thromboembolic events

- Incidence of thrombotic microangiopathy (TMA)

- Change from baseline in physical examination findings

- Change from baseline in and vital signs

- Change from baseline in ECG parameters

- Incidence of laboratory abnormalities

- Incidence and severity of injection-site reactions

- Incidence of AEs leading to drug discontinuation

- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

- Incidence and significance of anti-emicizumab antibodies

- Incidence of de novo development of FVIII inhibitor

Efficacy endpoints

Primary efficacy endpoint: Number of treated bleeds over time (i.e., bleed rate)

Annualized bleed rate (ABR) = (Number of bleeds/number of days during the efficacy period) × 365.25

72-hour rule*: Two bleeds of the same type (e.g., "joint", "muscle", or "other") and at the same anatomical location were considered to be one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed.*

Secondary efficacy endpoints:

- Number of all bleeds (i.e., those treated and untreated with FVIII) over time

- Number of joint bleeds over time

- Number of target joint bleeds over time. Target joints are defined as joints with ≥3 bleeds occurring in the same joint during the last 24 weeks or unresolved target joints (defined as a target joint that does not fulfil the criterion of ≤2 bleeds into this joint within a consecutive 12-month period.)

- Number of spontaneous bleeds over time (spontaneous bleed rate)

- Joint health, as assessed through use of the Haemophilia Joint Health Score (HJHS) at specified timepoints

- Health-related quality of life (HRQoL), as assessed through use of the Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) Questionnaire over time

- Preference for emicizumab compared with previous FVIII regimen, as assessed through use of the Emicizumab Preference Survey (EmiPref) at Week 17

- Effect of emicizumab prophylaxis treatment on physical activity compared with physical activity at baseline

- Effect of emicizumab prophylaxis treatment on menstruation heaviness and menstruation-related quality of life in female patients of childbearing potential, as assessed through the use of the Menstrual Bleeding Questionnaire (MBQ) and the Menstruation Diary (MD) with the Pictorial Blood Assessment Chart (PBAC) over time.

PK endpoints: Plasma concentration of emicizumab at specified timepoints

Immunogenicity endpoints:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

- Number and proportion of patients who develop anti-FVIII inhibitors (titer≥0.6 BU/mL) at specified timepoints

Exploratory endpoints:

Biomarker: PD parameters including but not limited to thrombin generation, FVIII activity, FVIII protein, D-dimer, and prothrombin fragment 1+2 (PF1+2) at regular intervals throughout the study and at times

of treated bleeds. Changes over time in biomarkers related to bone and joint health may also be explored.

Health status utility*:* change from baseline in EuroQol 5-Dimension 5-level Questionnaire (EQ-5D-5L) index utility and visual analog scale (VAS) scores at specified timepoints.

Assessment

Clinical outcomes assessments were collected through use of the following instruments:

Bleed medication questionnaire (BMQ), CATCH, EmiPref, EQ-5D-5L, MBQ, and MD with PBAC.

Sample size

The overall sample size of approximately 70 patients (approximately 50 patients with moderate disease and approximately 20 patients with mild disease) was based primarily on feasibility and clinical considerations, taking into account the limited number of patients with non-severe haemophilia A.

The current interim analysis, intended for regulatory submissions, was performed once 50 patients with moderate haemophilia A had completed 24 weeks of emicizumab treatment, were lost to follow-up, or withdrawn, whichever occurred first. This was considered to be a sufficient period of time to reliably assess the effect of emicizumab prophylaxis on bleed rate reduction.

Additional interim data reviews may be performed at various time points for regulatory submissions.

Randomisation

Not applicable, this is a single arm open-label study.

Blinding (masking)

Not applicable, this is a single arm open-label study.

Statistical methods

Analysis populations

The Treated population corresponds to all patients who received at least one dose of emicizumab. This population was the primary population for efficacy and safety analyses.

Multiplicity adjustment

There was no multiplicity adjustment planned for this study. The efficacy objectives of this study were investigated without any formal hypothesis testing. All analyses were of descriptive nature only.

Analysis of efficacy endpoints

Efficacy period

The efficacy period for each individual patient is defined as the number of days starting from the day of first emicizumab dose to the day of clinical cut-off or withdrawal from the study, whichever is earlier. For patients whose dose is up-titrated, the efficacy period ends a day prior to the first day on the up-titrated dose.

Bleed Rate

The efficacy of emicizumab was characterised by the number of bleeds over time. This was calculated using a negative binomial (NB) regression model, which accounts for different follow-up times, with time that each patient stayed in the study (efficacy period) included as an offset in the model. In addition, the number of bleeds was also annualized for each patient using the following formula:

Annualized bleed rate (ABR) = (Number of bleeds/number of days during the efficacy period) × 365.25.

The mean and median ABR based on the above formula using the observed numbers of bleeds instead of the number resulting from the model was calculated. In the case where the negative binomial model did not converge, this alternative derivation of the ABR were used as the sole method of analysis.

ABR corresponding to treated bleeds, all bleeds, treated joint bleeds, treated target joint bleeds, and treated spontaneous bleeds were analysed in a similar manner. These were summarised for all patients and listed for each patient individually. Several exploratory analyses were conducted to characterise the type (joint bleed, muscle bleed, other bleed), location, and frequency.

72-Hour Rule:

For treated bleeds, two bleeds of the same type (e.g., "joint", "muscle", or "other") and at the same anatomical location were considered to be one bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. The last treatment was defined as the last treatment before a new bleed occurred, either in the same or in a different location.

For non-treated bleeds (not followed by any treatments with coagulation factors before the recording of a subsequent bleed), this "72-Hour rule" is implemented by calculating a treatment-free period of 72 hours from the bleed itself. When implementing the 72-Hour rule, bleeds due to surgeries or procedures are excluded.

Health-Related Quality of Life (HRQoL)

For the CATCH questionnaire, descriptive analyses including summaries and 95% confidence intervals of change from baseline for each individual subscale were performed. Patient compliance with the CATCH was summarized at each assessed time point.

For the EmiPref patient preference questionnaire, the proportion of patients/caregivers preferring either emicizumab after 17 weeks of treatment or previous haemophilia treatment regimen was presented with 95% CIs. The proportion of patients selecting each reason for their preference and the top three preferred reasons affecting the patient preference were also summarized. Patient/caregiver compliance with the EmiPref was summarized for Week 17.

Summary statistics of the number and proportion of days away from school/work and days hospitalized was presented.

Joint Health and Physical Activity

The HJHS measures joint health of the joints most commonly affected by bleeding in haemophilia. The HJHS 2.1 provides joint specific total scores which are added to obtain the sum of joints totals and also a global gait score. These two scores are then added to obtain HJHS total score. For the HJHS, descriptive analyses were presented by time point.

Analyses were presented by time point.

Patients (≥5 years of age) were instructed to wear an accelerometer continuously (24 hr/day) every day for designated 2-week periods during the study as follows: Weeks 1-2, Weeks 12-13, Weeks 24-25, Weeks 36-37, and Weeks 48-49. All enrolled subjects who contributed to valid activity data were

analysed for activity. Relative change from baseline (Weeks 1−2 period) at Weeks 13 (Weeks 12−13 period), 25 (Weeks 24−25 period), 37 (Weeks 36−37 period), and 49 (Weeks 48−49 period) in mean moderate to vigorous physical activity (MVPA) and daily step count (DSC) were calculated and summarised. Subject-level data were also presented at each time point.

Menstruation Heaviness and Menstruation-related Quality of Life

MBQ was summarized descriptively over time, including change from baseline for individual subscales (heaviness, quality of life, irregularity, and pain) and total score. PBAC scores were summarized descriptively over time. If the number of female patients of childbearing potential was too low to provide reliable summaries, the data were listed and presented in individual patient plots, where applicable.

Missing data

On the electronic handheld device, it is not possible to leave questions unanswered or to enter partial data in one BMQ.

In the site data entry system, it is possible to leave the time (but not the date) of a treatment or a bleed blank because the caregiver might not be able to remember these in a reliable way.

In order to implement the 72-hour rule, it is assumed that the bleeds and treatments with missing time occurred at 12:00 a.m. If at a given day only the treatment time or the bleed time is partial and the other one complete, the partial time is assumed to be the same as the complete time. In case of multiple events per day, the last complete time is used.

Subgroup analyses

Additional descriptive summaries of both treated bleeds and all bleeds were computed for various subgroups of the study. The summaries included subgroup ABR and its 95% CIs. The main pre-specified subgroups are as follows:

- Age: 0 to <2, 2 to <6, 6 to <12, 12 to <18, 18 to <65, ≥65 years
- Race: Asian, Black or African American, White, Other
- Haemophilia severity: mild, moderate
- Number of target joints at study entry: no target joint, any target joint
- Previous treatment regimen: prior episodic, prior prophylactic
- Prior FVIII inhibitor: Yes/No
- Female patient: Yes/No
- Dosing regimens at enrolment: 1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W

Changes to planned analyses

The study first patient enrolled was on 10 February 2020, and the data cut-off for this interim was 16 April 2021. The Statistical Analysis Plan (SAP) was finalised on 15 June 2020 (4 months after first patient enrolled).

There were no changes in the planned analyses for the study before database lock.

Following database lock, coagulation marker (aPTT and PT/INR) values at four centres needed additional cleaning; thus these data were re-cleaned after the original lock date.

At the pre-submission meeting on 12th July 2021, several additional outputs were discussed and were subsequently generated. These included comparisons of bleeds before and after study entry (i.e., baseline vs post-baseline), as well as additional plots of coagulation markers.

Results

The submitted data present an interim analysis of efficacy, safety, PD, and PK data in Study HAVEN 6 based on a clinical cut-off date of 16 April 2021, after 50 patients with moderate HA without inhibitors had completed 24 weeks of emicizumab treatment, or withdrawn from treatment, or were lost to follow-up, whichever occurred first.

Participant flow

Of the 81 patients screened, 72 patients were enrolled in the study. The main reasons for screen failure were:

- meeting one of the exclusion criteria (3 patients),

- not meeting one of the inclusion criteria (3 patients)

- or other (not respecting the screening window/withdrew consent, other) (3 patients).

Table 2 Patient Disposition (All Enrolled Patients)

Patient Disposition, All Enrolled Patients
Protocol: BO41423 Snapshot Date: 26MAY2021 Cutoff Date: 16APR2021

Status	Emicizumab (N=72)
Patients enrolled	72 (100%)
Patients treated	71 (98.6%)
Patients who discontinued prematurely prior to 1st emicizumab administration	1 (1.4%)
Patients with duration of efficacy period <24 weeks	13 (18.1%)
Patients who completed 24 weeks in the study	59 (81.9%)
Patients with dose up-titration	0
Patients who started safety follow-up	0
Patients who completed safety follow-up	0
Patients who discontinued from the study	0
Patients who discontinued from treatment	0
Patients who completed the study	0

Patients can contribute to multiple statistics.

Program: root/clinical_studies/RO5534262/CDT30282/BO41423/share/data_analysis/prod/program/t_ds.sas
Output:
root/clinical_studies/RO5534262/CDT30282/BO41423/data_analysis/202106_CSRInterim/prod/output/t_ds_ALL_16APR2021_4I423.out
15JUL2021 11:14

Recruitment

First patient in: 10 February 2020. The 50th patient with moderate HA without inhibitors for triggering this interim analysis was enrolled on 30 October 2020. The recruitment is ongoing.

The cutoff date for analyses is 16 April 2021.

Patients were enrolled at 22 sites in 10 countries: UK (n=11), France (n=11), US (n=10), Germany (n=9), Belgium (n=8), South Africa (n=6), Spain (n=5), Canada (n=5), Poland (n=4) and The Netherlands (n=3).

Due to disruption of COVID-19, enrollment in the trial was paused from 25 March to 20 May 2020 at all sites and restarted. The impact of the pandemic was limited as the study was at the stage of recruitment

start with only 2 patients having been enrolled (in South Africa) when the pandemic occurred. Those 2 patients continued to receive treatment at home.

An eResearch Technology (ERT) security incident has happened on 20 September 2020 after 3 patients enrolled. The recruitment has been paused until full system restoration on 1st October 2020. There were no protocol deviations attributed to the incident or the management of the incident.

Conduct of the study

An amendment to protocol was approved on 18 November 2020. Key changes to the protocol are summarised below:

- The definition of target joint bleeds was clarified to include unresolved target joints: a target joint that does not fulfil the criterion of ≤ 2 bleeds into this joint within a consecutive 12-month period.

- Wording was corrected for consistency to state that the primary analysis will be conducted after 50 patients (not all patients) with moderate hemophilia A have completed 52 weeks of emicizumab treatment, are lost to follow-up, or have withdrawn, whichever occurs first

- Clarification was added to state that a mobile nurse may administer emicizumab or perform other assessments during home visits if necessary.

Protocol deviations

A total of 48 patients (67.6%) had 117 major protocol deviations. The deviations were most frequently related to activity monitor assessment with ≥3 days missing (n=28), absent BMQ data recorded on handheld device for > 2 consecutive weeks (n=15) and missing entire scheduled hematology and blood chemistry lab panels (n=14), missing HJHS and plasma samples not collected within the 48h of the initial FVIII given for bleed (n=6 each). 12 patients had 18 major protocol deviations due to the COVID-19 pandemic. Patients with missing BMQ records were interviewed by the investigator (or designee) for retrospective reporting of bleeding events and none of the reported major protocol deviations affected the evaluation of patient safety or efficacy.

No deviations led to exclusion of data from the analysis.

Table 3 Major Protocol Deviations (All Treated Patients)

Category Description	Emicizumab (N=71)
Total number of patients with at least one major protocol deviation	48 (67.6%)
Total number of major protocol deviations	117
Procedural	
Total patients	48 (67.6%)
Total protocol deviations	108
Activity monitor assessment with >= 3 days missing during Week 1-2, 12-13, 24-25, 36-37 or 48-49	28 (39.4%)
Absent BMQ data recorded on handheld device for more than 2 consecutive weeks	15 (21.1%)
Missing entire scheduled hematology and blood chemistry lab panels	14 (19.7%)
HJHS missing at baseline, week25, or week49	6 (8.5%)
Plasma samples not collected within the 48 hours of the initial coag. factor given for bleed	6 (8.5%)
Missing/incomplete EQ-5D-5L at baseline, Week25 or Week49	5 (7.0%)
Missing/incomplete CATCH at baseline, Week25 or Week49	3 (4.2%)
Missing/incomplete EmiPref at week17	2 (2.8%)
FVIII Inhibitor sample not collected at screening/week1 or at any subsequent time point	1 (1.4%)
Missing Menstrual Bleed Questionnaire	1 (1.4%)
Medication	
Total patients	5 (7.0%)
Total protocol deviations	6
Use of a prohibited therapy	3 (4.2%)
Emicizumab not received on QW, Q2W or Q4W basis, or delayed for more than 1 week	2 (2.8%)
Incorrect medication received or emicizumab dose deviation	1 (1.4%)
Inclusion Criteria	
Total patients	3 (4.2%)
Total protocol deviations	3
A negative test for inhibitor within 8 weeks prior to enrollment	1 (1.4%)
No adequate hematological function	1 (1.4%)
No adequate liver function	1 (1.4%)

Percentages are based on N in the column headings.

Program: root/clinical_studies/RO5534262/CDT30282/BO41423/share/data_analysis/prod/program/t_pd.sas
Output: root/clinical_studies/RO5534262/CDT30282/BO41423/data_analysis/202106_CSRInterim/prod/output/t_pd_TRT_16APR2021_41423.out
28MAY2021 15:19

Baseline data

Demographic characteristic

The majority of treated patients were male (69/71, 97.2%), and 2 female patients (2.8%) were treated. The median age was 23.0 years (range: 2-71) with 30 patients (42.3%) < 18 years and 41 patients (57.7%) ≥ 18 years of age. The median weight of patients at baseline was 75.0 kg (range: 13.5-141.0), and the median BMI was 25.16 kg/m2 (range: 14.1-45.0). The majority of patients were white (84.5%).

Table 4 Summary of Demographic Characteristics (Treated Population)

	Emicizumab (N=71)
Hemophilia Severity	
n	71
Mild	20 (28.2%)
Moderate	51 (71.8%)
Sex	
n	71
Male	69 (97.2%)
Female	2 (2.8%)
Age (years)	
n	71
Mean	25.9
SD	17.2
SEM	2
Median	23.0
Min - Max	2 - 71
Age Category 1	
n	71
< 18	30 (42.3%)
>= 18	41 (57.7%)
Age Category 2	
n	71
< 65	69 (97.2%)
>= 65	2 (2.8%)
Age Category 3	
n	71
2 - < 6	5 (7.0%)
6 - <12	11 (15.5%)
12 - <18	14 (19.7%)
18 - <65	39 (54.9%)
>= 65	2 (2.8%)
Race	
n	71
Asian	3 (4.2%)
Black or African American	6 (8.5%)
White	60 (84.5%)
Unknown	2 (2.8%)
Ethnicity	
n	71
Hispanic or Latino	1 (1.4%)
Not Hispanic or Latino	60 (84.5%)
Not Reported	7 (9.9%)
Unknown	3 (4.2%)

Baseline Haemophilia A Disease and Haemophilia A Treatment Characteristics

51 patients (71.8%) had moderate HA and 20 patients (28.2%) had mild HA without inhibitors.

At study entry, 37 patients (52.1%) were on prophylactic treatment and 34 patients (47.9%) were on episodic treatment. The primary reasons investigators considered prophylaxis warranted for patients was a history of frequent bleeds (39/71, 54.9%), and/or history of frequent joint bleeds (32/71, 45.1%), and/or history of severe bleeding (15/71, 21.1%), and/or prevention of traumatic bleeds (9/71, 12.7%) and other (5/71, 7.0%). Two female patients were menarchal and had menstrual bleed history. Neither had heavy bleeding patterns but one had moderate flow and bleeding duration of 8-13 days.

In the 24 weeks prior to enrolment, the median number of bleeds was 2.0 (range: 0-60). The overall proportion of patients with target joints (defined as at least 3 bleeds into the same joint over 24 weeks, or an unresolved target joint) was 33.8%. Target joints most frequently included the knee and ankle. 38 treated patients (53.5%) received prophylactic FVIII treatment (57.9% of patients were using FVIII short acting and 42.1% were using FVIII long acting) and 34 patients (46.5%) received episodic FVIII treatment (87.2% receiving FVIII and 15.4% receiving FVIII long acting).

Table 5 Hemophilia A History (Treated Population)

	Emicizumab (N=71)
Hemophilia severity at baseline	
n	71
Mild	20 (28.2%)
Moderate	51 (71.8%)
Current Prophylactic/Episodic Status	
n	71
Prophylactic	37 (52.1%)
Episodic	34 (47.9%)
Reason why patient warrant prophylaxis*	
n	71
History of Frequent Bleeding	39 (54.9%)
History of Frequent Joint Bleeding	32 (45.1%)
History of Severe Bleeding	15 (21.1%)
Prevention of Traumatic Bleeds	9 (12.7%)
Other	5 (7.0%)
Location of severe bleeding (reason why patient warrant prophylaxis)*	
n	15
Joint Bleed	9 (60.0%)
Muscle Bleed	4 (26.7%)
Other Bleed	4 (26.7%)
Number of bleeds per year prior to study entry/regular prophylaxis	
n	24
Mean (SD)	8.4 (12.5)
Median	4.5
Min - Max	0 - 60
Number of joint bleeds per year prior to study entry/regular prophylaxis	
n	17
Mean (SD)	11.9 (28.4)
Median	3.0
Min - Max	0 - 120
Prior episodic treatment in the last 24 weeks*	
n	39
Factor VIII	34 (87.2%)
Factor VIII long acting	6 (15.4%)
Desmopressin (DDAVP)	1 (2.6%)
Aminocaproic acid	0
Tranexamic acid	3 (7.7%)
Prior prophylactic treatment in the last 24 weeks*	
n	38
Factor VIII	22 (57.9%)
Factor VIII long acting	16 (42.1%)

* Multiple answers are possible.
n represents the number of patients contributing to summary statistics.
Percentages are based on n.

Table 6 Summary of Bleeding Events in the Last 24 Weeks Prior to Study Entry (Treated Population)

	Emicizumab (N=71)
Number of bleeds in the past 24 weeks	
n	71
Mean (SD)	3.4 (7.5)
Median	2.0
IQR	0.0 - 4.0
Min - Max	0 - 60
<9	67 (94.4%)
>=9	4 (5.6%)
Number of target joints prior to study entry	
n	71
Mean (SD)	0.6 (1.2)
Median	0.0
IQR	0.0 - 1.0
Min - Max	0 - 8
No target joint	47 (66.2%)
Any target joint(s)	24 (33.8%)
1 joint	13 (54.2%)
>1 joints	11 (45.8%)
Location of target joint(s) at study entry*	
n	24
Left shoulder	1 (4.2%)
Left elbow	3 (12.5%)
Left hip	2 (8.3%)
Left knee	7 (29.2%)
Right elbow	3 (12.5%)
Right hip	2 (8.3%)
Right knee	11 (45.8%)
Right ankle	10 (41.7%)

* Multiple answers are possible.
All data as collected on eCRF.
n represents the number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).

Prior disease other than Haemophilia A

The majority of the enrolled patients (71.8%) reported at least one baseline medical condition other than HA. The most frequently reported disorders were haemophilic arthropathy (11.3%), hypertension (9.9%), arthropathy (8.5%), seasonal allergy (7.0%), headache (7.0%), and pain (7%).

Surgeries and Procedures

A total of 43 patients (60.6%) reported surgeries and procedures prior to participating in the study. There was not a specific type of surgery/procedure that was commonly reported across patients as each surgery/procedure type was reported in ≤2 patients each.

Previous and concomitant treatments

Concerning the concomitant Haemophilia A treatments, the most frequently used class was antihemorrhagics (FVIII) reported in 8 (11.3%) patients.

Regarding non-haemophilia A treatment, the majority of patients (57.7%) were receiving at least one treatment at baseline. The most common treatment (i.e., received by > 10% patients) were analgesics, reported for 14 (19.7%) patients.

Numbers analysed

At the CCOD for this interim CSR, 71 patients started study treatment, a total of 59 (83.1%) patients completed at least 24 weeks in the efficacy period (10 with mild HA and 49 with moderate HA).

Outcomes and estimation

Table 7 Observation time (Treated Population)

	Emicizumab (N=71)
Efficacy Period (weeks)	
n	71
Mean (SD)	29.47 (8.77)
Median	27.57
IQR	24.29 - 33.57
Min - Max	6.6 - 61.7
Efficacy Period (week categories)	
>0 w	71 (100%)
>=4 w	71 (100%)
>=12 w	70 (98.6%)
>=24 w	59 (83.1%)
>=36 w	14 (19.7%)
>=48 w	2 (2.8%)

n represents the number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).

The efficacy period was defined as the number of days starting from the fist emicizumab dose to the day of CCOD or withdrawal from the study whichever is earlier. The median efficacy period duration was 27.57 weeks for all treated patients, 23.86 weeks for patients with mild HA, and 30.29 weeks for patients with moderate HA.

Primary efficacy endpoint: treated bleeds

"Treated bleeds" was defined as bleed followed by "treatment for bleed", bleeds due to surgery/procedure are excluded. The negative binomial regression model-based ABR for treated bleeds was 0.8 (95% CI: 0.41, 1.46). The calculated mean ABR (0.7 [95% CI: 0.01, 5.13]) was consistent with the model based ABR. The median ABR was 0 (IQR: 0.0-0.00)

68 patients (95.8%) had 0-3 treated bleeds while receiving emicizumab prophylaxis including 57 patients (80.3%) experienced zero treated bleeds.

Secondary Bleed-Related Endpoints

All Bleeds

"All bleeds" included both treated and non-treated bleeds, bleeds due to surgery/procedure are excluded. The NB regression model-based ABR "All bleeds" (those treated and untreated with coagulation factors) was 2.3 (95% CI: 1.63, 3.10). The calculated mean ABR (2.2 [95% CI: 0.31, 7.53]) was consistent with the model-based ABR. The median ABR was 1.5 (IQR: 0.00-3.79).

62 patients (87.3%) experienced 0-3 all bleeds while receiving emicizumab prophylaxis including 33 patients (46.5%) experienced zero all bleeds. Among all treated patients, 14 patients had >2 all bleeds (5 patients with 3 bleeds, 6 patients with 4 bleeds, 1 patient with 5 bleeds, 1 patient with 8 bleeds, and 1 patient with 10 bleeds). All 3 patients with >4 bleeds had moderate HA.

Treated Joint Bleeds

The NB regression model-based ABR for treated joint bleeds was 0.3 (95% CI: 0.12, 0.65). The calculated mean ABR (0.3 [95% CI: 0.00, 4.24]) was consistent with the model-based ABR. The median ABR was 0.0 (IQR: 0.00-0.00).

70 patients (98.6%) experienced 0-3 treated joint bleeds while receiving emicizumab prophylaxis including 64 patients (90.1%) had zero treated joint bleeds, 5 patients had 1 treated joint bleed, 1 patient had 2 treated joint bleeds. Only 1 patient experienced 4 treated joint bleeds, of which 1 was a target joint site (right hip). This patient has frequent joint bleeding recorded in the hemophilia history

with 9 joint bleeds experienced in the 24 weeks prior to study entry (4 spontaneous and 5 traumatic). All reported treated joint bleeds were traumatic (11 out of 11 bleeds).

Treated Spontaneous Bleeds

The NB regression model-based ABR for treated spontaneous bleeds was 0.1 (95% CI: 0.02, 0.23). The calculated mean ABR (0.1 [95% CI: 0.00, 3.82]) was consistent with the model-based ABR. The median ABR was 0.0 (IQR: 0.00-0.00). 68 patients (95.8%) experienced zero treated spontaneous bleeds while receiving emicizumab prophylaxis was 95.8% (68 patients). Overall, 3 patients experienced 1 spontaneous treated bleed. The site location of these bleeds was categorized as "Other" (i.e., not joint or muscle).

Treated Target Joint Bleeds

The NB regression model-based ABR for treated target joint bleeds (including unresolved target joints) did not converge due to a low number of bleeds with short follow-up times. The calculated mean ABR was 0.1 (95% CI: 0.00, 3.93). The median ABR was 0.00 (IQR: 0.00-0.00). 67 patients (94.4%) experienced zero treated target joint bleeds while receiving emicizumab prophylaxis. 4 patients had 1 treated target joint bleed. One patient experienced a traumatic joint bleed during loading phase of emicizumab, through which this joint newly met conservative criteria of target joint (i.e., ≥3 joint bleeds, including traumatic bleeds, within a 6-month period), otherwise no patients experienced joint bleeds by which criteria of target joint would have been met.

Table 8 Summary of Bleed-Related Endpoints (BO41423 [HAVEN 6], All Treated Patients)

	Emicizumab (N=71)
PRIMARY EFFICACY ENDPOINT: TREATED BLEEDS [a]	
Patients with zero bleeds, n (%)	57 (80.3)
ABR, Model Based (95% CI)	0.8 (0.41, 1.46)
Mean ABR, Calculated (95% CI) [Min–Max]	0.7 (0.01, 5.13) [0.00–10.86]
Median ABR, Calculated (IQR)	0.0 (0.00–0.00)
SECONDARY BLEED-RELATED ENDPOINTS	
All bleeds [b]	
Patients with zero bleeds, n (%)	33 (46.5)
ABR, model based (95% CI)	2.3 (1.63, 3.10)
Mean ABR, calculated (95% CI) [min–max]	2.2 (0.31, 7.53) [0.00–15.14]
Median ABR, calculated (IQR)	1.5 (0.00–3.79)
Treated joint bleeds [c]	
Patients with zero bleeds, n (%)	64 (90.1)
ABR, model based (95% CI)	0.3 (0.12, 0.65)
Mean ABR, calculated (95% CI) [min–max]	0.3 (0.00, 4.24) [0.00–7.09]
Median ABR, calculated (IQR)	0.0 (0.00–0.00)

	Emicizumab (N=71)
Treated spontaneous bleeds [d]	
Patients with zero bleeds, n (%)	68 (95.8)
ABR, model based (95% CI)	0.1 (0.02, 0.23)
Mean ABR, calculated (95% CI) [min–max]	0.1 (0.00, 3.82) [0.00–1.89]
Median ABR, calculated (IQR)	0.0 (0.00–0.00)
Treated target joint bleeds [e]	
Patients with zero bleeds, n (%)	67 (94.4)
ABR, model based (95% CI)	Did not converge
Mean ABR, calculated (95% CI) [min–max]	0.1 (0.00, 3.93) [0.00–2.54]
Median ABR, calculated (IQR)	0.0 (0.00–0.00)

ABR=annualized bleeding rate; CI=confidence interval; IQR=interquartile range; min=minimum; max=maximum.

[a] Treated bleed: bleed followed by "treatment for bleed". Bleeds due to surgery/procedure are excluded.

[b] All bleeds: includes both treated and non-treated bleeds. Bleeds due to surgery/procedure are excluded.

[c] Treated joint bleeds: treated bleeds where bleed type is "joint" as reported in the Bleed and Medication Questionnaire with at least one of following symptoms: "increasing swelling or warmth of the skin over the joint", "increasing pain", or "decreased range of motion or difficulty using the joint compared with baseline" (primary definition). Bleeds due to surgery/procedure are excluded.

[d] Treated spontaneous bleed: a treated bleed with no other known contributing factor such as trauma or procedure/surgery. Bleeds due to surgery/procedure are excluded.

[e] Treated target joint bleeds: treated joint bleeds which occur in a target joint, defined as a joint in which ≥3 treated joint bleeds occurred during the last 24 weeks prior to study entry. Bleeds due to surgery/procedure are excluded.

Clinical cutoff date: 16 April 2021.

Source: Interim CSR BO41423, Report 1107300, Table 15, Table 17, Table 20, Table 21, Table 22.

Table 9 Overview of Efficacy – Bleed Related Endpoints (data cut-off, October 2021)

	Emicizumab (N=72)
Number of Patients	72
Treated Bleeds	
Patients with zero bleeds	48 (66.7%)
ABR, model based (95% CI)	0.9 [0.55;1.52]
Mean ABR, Calculated (95% CI)	0.9 [0.02; 5.48]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.98]
Min-Max, Calculated ABR	[0.00-7.05]
All Bleeds	
Patients with zero bleeds	24 (33.3%)
ABR, model based (95% CI)	2.3 [1.67;3.12]
Mean ABR, Calculated (95% CI)	2.3 [0.35; 7.75]
Median ABR, Calculated (IQR)	1.0 [0.00; 3.11]
Min-Max, Calculated ABR	[0.00-21.04]
Treated Spontaneous Bleeds	
Patients with zero bleeds	59 (81.9%)
ABR, model based (95% CI)	0.2 [0.11;0.33]
Mean ABR, Calculated (95% CI)	0.3 [0.00; 4.23]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-6.09]
Treated Joint Bleeds	
Patients with zero bleeds	64 (88.9%)
ABR, model based (95% CI)	0.2 [0.09;0.57]
Mean ABR, Calculated (95% CI)	0.2 [0.00; 4.15]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-3.63]
Treated Target Joint Bleeds	
Patients with zero bleeds	68 (94.4%)
ABR, model based (95% CI)	0.1 [0.03;0.40]
Mean ABR, Calculated (95% CI)	0.1 [0.00; 3.92]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-3.21]

Bleeds due to surgery/procedure are excluded.

Exploratory Bleed-Related Endpoints

Bleeds by location and type

Treated bleeds occurred most frequently in the joints (48.5%, 16/33 bleeds) and in other locations (i.e, not joint or muscle) (45.5%, 15/33 bleeds). Only a minority of treated bleeds occurred in the muscles (6.1%, 2/33). Treated bleeds most frequently occurred in the knee (other bleed; 5/33 bleeds), ankle (joint bleed, 4/33 bleeds), and knee (joint bleed, 4/33 bleeds).

Bleeds by cause

For treated bleeds, 90.9% (30 of 33 bleeds) were traumatic bleeds while the rest 9.1% (3/33 bleeds), were spontaneous bleeds (excluding bleeds due to surgery/procedure).

For all bleeds (irrespective of the 72-hour rule and including bleeds due to surgery/procedure), 67.9% (74/109 bleeds) were traumatic bleeds, 22.9% (25/109 bleeds) were spontaneous bleeds, and 9.2% (10/109 bleeds) were due to surgery/procedure.

Symptoms of joint bleeds

Bleed-associated symptoms were collected for muscle and joint bleeds in patients 12 years and older. There were 28 joint bleeds. The most common symptoms of treated joint bleeds were increased pain (39.3%, 11/28 bleeds), decreased range of motion/difficulty using arm or leg compared to baseline (35.7%, 10/28 bleeds), and increased swelling/warmth of the skin (17.9%, 5/28 bleeds).

The most common symptoms of all bleeds in a joint were increased pain (50.0%, 14/28 bleeds), decreased range of motion/difficulty using arm or leg compared to baseline (46.4%, 13/28 bleeds), and increased swelling/warmth of the skin (32.1%, 9/28 bleeds).

All bleeds irrespective of the 72-hour rule and including bleeds due to surgery/procedure

A total of 109 bleeds irrespective of the 72-hour rule and including bleeds due to surgery/procedure were reported. They occurred most frequently (70.6%, 77/109 bleeds) in locations other than joints or muscle in 28 patients. All bleeds occurred predominantly in the nose (17/109 bleeds), fingers/thumb (other; 11/109 bleeds), and mouth (11/109 bleeds). The number of patients who experienced joint bleeds and muscle bleeds is 15 and 4 respectively.

Post-hoc analysis of ABR for All bleeds

Table 10 Median ABR Prior to Study *versus* ABR at Week 25 (All Bleeds) by Subgroup

	Estimated ABR* Prior to Study Entry (Median [IQR])	Calculated ABR for All Bleeds (72-hr rule) (Median [IQR])
All Treated Patients	4.3 [0.00-8.69]	1.5 [0.00-3.79]
Hemophilia Severity at Baseline		
Mild	2.2 [0.00-8.69]	0.0 [0.00-2.34]
Moderate	4.3 [0.00-8.69]	1.7 [0.00-3.90]
Baseline Treatment Regimen		
Episodic	6.5 [2.17-13.04]	0.9 [0.00-4.07]
Prophylactic	2.2 [0.00-4.35]	1.5 [0.00-3.32]

ABR=annualized bleed rate; IQR=interquartile range

*The estimated Annualized Bleed Rate (ABR) prior to study-entry is derived from patient's number of bleeds over the last 24 weeks prior to study annualized by dividing by 168 days and then multiplying by 365.25 days.

Post-hoc analysis showed that the ABR for All Bleeds was numerically reduced from an estimated 4.3 (0.0-8.7) median calculated ABR prior to study entry to an ABR of 1.5 (0.0-3.4) in the study, irrespective of haemophilia severity or previous use of episodic or prophylactic FVIII. 13 patients had an increase in their ABR during emicizumab treatment compared to estimated ABR prior to study entry. Most of these bleeds were traumatic or procedure/surgery-related and without treatment. Spontaneous bleeds (n=7) were mostly nosebleeds (n=4). One patient recorded one spontaneous treated bleed. 20 patients had stable ABR and 38 patients had a decrease in ABR during emicizumab treatment. 7 of the 38 patients with a decrease in ABR during emicizumab treatment had a major decrease to an ABR <1 compared to an estimated ABR >10 prior study entry. This occurred more frequently in patients on prior episodic treatment (n=5) and was observed both in patients with mild (n=3) and moderate (n=4) HA.

Of the 24 patients (33.8%, including 6 patients with mild HA) who presented target joint bleeds (including unresolved target joints) prior to treatment start, 7 had bleeds in their target joints and of those 4 required additional treatment for target joint bleeds during the efficacy period.

ABR subgroup analysis

Table 11 Subgroup Analysis: Model-Based ABR for Treated Bleeds

		Emicizumab		
Subgroup		**Patients**	**ABR**	**95% CI**
All		71	0.8	0.41, 1.46
Age	<18	30	0.9	0.29, 3.09
	≥18	41	0.6	0.29, 1.25
Hemophilia severity	Mild	20	0.3	0.10, 0.97
	Moderate	51	0.9	0.43, 1.89
Presence of target joints	No target joint	47	0.6	0.24, 1.54
	Any target joint	24	1.1	0.45, 2.59
Previous treatment regimen	Episodic	34	1.1	0.47, 2.70
	Prophylactic	37	0.4	0.19, 1.07
Dosing regimen at enrollment	1.5 mg/kg QW	24	1.0	0.46, 2.28
	3 mg/kg Q2W	39	0.5	0.17, 1.67
	6 mg/kg Q4W	8	1.3	0.23, 6.84

ABR=annualized bleeding rate; CI=confidence interval; QW=every week; Q2W=every 2 weeks; Q4W=every 4 weeks.

Note: Treated bleed is a bleed followed by "treatment for bleed". Bleeds due to surgery/procedure are excluded.

Source: Interim CSR BO41423, Report 1107300, Table 23.

Secondary Health-Related Quality of Life and Health Status Endpoints

CATCH Questionnaire (Weeks 1, 13, and 25)

Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) questionnaire was used to assess the benefit of emicizumab therapy.

Adult patients: By Week 25, there were few changes from baseline in most of the CATCH domains, with the exception of Treatment Burden which had a mean (SD) 15.25-point (21.41) improvement.

Pediatric patients (<18 years): By Week 25, there were few changes from baseline in most of the domains, with the exception of Treatment Burden which showed a mean (SD) 22.17-point (26.74) increase (indicating lower perceived treatment burden of hemophilia) as well as a reduction in Recreational Activity risk perception (mean [SD] change of -10.27 [24.60] from baseline; however given the interquartile range, it should be interpreted with caution). A smaller change in Social Activity risk perception was also observed (mean [SD] change of -6.72 [13.71] from baseline).

Caregivers: CATCH assessments included only domains for preoccupation and treatment burden. Given the small sample size, results should be interpreted with caution. For both domains, a decrease in raw score was observed at Week 25 compared with baseline (Table 26), indicating an improvement in preoccupation related to hemophilia (mean [SD] change of -12.24 [7.91] from baseline) and a reduced perceived burden of hemophilia treatment (mean [SD] change of -14.29 [10.63] from baseline).

Treatment burden demonstrated improvement in both the treated adult and pediatric population. Among caregivers, the treatment burden and preoccupation domains of the CATCH indicated an improvement, but given the sample size these trends should be interpreted with caution.

Emicizumab Preference Survey (EmiPref at Week 17)

Based on the EmiPref, 96.0% of patients (48 of 50 patients) preferred SC emicizumab over their former IV hemophilia treatment and the results were aligned across almost all adolescent, adults, and caregivers. The most frequently reported reasons for this preference were "route of administration was easier" (27.1%), "frequency of treatment was lower" (20.8%), and "administration was easier" (16.7%).

Joint Health (Hemophilia Joint Health Survey HJHS at week 25)

For HJHS, a higher score indicates worse joint health. Clinically relevant improvements are defined as a ≥4-point reduction in Total HJHS or a ≥2-point reduction in HJHS joints domain. At Week 25, a trend toward improvement in joint health from baseline to Week 25 was observed in HAVEN 6 among the 48 patients who had scores. The mean (SD) change from baseline to Week 25 in HJHS total score was -1.58 (3.17). The change from baseline to Week 25 for Calculated Sum of Joint Totals was -1.77 (2.94).

Physical Activity

Overall, the daily step count (DSC) was stable among treated patients between baseline (5922 median DSC) and Week 25 (6117 median DSC). A stable trend was also observed for the time spent by the treated patients in moderate to vigorous physical activity at baseline and at Week 25. The mean change (SD) from baseline to Week 25 in moderate physical activity was 5 (43) minutes (12.5% [42.8%]) and in vigorous physical activity was -3 (14) minutes (7.7% [66.2%]).

Menstruation Heaviness and Menstruation-Related Quality of Life (MBQ Menstrual Bleeding Questionnaire and PBAC Menstruation Diary with the Pictorial Blood Assessment Chart)

Health Status: EQ-5D-5L

EQ-5D-5L Visual Analog Scale Results at Week 25: The VAS is scored on a scale of 0-100. Higher scores are reflective of better health status. The mean (SD) EQ-5D-5L VAS score at baseline was high at 76.27 (18.99). At Week 25, the score was 80.49 (16.39), representing a mean change from baseline of 3.43 (10.03).

EQ-5D-5L Index Utility Score at Week 25: The EQ-5D-5L Index Utility Score is scored on a scale of 0-1. Higher scores are indicative of better health status. The mean (SD) EQ-5D-5L Index Utility score at baseline was high at 0.79 (0.21). At Week 25, the score was 0.80 (0.22).

Concomitant treatments for hemophilia A during the study

A total of 35 patients (49.3%) received a non-emicizumab hemophilia medication during the study, all of which were FVIII. Of these 35 patients, 15 patients were allowed to continue their hemophilia treatments up to the 2nd loading dose of emicizumab to ensure adequate bleed control until effective emicizumab levels were achieved; and 20 patients received a non-emicizumab hemophilia medication after their 2nd loading dose of emicizumab. 18 of whom used FVIII as treatment for a bleed, 7 of whom used FVIII as preventative for surgery/procedure, and 1 who used FVIII as preventative before activity.

Table 12 Non-emicizumab Hemophilia Medication (Treated Population), post 2nd Emicizumab Dose

	Emicizumab (N=71)
TOTAL	
Total number of patients with at least one treatment	20 (28.2%)
Total number of treatments	123
Purpose of the medication	
Preventative dose before activity	1 (1.4%)
Preventative dose for procedure/surgery	7 (9.9%)
Treatment for bleed	18 (25.4%)
FACTOR VIII (LONG-ACTING) [E.G. ELOCTA]	
Total number of patients with at least one treatment	8 (11.3%)
Total number of treatments	21
Purpose of the medication	
Preventative dose before activity	1 (1.4%)
Preventative dose for procedure/surgery	3 (4.2%)
Treatment for bleed	6 (8.5%)
FACTOR VIII (SHORT-ACTING) [E.G. ADVATE]	
Total number of patients with at least one treatment	12 (16.9%)
Total number of treatments	102
Purpose of the medication	
Preventative dose for procedure/surgery	4 (5.6%)
Treatment for bleed	12 (16.9%)

The majority of bleeds (n = 29) were treated with short-acting FVIII. The median cumulative dose per bleed was 58.48 units/kg (range: 21.7-902.7), and the duration of treatment was 1 day for the majority (16 bleeds, 55.2%).

4 patients (all enrolled at one study site) had received higher amounts of short-acting FVIII treatment that constitute the upper quartile of cumulative dose of short-acting FVIII administered per bleed. Those patients were males with moderate hemophilia A and ages of 12-19 years. Duration of FVIII for treatment varied from 3-16 days and was administered for traumatic, spontaneous, as well as procedure-related bleeds. The highest cumulative doses of short-acting FVIII were administered in a 13-year-old male, who received 16 days of FVIII for a spontaneous bleed.

No other hemophilia treatments (e.g., recombinant FVIIa, PCC, fresh frozen plasma, cryoprecipitate, or DDAVP) were used to treat bleeds in the study.

Table 13 Treatment with FVIII per Treated Bleed (Treated Population)

	Emicizumab (N=71)			
	Only Short-Acting FVIII	Only Long-Acting FVIII	Both Short-Acting and Long-Acting FVIII	All Treated Bleeds
Cumulative Dose of Short-Acting FVIII administered per bleed [UNIT/kg]				
n	29		0	29
Mean (SD)	156.18 (224.17)		NE (NE)	156.18 (224.17)
Median	58.48		NE	58.48
IQR	37.31 - 169.97		NE - NE	37.31 - 169.97
Min - Max	21.7 - 902.7		NE - NE	21.7 - 902.7
Cumulative Dose of Long-Acting FVIII administered per bleed [UNIT/kg]				
n		4	0	4
Mean (SD)		53.70 (19.16)	NE (NE)	53.70 (19.16)
Median		46.36	NE	46.36
IQR		42.11 - 65.28	NE - NE	42.11 - 65.28
Min - Max		40.1 - 82.0	NE - NE	40.1 - 82.0
Cumulative Dose of Short-Acting FVIII administered per bleed [UNIT/kg]				
n	29		0	29
<25	3 (10.3%)		0	3 (10.3%)
25-50	10 (34.5%)		0	10 (34.5%)
51-100	4 (13.8%)		0	4 (13.8%)
101-150	4 (13.8%)		0	4 (13.8%)
>150	8 (27.6%)		0	8 (27.6%)
Cumulative Dose of Long-Acting FVIII administered per bleed [UNIT/kg]				
n		4	0	4
<25		0	0	0
25-50		3 (75.0%)	0	3 (75.0%)
51-100		1 (25.0%)	0	1 (25.0%)
101-150		0	0	0
>150		0	0	0
Duration of Short-Acting FVIII per bleed (days)				
n	29		0	29
1	16 (55.2%)		0	16 (55.2%)
2	5 (17.2%)		0	5 (17.2%)
3	3 (10.3%)		0	3 (10.3%)
4	1 (3.4%)		0	1 (3.4%)
>4	4 (13.8%)		0	4 (13.8%)
Duration of Long-Acting FVIII per bleed (days)				
n		4	0	4
1		1 (25.0%)	0	1 (25.0%)
2		2 (50.0%)	0	2 (50.0%)
3		1 (25.0%)	0	1 (25.0%)
4		0	0	0
>4		0	0	0

n is the number of cumulative doses administered to treat a bleed.

Table of ABR applying and ignoring 72 hours rule, and including and excluding surgery/procedure related bleeds, respectively

	On Study ABR		Prior Study ABR		
			Extended hemophilia page		main hemophilia page
	without 72 hours rule, incl. surg/proc bleed	with 72 hours rule, excl. surg/proc bleed	without 72 hours rule, incl. surg/proc bleed	with 72 hours rule, excl. surg/proc bleed	
number of patients	69	69	69	69	69
patients with zero bleeds	30 (43.5%)	31 (44.9%)	21 (30.4%)	21 (30.4%)	21 (30.4%)
model-based ABR {95% CI}	2.8 [2.00;3.91]	2.3 [1.70;3.25]	5.6 [4.22;7.53]	5.2 [3.88;6.88]	5.6 [4.22;7.53]
median ABR, calculated, {IQR}	1.8 [0.00; 4.07]	1.7 [0.00; 3.79]	4.3 [0.00; 8.70]	2.2 [0.00; 6.52]	4.3 [0.00; 8.69]

All data at snapshot date 20 December 2021 and cutoff date 16 April 2021

Concomitant Medications for Conditions Other than Hemophilia A

The majority of patients (70.4%) received at least one concomitant treatment after baseline. The most common treatments (i.e., received by > 20% patients) were reported in the following classes: analgesics (26.8% of patients), other dermatological preparations (25.4% of patients), stomatological preparations (25.4% of patients) and vaccines (21.1% of patients).

Surgeries and Procedures

20 patients (28.2%) reported surgeries (n=12) and/or procedures (n=8) during the study.

2 of 12 patients had 2 major surgeries (i.e. 1 circumcision and 1 inguinal hernia repair), both were managed with prophylactic hemophilia treatment, 1 of which also required treatment for a post-operative bleed.

Another 10 patients had 19 minor surgeries including 11 dental surgeries, 1 central venous access device removal, 1 endoscopic procedure, 3 joint surgeries (synoviorthesis), 1 continuous glucose monitor removal and 1 cryotherapy. 12 (63.2%) minor surgeries were managed with prophylactic hemophilia treatment, 3 of which also required treatment of postoperative bleeds.

All patients who received prophylactic medication for surgery/procedures or treatment for a post-surgical bleed received FVIII (either long or short acting).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14 Summary of Efficacy for trial HAVEN 6

Title: A multicentre, open-label study to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients with mild or moderate haemophilia A (HA) without FVIII inhibitors.		
Study identifier	BO41423 (Haven 6)	
Design	Single arm, descriptive, open-label, multicentre study Retrospective design: collection of baseline data based on historic information collected by patients. First patient in (FPI): 10 February 2020 Study is ongoing. Interim analysis is submitted: the sample size and timing for this specific interim analysis were not defined in the study protocol, only mentioned in SAP. SAP: finalised on 15 June 2020 while the study was ongoing	
	Duration of main phase:	27.57 weeks

Hypothesis	No formal hypothesis testing in this study whose primary endpoint is safety. Descriptive and exploratory nature of efficacy analyses		
Treatment group	Emicizumab		4 loading doses at 3mg/kg SC QW for 4 weeks followed by a maintenance dose of either 1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W based on patient preference
Endpoints and definitions	Primary endpoint		Safety: AE, thrombotic events, TMA, immunogenicity etc.
	Primary efficacy endpoint	ABR estimated using a negative binomial regression model	N of bleeds/n of days during the efficacy period) × 365.25 - 72-hour rule: 2 bleeds of the same type and at the same anatomical location were considered to be 1 bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. - Exclusion of surgery/procedure related bleeds
	Secondary bleed-related endpoints		All bleeds (treated and untreated with FVIII) Joint bleeds Target joint bleeds Spontaneous bleeds - 72-hour rule - Exclusion of surgery/procedure related bleeds
	Other secondary endpoints	HJHS HRQoL EmiPref MBQ CATCH	- Hemophilia Joint Health Score - Health-related quality of life - Emicizumab Preference Survey at W17 - Menstrual Bleeding Questionnaire - Comprehensive Assessment Tool of Challenges in Hemophilia - Physical activity - PK
	Exploratory endpoints	Biomarker	thrombin generation, FVIII activity, FVIII protein, D-dimer, prothrombin fragment 1+2

Database lock	16 April 2021
Results and Analysis	
Analysis description	**Primary Analysis**
Analysis population and time point description	Treated population n=71 (20 mild and 51 moderate HA without inhibitor)
Results	The median duration of the efficacy period for 71 patients treated was 27.57 weeks (range 6.7-61.7): 23.86 weeks for patients with mild HA, and 30.29 weeks for patients with moderate HA. Treated bleeds: Negative binomial regression model-based ABR = 0.8 (95% CI: 0.41, 1.46). All bleeds: NB regression model-based ABR = 2.3 (95% CI: 1.63, 3.10). 38 (53.5%) patients experienced bleeds during the study by excluding all bleeds due to surgery/ procedure and by implementing 72 hour-rule. Treated Joint Bleeds NB regression model-based ABR = 0.3 (95% CI: 0.12, 0.65) Treated Spontaneous Bleeds NB regression model-based ABR = 0.1 (95% CI: 0.02, 0.23) Post-hoc analysis by comparing ABR for all bleeds retrospectively collected by patients in the last 24 weeks prior to study entry to ABR collected during the study Estimated ABR prior to study entry: Median (IQR) 4.3 (0.00-8.69) Calculated ABR for All Bleeds in the study (72hr rule and exclusion of bleeds due to surgery/procedure): 1.5 (0.00-3.79)
Notes	- High rate of major protocol deviation: 117 major protocol deviations reported in 48 of 71 patients (67.6%). - Bleeds due to surgery/procedure were excluded and 72-h rule was implemented for calculated ABR in study, but not in estimated ABR prior to study. - Retrospective collection of baseline data based on historic information collected by patients. - No patient younger than 2 years of age was enrolled - Heterogeneous population: 52.1% on FVIII prophylaxis and 47.9% on episodic treatment at study entry. The need for prophylaxis only based on investigator's individual decision.

Supportive studies

Phase III Clinical Trials HAVEN 1 to HAVEN 4: Bleed-Related Efficacy Endpoints

The efficacy of emicizumab in patients with HA (with and without FVIII inhibitors) has been evaluated in four prior pivotal HAVEN Phase III studies, namely, BH29884 (HAVEN 1), BH29992 (HAVEN 2), BH30071 (HAVEN 3), and BO39182 (HAVEN 4). Please see Table 1 in this AR for study design.

Data from prior experience with emicizumab have shown the following:

• BH29884 (HAVEN 1, HA patients with inhibitors against FVIII, QW regimen): An 87% risk reduction in treated bleeds ABR (model based) compared with no prophylaxis and an 80% risk reduction for all bleeds ABR were observed. Additionally, intra-individual comparisons demonstrated risk reductions of 89% and 77% for all bleeds ABR compared with prior episodic BPAs and prior prophylactic BPAs, respectively. The mean calculated ABR for treated bleeds (4.7) at the time of the primary CSR analysis improved further over time and the improvement was sustained beyond Week 48, whereas the median remained at 0.

Overall, all three dosing regimens (loading doses of 3 mg/kg QW for 4 weeks followed by either 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W), using an equivalent cumulative dose, provided outstanding efficacy in children, adolescents and adults with ≥55% of patients in all emicizumab treatment arms experiencing zero treated bleeds and more than 90% of patients on emicizumab prophylaxis experiencing only 0-3 treated bleeds.

Intra-individual comparison in Study BH29884 (HAVEN 1) demonstrated risk reductions of 95% and 88% for all bleeds ABR compared to prior episodic Bypassing agents (BPAs) and prior prophylactic BPAs, respectively. Intra-individual comparison (QW, n=18) in Study BH29992 (HAVEN 2) showed a reduction of 99% in the bleed rate for emicizumab prophylaxis compared with previous prophylactic/episodic treatment with the BPA. And similarly, in the Study BH30071 (HAVEN 3) study intra-individual comparison did show a 68% risk reduction of ABR in the emicizumab QW treated participants compared to prior FVIII prophylaxis.

Bleed related endpoints are the primary and main secondary efficacy endpoints in the HAVEN Phase III studies. These studies used similar methodology to collect information about bleeds and their treatment, and applied uniform definitions and analysis.

Table 15 shows a brief comparison of the primary analysis data from HAVEN 1 – HAVEN 4 Studies for treated bleeds and all bleeds efficacy endpoints.

Table 15: emicizumab: pivotal clinical trial results (study BH29884 (HAVEN 1), study BH29992 (HAVEN 2), study BH300071 (HAVEN 3), study BO39182 (HAVEN 4) – Clinical trials, Phase III

	BH29884 (Patients with inhibitors) CCOD – 25 October 2016 HAVEN 1	BH29992 (Pediatric patients with inhibitors) CCOD - 30 April 2018 HAVEN 2			BH30071 (Patients without inhibitors) CCOD – 15 September 2017 HAVEN 3		BO39182 (Patients with or without inhibitors) CCOD – 15 December 2017 HAVEN 4
Efficacy Parameter	Emicizumab QW (1.5 mg/kg) Arm A (N = 35)	Emicizumab QW (1.5 mg/kg) (N = 65)	Emicizumab Q2W (3 mg/kg) (N = 10)	Emicizumab Q4W (6 mg/kg) (N = 10)	Emicizumab QW (1.5 mg/kg) Arm A (N = 36)	Emicizumab Q2W (3 mg/kg) Arm B (N = 35)	Emicizumab Q4W (6 mg/kg) (N = 41)
Median efficacy period duration (range)	29.3 Weeks (0.1 – 48.9)	57.6 Weeks (17.9 – 92.6)	21.3 Weeks (18.6 - 24.1)	19.9 Weeks (8.9 - 24.1)	29.6 Weeks (17.3 – 49.6)	31.3 weeks (7.3 – 50.6)	25.6 Weeks (24.1 – 29.4)
Model based ABR (95% CI) – Treated Bleeds	2.9 (1.69; 5.02)	0. 3 (0.17; 0.50)	0.2 (0.03; 1.72)	2.2 (0.69; 6.81)	1.5 (0.89; 2.47)	1.3 (0.75; 2.25)	2.4 (1.38; 4.28)
Median ABR (IQR) – Treated Bleeds	0.0 (0.00; 3.73)	0.0 (0.00; 0.00)	0.0 (0.00; 0.00)	0.0 (0.00; 3.26)	0.0 (0.00; 2.54)	0.0 (0.00; 1.89)	0.0 (0.00; 2.08)
Patients with 0 bleeds (%) (95% CI) - Treated Bleeds	62.9 (44.9; 78.5)	76.9 (64.8; 86.5)	90.0 (55.5; 99.7)	60.0 (26.2; 87.8)	55.6 (38.1; 72.1)	60.0 (42.1; 76.1)	56.1 (39.7; 71.5)
Model based ABR (95% CI) – All Bleeds	5.5 (3.58; 8.60)	3.2 (1.94; 5.22)	1.5 (0.62; 3.40)	H3.8 (1.42;10.11)	2.5 (1.63; 3.90)	2.6 (1.63; 4.29)	4.5 (3.10; 6.60)
Median ABR (IQR) – All Bleeds	2.0 (0.00; 9.87)	0.6 (0.00; 2.92)	0.0 (0.00; 2.81)	1.6 (0.00; 4.84)	0.6 (0.00; 3.85)	1.6 (0.00; 3.95)	2.1 (0.00; 5.89)
Patients with 0 bleeds (%) (95% CI) - All Bleeds	37.1 (21.5; 55.1)	49.2 (36.6; 61.9)	60.0 (26.2; 87.8)	50.0 (18.7; 81.3)	50.0 (32.9; 67.1)	40.0 (23.9; 57.9)	29.3 (16.1; 45.5)

Data Source: CSR Study BH29884 (HAVEN 1) Report 1103649, Study BH29992 (HAVEN 2) Report 1103867, Study BH30071 (HAVEN 3) Report 1082237, and Study BO39182 (HAVEN 4) Report 1085099

Real World Data Studies

Data from the TSUBASA and ADELPHI studies are provided as supportive efficacy information.

TSUBASA

The TSUBASA study is an ongoing, prospective, multicentre, observational study conducted in Japan that aims to evaluate the relationship between physical activity and bleeding, the quality and content of daily life, and the safety of emicizumab in patients with HA without FVIII inhibitors. At the interim analysis with data cut-off of 31 May 2021, 107 patients were enrolled (91 patients with severe disease and 15 with moderate disease). Preliminary analyses demonstrated the effectiveness of emicizumab in patients with moderate HA, with bleed outcomes in line with the results of the BO41423 (HAVEN 6) study (calculated mean ABR [SD] in the 15 patients with moderate HA: 0.86±3.41).

ADELPHI

The ADELPHI study was a research survey of U.S. physicians treating patients with mild to moderate HA. The main objective of this analysis was to understand the change in ABR in patients with mild to moderate HA after 12 months of treatment with emicizumab. The study described the potential improvements in ABR in a small cohort of patients (5 patients with mild and 9 patients with moderate HA): the mean ABR (SD) for all bleeds in the 9 patients with mild or moderate disease that were followed up for at least 12 months was 0.7±0.71.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This application includes data from the new Phase III Study BO41423 (HAVEN 6), which was designed to provide clinical safety and efficacy evidence to support the extension of indication to include adult and paediatric patients of all ages with mild and moderate HA without inhibitors to FVIII that warrant prophylactic treatment.

Study design

To support this variation, a single-arm, open label, ongoing, multicentre pivotal study was submitted. The main limitations of this pivotal study are the retrospective design and the lack of comparator (comparison of on-study data *versus* retrospectively recalled baseline data). The primary focus of this study was safety. Primary efficacy endpoint was the number of treated bleeds over time (ABR) with the implementation of 72-hour rule and the exclusion of bleeds due to surgery/procedure only for on-study ABR.

Statistical methodology

The pivotal trial is a single arm open-label study. The absence of a control group is a clear limitation to the interpretation of the study data. The overall sample size was based on feasibility without further statistical considerations.

The sample size and timing for this specific interim analyses (IA) were not defined in the study protocol, and potential additional IAs were left undefined.

All efficacy analyses are of descriptive nature in this study. There is no formal hypothesis testing (and therefore no multiplicity adjustment either), so that all analyses should be viewed as exploratory.

The ABR calculations based on a negative binomial model are deemed appropriate. Regarding ABR descriptive statistics (based on the formula ABR = [n of bleeds/n of days during the efficacy period] × 365.25), the MAH clarified the method used for deriving the 95% confidence interval around the calculated mean ABR, which is the exact Poisson method.

The number of bleeds in the last 24 weeks before study entry has been collected retrospectively. This raises a general concern of accuracy for the summary of baseline bleeds, and is a clear limitation to the interpretation of baseline bleeds in comparison with post-baseline data. The MAH described that a haemophilia history extended eCRF page was implemented to provide additional details of all bleeds patients had during the last 24 weeks prior to enrolment. This page was generally completed with the exception of 2 participants. Although this provides some reassurance on the reliability of the retrospective collection, bias is still of concern due to the retrospective nature of pre-study data, and its comparability with post-baseline data remains doubtful.

The 72-hour rule for combining bleeds of the same type and location was not initially applied to the 24-week period prior to study entry. Similarly, the exclusions due to surgery/procedure were not applied to baseline bleed summaries. As requested, the MAH has conducted a sensitivity analysis where ABR statistics are derived for on-study ABR and prior study ABR, both with and without the 72 hour rule.

According to the SAP, questions cannot be left unanswered in the BMQ. The fact that the entry system does not allow for missing or partial information had raised a concern of unreported bleeds in the study database. The MAH further clarified that several procedures were in place to optimise the completeness of data collection.

Without a control group the interpretation of any subgroup analyses remains challenging. In case of inconsistency, it may be difficult to differentiate between prognostic and predictive baseline factors.

Study population

HAVEN 6 enrolled patients with mild (FVIII > 5% and < 40%) and moderate HA (FVIII ≥ 1% and ≤ 5%) without FVIII inhibitors; who had been able to provide documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes during the last 24 weeks prior to enrolment. Their "need for prophylaxis" at inclusion was only based on investigator's individual assessment. The reason for which patients needed prophylaxis as well as treatment purpose was not defined. All patients either on prophylactic or on episodic FVIII treatment were eligible. The imprecision of these key criteria provided a highly heterogeneous population in this study. This further complicates the retrospective single arm study design with significant weakness making difficult to assess consistent efficacy across such heterogeneous population. It is regrettable that the relevant population advised of SAG has not been taken into account (i.e. "Moderate haemophilia A patients with FVIII levels equal to or less than 5%: • who had a first spontaneous intra-articular bleed before the age of 5 years or • who were already started on a prophylaxis regimen with a long-term prophylaxis intention"). Indeed, this advice is in line with the recommendation of the WFH i.e. "*Prophylaxis is the standard of care for people with severe hemophilia, and for some people with moderate hemophilia, or for those with another congenital bleeding disorder that is associated with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding*".

The ad hoc expert group's advice is also consistent with recently published experts' opinion submitted by the MAH in response package (Valentino LA, Khair K, *Prophylaxis for hemophilia A without inhibitors: treatment options and considerations.* Expert Rev Hematol. 2020 Jul;13(7):731-743, response to OC15). Experts highlight that early prophylaxis may also be appropriate for children with moderate haemophilia A who experience joint bleeding prior to age 5 years and have a more severe bleeding pattern. Indeed, as discussed by experts, hemarthrosis accounts for more than 90% of all serious bleeding events, this hallmark typically begins early in childhood and one paramount benefit of long-term prophylaxis is joint protection. Although the subcutaneous administration with long-effect of emicizumab is an undeniably appealing prophylactic option for haemophilia, a major challenge to the widespread use of emicizumab and other pro-coagulant therapies is a lack of data regarding the overlap between the therapeutic window, where bleeding is prevented, and the toxicity window, where the risk of thrombosis increases. Experts recommend also that large, multicentre studies are needed comparing ABR/AJBR in patients receiving FVIII *versus* emicizumab prophylaxis to justify the higher cost of this non factor therapy.

HAVEN 6 was designed to be inclusive of the full spectrum of reasons why a patient with m/m HA without inhibitor warrants prophylaxis irrespective of their prior treatment (PUP or PTP, episodic or prophylactic). It is regrettable that the WFH recommendation as well as SAG and US experts' opinion have not been taken into account, leading to a highly heterogeneous population in this study which makes assessment further difficult to extend beyond retrospective, exploratory and descriptive design of this single arm open pivotal study.

Emicizumab treatment

The emicizumab dosing regimen was 4 loading doses of emicizumab 3 mg/kg SC QW for 4 weeks followed by a maintenance dose of either 1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W based on patient preference in this single-arm study. The chosen regimen needed to be maintained throughout the study until completion of at least 52W. Regular FVIII prophylaxis may continue until the 2nd emicizumab loading dose to avoid bleeds before adequate emicizumab levels are reached. For the treatment of breakthrough bleeds, FVIII should be used at the lowest dose expected to achieve haemostasis. Other drugs intended to control bleeds e.g., bypassing agents, DDAVP, or antifibrinolytics were permitted.

Study conduct

The First Patient In is 10 February 2020. The cut-off date for analyses is 16 April 2021. The interim analysis was triggered after 50 patients with moderate HA without inhibitors had completed 24 weeks of emicizumab treatment.

An update to the interim analysis has been provided in the evaluation. The clinical cut-off date of the primary analysis was 30 October 2021 resulting in a median emicizumab exposure of 54.29 weeks (range: 8.1- 89.1), which is more than double the median follow-up time of the interim analysis. Of note, the study continues after primary analysis. Overall, the results of this updated analysis of HAVEN 6 show that the safety and efficacy profile of emicizumab in patients with mild and moderate HA without FVIII inhibitors are consistent with data previously observed at interim analysis.

Efficacy data and additional analyses

71 patients had started emicizumab in the study (treated population). A total of 59 treated patients had completed at least 24 weeks including 10 mild and 49 moderate HA without inhibitor patients. Patients were treated with emicizumab maintenance dose of 1.5 mg/kg QW (n=24), 3 mg/kg Q2W (n=39), and 6 mg/kg Q4W (n=8).

The median observation time was 27.57 weeks (range 6.7-61.7), 23.86 weeks for patients with mild HA, and 30.29 weeks for patients with moderate HA.

A total of 117 major protocol deviations were reported in 48 of 71 patients (67.6%). All 48 patients had at least one procedural major deviation, 5 patients of them had medication deviations including use of a prohibited therapy in 3 patients. Such a high rate of procedural major procedural deviations may have an impact on the integrity of the study data and further hamper the study outcomes. The MAH clarified that paper BMQ as back-up to the handheld device were available to patients; in case of such a major protocol deviation, study sites were required to contact the patient in a timely manner and recorded bleeds on paper BMQ were entered by the site via data entry system.

Baseline data

The median age of treated population (n=71) was 23.0 years, no patient younger than 2 years of age was enrolled. The potentials of coagulation, anticoagulation, and fibrinolysis in new-borns and infants clearly differ with those older children and adults. The PK exposure is also likely to be less than in subjects under 6 months than older children. The MAH provided the following evidence for the subgroup of young patients < 2 years of age.

- 8 patients under the age of 2 years were in enrolled in prior studies of emicizumab, according to the MAH, the available data show consistent efficacy and safety between the < 2 year age group and older patients, no safety concerns have arisen in the post-marketing setting that are specific to the <2 year age group, the available real world data also support the consistently favourable benefit-risk profile across all ages and post-marketing safety data include data of subjects < 2 year age from countries where emicizumab is approved for patients with m/m HA without inhibitors.

It should be noted that the available data of subjects under the age of 2 years were mostly obtained from patients with severe HA with or without inhibitors. The MAH provided an analysis by age category (<6 months, 6-12 months, 12-24 months) all clinical data (PK, PD, efficacy and safety) from 8 subjects < 2 years enrolled in prior studies of emicizumab, as well as post-marketing safety data of subjects < 2 years age with m/m HA; and compare to older patients setting.

The MAH provided the requested analysis from HAVEN 2 for the 8 patients < 2 years with HA with FVIII inhibitors, a comparison to those > 2 years has also been made. Overall, efficacy, safety, PK and PD

profiles in participants <2 years with HA with FVIII inhibitors were consistent with those observed in older patients. It is noted that the median age is 16 months (range 14-23 months) for 8 patients < 2 years. Thus, there was no patient <1 year in this study. A slightly higher emicizumab exposure was observed in 0-2 years group than older age group. Although emicizumab is approved in the USA, Australia and Japan with no restrictions on age or disease severity, the Safety Database search retrieved 0 cases reporting post-marketing safety data from patients < 2 years of age with mild or moderate HA.

- HAVEN 7 study (MO41787) is currently ongoing. This study, which evaluates the safety, efficacy, PK and PD of emicizumab in patients with severe HA without inhibitors who are less than 1 year old at study entry, was designed to provide additional data as suggested with the prior submission of the non-inhibitor extension of indication (EMEA/H/C/004406/II/0002). The MAH provided an interim data including the safety and efficacy endpoints as well as the available PK, PD, and immunogenicity results until CCOD (31 March 2022) for 24 infants aged < 3 months and 30 infants aged from ≥ 3 months to ≤ 12 months at the time of enrolment. The mean age at enrolment of the participants was 5.1 months. The available interim data support the efficacy of emicizumab prophylaxis in infants with severe HA without FVIII inhibitors across all bleed related endpoints. The safety profile was consistent with that previously observed in HAVEN studies, and there were no new safety signals. The interim PK analyses demonstrated sufficient levels of drug exposure while these analyses are limited by small numbers of samples in some of the subgroups. PD data showed a tendency of increased FVIII-like activity and thrombin generation with age. The MAH thought that this increase in pharmacodynamic markers (FVIII-like activity and thrombin generation) with age is most likely related to the age effect seen on FIX and FX antigen concentrations, aPTT remained fully normalised regardless of age. These data support the favourable efficacy and safety in subpopulation of patients < 1 years with severe HA without inhibitors. The ongoing HAVEN 7 study will continue to generate efficacy, safety, PK and PD data on the use of emicizumab in young patients with the final CSR expected in 2030 at the conclusion of a 7-year long term follow-up.

- No m/m patient under 2 years of age were enrolled in HAVEN 6. As reported by French and US studies, the majority of moderate forms are diagnosed after 8-9 months and mild forms after 29-36 months. In contrast to the situation for severe HA where spontaneous bleeding with severe bleeding phenotype are frequent, few patients with m/m HA would be expected to start prophylaxis within the first 2 years of life.

As discussed in the review "*Spotlight on emicizumab in the management of hemophilia A: patient selection and special considerations,* Koji et al, Journal of Blood Medicine 2019:10 171–181", one of the biggest problems at an early stage after birth is how to avoid the occurrence of intracranial haemorrhage (ICH). However, considering the PK of subcutaneous emicizumab, it might NOT be expected to exert a haemostatic effect immediately even if administered at an early stage after birth. After 1 or 2 years, bleeding frequency increases due to an increase in activity associated with normal growth and development of infants, trauma, and patients most often experience initial joint bleeding. Hence, in response to an increase in the bleeding risk, this stage is generally the time to introduce prophylactic replacement therapy.

- The Pednet study (Kenet G et al. data cut January 2021) reports the bleed rates in patients under 2 years of age with severe HA. ABR (95% CI) for all bleeds appears higher for children under 2 years of age 2.34 (1.44;3.80) compared to the ABR for all bleeds 1.32 (0.99;1.77) in the full paediatric population. There were 32 children < 2 years of age out of 141 patients under 18 years of age. Median treatment duration (IQR) was 9.8 months (3.6-19.8) for all patients, 17.9 (7.9-28.1) for inhibitor patients and 3.7 (2.3-9.3) for non-inhibitor patients reflecting the earlier adoption of emicizumab in inhibitor patients.

In conclusion, there are limited clinical trial data on the use of emicizumab in patients under 2 years with severe HA, the data are missing in patients < 2 years with m/m HA without inhibitors. Prospective clinical data collection concurrent with the use of emicizumab in this age group (PK, PD including haemostasis

speed, efficacy and safety), through sponsored clinical trials and particularly in children < 6 months is strongly encouraged. Data should also be available from the registry studies (please see RMP).

As a reminder, in 2018, the MAH had already sought the EOI including m/m HA without inhibitors for Hemlibra (EMEA/H/C/004406/II/0002). At the time, the SAG concluded that "the lack of data in children less than 1 year and the need to generate data in this group given that not only PK but also the coagulation system is likely to be different in the new born children was also raised".

The majority of the patients enrolled in this study had moderate HA without inhibitor (51/71, 71.8%) and 20 patients (28.2%) had mild HA without inhibitor. At study entry, half of patients were on prophylactic treatment (n=37, 52.1%) all with FVIII, and 34 patients (47.9%) were on episodic treatment.

A total number of 239 bleeds was retrospectively collected by 71 patients in the last 24W (median 2.0, range: 0-60). The majority of patients (51/71, 71.8%) experienced 0-3 bleeds including 22 patients with 0 bleed.

A total of 203 joint bleeds per year prior to study entry were recalled by 71 patients.

It is noted one patient had experienced a total of 60 bleeds in the last 24 W and 120 joint bleeds per year prior to study entry while 0 bleeds in the last 24 weeks prior to study.

The number of bleeds recalled by patient varied greatly over time prior to study. For example, two patients collected 60 and 15 bleeds per year respectively while 0 bleeds in the last 24 week prior to study.

The number of joint bleeds per year prior to study entry were missing or unknown for the majority of patients (76.1%, 54/71, cf Approved listing of hemophilia history: reason of warranting prophylaxis, all treated patients in CSR). However, "history of frequent joint bleeds" was the primary reasons of warranted prophylaxis for 32 patients (45.1%). The MAH clarified that such discrepancy is probably due to the eCRF design, requesting to provide the information in the field "Number of joint bleeds per year prior to study entry/Regular prophylaxis" only for participants indicating "History of frequent joint bleeding" as a reason to warrant prophylaxis.

The major weakness of retrospective data is that they generate a great deal of missed data. The accuracy and completeness of these baseline data collected in a retrospective manner is questionable.

Baseline data of FVIII activity are provided and reflect the residual endogenous FVIII activity and the use of FVIII prior to study entry in some patients. (Please see section Pharmacodynamics of this AR).

Of 37 patients being on FVIII prophylaxis at baseline, 28 had moderate HA without inhibitors and 9 have minor disease. This prophylactic subpopulation seems very heterogeneous; and the reasons why patients warrant prophylaxis do not seem to consist with patient's bleeding history. Indeed, a half of patients with minor disease (5 of 9) received FVIII prophylaxis prior to study, while they had not experienced any bleed in the last 24W. In contrast, half of patients (5/11) with minor disease received only episodic treatment, while they all had a history of severe bleeding and/or frequent (joint) bleeding in the last 24W. This is not surprising since the protocol did not define any criterion regarding prophylaxis warranted at inclusion and patient's selection was only based on investigator's individual assessment "need for prophylaxis".

The need for prophylaxis depends on multiple factors (e.g. characteristics, age group, lifestyle, clinical conditions…). The analysis of the haemophilia history data from HAVEN 6 demonstrated the heterogeneity of reasons for warranting prophylaxis in the study participants with the most commonly reported reasons being history of frequent bleeding (56.3%), history of frequent joint bleeding (45.1%) and history of severe bleeding (21.1%). Additional subgroup analyses show the reasons for warranting prophylaxis were

similar for patients with mild or moderate HA, with some minor variations. However, the small sample size (n=5) of patients <18 years with mild HA limits interruption of this subgroup analysis.

Bleed-related endpoints

The primary (treated bleeds) and secondary efficacy analyses were based on the treated population, by **excluding all bleeds due to surgery/ procedure and by implementing 72 hour-rule**:

Follow up for a median of 27.5 weeks, the interim results indicated that:

- For treated bleeds, the NB regression model based ABR was 0.8 (95% CI: 0.41, 1.46) and the calculated mean ABR 0.7 (95% CI: 0.01, 5.13]). The majority of patients experience 0 treated bleeds while receiving emicizumab prophylaxis (80.3% 57 patients).

- For all bleeds (those treated and untreated with coagulation factors, the model based ABR was 2.3 (95% CI: 1.63, 3.10) and the calculated mean ABR was 2.2 (95% CI: 0.31, 7.53).

A total of 38 (53.5%) patients experienced all bleeds during the study by excluding bleeds due to surgery/ procedure and by implementing 72 hour-rule. Indeed, development of neutralising anti emicizumab antibodies with decreasing emicizumab concentration leading to loss of efficacy has been observed during clinical trials. The pooled data submitted in ongoing variation EMEA/H/C/004406/II/0025 showed that among 668 patients tested in 7 Phase III studies, 34 patients (5.1%) developed ADA, 88.2% detected within 6 months, 18 patients (2.7%) with neutralising antibodies and 4 patients with decreasing emicizumab concentrations/reduced PD effects. One post-marketing case of fatal intracranial haemorrhage, preceded by a presumptive loss of efficacy due to the development of ADAs, has also been reported.

The MAH confirmed that none of these 38 participants tested positive for ADA, and no bleeding events (treated or all bleeds) were reported by the 2 participants who were identified as ADA positive; neither were events of hypersensitivity or anaphylaxis associated with ADA reported, at the cut-off for the primary analysis on 30 October 2021 resulting in a median emicizumab exposure of 54.29 weeks (range: 8.1- 89.1), which is more than double the median follow-up time of the interim analysis.

Furthermore, it seems that there is no available commercially validated assay specific for testing the antidrug antibody status with emicizumab. In case of increase in breakthrough bleeding events, evocative sign of loss of efficacy, evaluation is currently based on PK (decrease in emicizumab exposure) and clinical assessment; the treatment decision-making can only rely on the experience and practices of specialised centres. This raises a concern for accurate assessment of etiologic factors in case of increase in bleeding events.

A total of 33 treated bleeds (primary endpoint) were reported in 14 (19.7%) of 71 patients; 90.9% (30 of 33 bleeds) were traumatic bleeds while the rest 9.1% (3/33 bleeds) were spontaneous bleeds (excluding bleeds due to surgery/procedure). Treated bleeds occurred most frequently in the joints (48.5%, 16/33 bleeds) reported in 7 patients (9.9%) including 4 (5.6%) patients with treated target joint bleeds.

- For treated joint bleeds and for treated spontaneous bleeds, the model-based ABR for was 0.3 (95% CI: 0.12, 0.65) and 0.1 (95% CI: 0.02, 0.23) respectively.

- For treated target joint bleeds (including unresolved target joints), the model-based ABR did not converge due to a low number of bleeds with short follow-up times. The calculated mean ABR was 0.1 (95% CI: 0.00, 3.93).

Exploratory analyses by including bleeds due to surgery/procedure and irrespective of the 72-hour rule: a total of 109 bleeds occurred in 71 treated patients; 67.9% (74/109 bleeds) were traumatic bleeds, 22.9% (25/109 bleeds) were spontaneous bleeds, and 9.2% (10/109 bleeds) were due to surgery/procedure.

Locations other than joints or muscle such as nose, mouth, and fingers/thumb represent 70.6% 77 of 109 bleeds reported in 28 patients.

Post-hoc analysis of ABR for All bleeds

A post-hoc analysis was performed to compare ABR for All bleeds retrospectively collected by the patients in the 24 weeks prior to study entry (**without** implementation of 72h-rule nor exclusion of surgery/procedure related bleeds) with ABR collected during efficacy period of this study (by implementing both 72h-rule and exclusion of surgery/procedure related bleeds). This analysis showed that the median estimated ABR prior to study entry was 4.3 (0.0-8.7) and the median calculated ABR for All Bleeds (72h-rule) was 1.5 (0.0-3.4).

A supplemental analysis was performed by the MAH to assess the potential bias in the retrospective collection of bleed data across previously submitted studies (HAVEN 1, 2, 3 and 4). The retrospective collection of bleeds in the eCRF (without the 72-hour rule) for patients who were not part of the Non-Interventional Study (NIS) BH29768 (the "non-NIS group") was compared to the prospective collection of bleeds (via the BMQ, and with the 72-hour rule) for patients in the NIS (the "NIS group"). Of note, this analysis was performed in patients with severe disease, such population may be notably different from that of m/m HA in terms of CRF collection manner, disease surveillance and management. Although the effort to assess bias between prospective and retrospective collection is appreciated, the comparability of the two patient subsets is questionable, and may in itself flaw the comparison. Bias cannot be excluded nor quantified based on these exploratory analyses. It is still of concern due to the retrospective nature of pre-study data, and the comparability between baseline and post-baseline data remains doubtful.

In addition, it is noted that the model-based ABR in the patient group with a retrospective collection of bleeds (without 72 hr rule) is slightly higher than with the prospective collection (with 72 hr rule). This could imply, as suspected, some bias when comparing post-baseline data with 72-hour rule to retrospective baseline data without any rule, with retrospective ABR being possibly under-estimated.

As requested, the MAH has conducted a sensitivity analysis where ABR statistics are derived for on-study ABR and prior study ABR, both with and without the 72 hour rule.

It is noted (consistently with the above supplemental analysis), that ABR model-based estimates are slightly lower when applying the 72-hour rule, for on-study ABR as well as for prior study ABR. On-study ABR model-based estimates are numerically smaller than prior study ABR, and a larger proportion of patients with zero bleeds is observed for post-baseline bleeds, with or without the 72-hour rule being applied. Nevertheless, it is also noted that pre-study median ABR reduced from 4.3 to 2.2 when applying the 72-hour rule. While this may reflect the skewed distribution of ABR in a relatively small sample size, this is another indication of the additional bias introduced when ignoring the 72h rule.

It is noted that at the approved dosing, emicizumab does not completely restore normal haemostasis in mild/moderate patients enrolled in this study and more than half of treated patients (38/71, 53.5%) still experience bleeds during the efficacy period. During emicizumab treatment, the ABR increased in 13 patients compared to their pre-study estimated ABR, 20 patients with stable ABR and 38 patients with decreased ABR respectively. Of the 24 patients who presented target joint bleeds prior to study, 7 had bleeds in their target joints and of those 4 required additional treatment for target joint bleeds during the efficacy period. Most of these bleeds were traumatic and without treatment.

There were some limitations with regards to the efficacy in joint bleed:

- The number of bleeds in the last 24 weeks before study entry was based on historical information collected by patients. This raises a general concern of accuracy for baseline bleeds and is a clear limitation to the interpretation of baseline bleeds in comparison with post-baseline data.

- All bleeds due to surgery and/or procedure were excluded for post-baseline data. However, all surgery or procedure related bleeds were not excluded from retrospective baseline data.

- The baseline bleeding characteristics (treated or not, spontaneous or trauma/surgery related, location, severity…) were not collected, thus cannot be taken into account into analysis.

- High ABR before enrolment seems driven by one patient who had experienced a total of 60 bleeds in the last 24 W before study entry. This patient experienced 0 on-study bleeds. The MAH clarified that this patient had history of joint bleeding, and due to haemophilic arthropathy of the left knee, he underwent total prosthesis replacement 210 Days prior to start of study treatment. All bleeds prior to study entry occurred in the left knee. The investigator considered improved bleed control on study being a result of emicizumab prophylaxis, however, the total prosthesis replacement on D210 prior to study entry could also contribute to 0 on-study bleeds reported in this patient. Of note, the MAH indicated that this Subject - had not used a bleed diary to list bleeding details and treatments prior to joining the study, his Haemophilia History Extended eCRF page was not completed, therefore we assume this subject was one of 2 subjects excluded from sensitivity analysis.

- the inclusion in the emicizumab treated cohort was conditioned by previous data collection, only patients who had the capacity to provide "Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks prior to enrolment" were enrolled. This may raise the question of representativeness especially for patients with mild disease whose daily lifestyle may have significant consequences to manage their disease.

In conclusion, any before/after differences in this pivotal HAVEN 6 study need to be interpreted with extreme caution and no firm conclusions can be drawn from this post-hoc analysis in a single-arm open pivotal study with a retrospective design.

ABR subgroup analysis

Additional descriptive subgroup analysis of treated bleeds were computed on the basis of age (<65 vs. ≥65 years, <18 vs. ≥18 years), haemophilia severity (mild vs. moderate), presence of target joints, previous treatment regimen (episodic vs. prophylactic), and dosing regimen at enrolment.

For some subgroups (age<6 years, race, previous FVIII inhibitors, female patients), the number of patients was too small to adequately evaluate ABR.

Due to the small sample size, the descriptive and exploratory nature of this study, subgroups analyses should be interpreted with caution. No conclusion can be drawn from these analyses.

Secondary health-related QoL and health status endpoints

HAVEN 6 assessed the benefit of emicizumab on health-related QoL by using CATCH questionnaire, the emicizumab patient preference questionnaire, the HJHS for joint health, an accelerometer for physical activity, menstruation-related quality of life information and EQ-5D-5L for health status.

The results seem to reflect improved aspects of patient health-related QoL and caregiver burden, as demonstrated in prior HAVEN studies. But given the sample size and the study design, these trends should be interpreted with caution. No conclusions can be drawn.

Concomitant treatments for haemophilia A during the study

A total of 35 patients (49.3%) received a FVIII medication during the study. Of these 35 patients, 20 patients received a FVIII after their 2nd loading dose of emicizumab. 18 of whom used FVIII as treatment for a bleed, 7 of whom used FVIII as preventative for surgery/procedure, and 1 who used FVIII as preventative before activity.

15 of 71 patients continued their FVIII prophylaxis up to the 2nd emicizumab loading dose to avoid bleeds before adequate emicizumab levels are reached, this is understood. Although the concomitant use of FVIII and emicizumab was of short duration, this confounding factor could affect the efficacy endpoints in the analysis in this single-arm study and further hampers the interpretation of efficacy outcomes.

The MAH clarified that due to design of BMQ option and since regular prophylaxis other than emicizumab is not permitted on study beyond the second loading dose, participants were advised to select "Preventative dose before activity" in the BMQ instead of "prophylaxis" for continued prophylaxis up to the second loading dose. A total of 22 subjects were identified who continued their FVIII prophylaxis in the first week of emicizumab loading doses, 6 of them reported 8 bleed events in the 1st week of emicizumab treatment and received FVIII in addition as treatment for bleeds. The treated bleeds and all bleeds model based ABR for the 22 participants who continued prophylaxis during the first week on study was 0.7 (0.26, 1.68) and 2.1 (1.37, 3.13) respectively. The proportion of participants who experienced zero all bleeds during the efficacy period was 36.4% (8 out of 22 participants), which is slightly lower than observed in the overall study population (46.5%), reflecting the possible higher risk bleeding phenotype in this subset patients who continued FVIII prophylaxis until the second loading dose being selected.

5 patients had medication deviations including use of a prohibited therapy in 3 patients. Overall compliance with expected dosing of emicizumab was high in the study (93%, 66 of 71) and the limited number of these medication deviations is not considered to have a meaningful impact on the overall results and conclusions of the efficacy analysis.

Per protocol, other drugs intended to control bleeds e.g., bypassing agents, DDAVP, or antifibrinolytics were permitted. The MAH confirmed that no participants received these drugs on a routine or regular basis during the study. Treatment with antifibrinolytic agent (tranexamic acid) was reported for 11 participants (15.5%) as concomitant therapy in a total of 20 episodes. Overall, the generally limited duration of treatment with tranexamic acid is not expected to impact results of ABR significantly.

The majority of bleeds (n=29) were treated with short-acting FVIII. The median cumulative dose per bleed was 58.48 units/kg (range: 21.7-902.7) and the median number of doses administered was 3.0 (range: 1-44). This median cumulative dose of short-acting FVIII per bleed administered in HAVEN 6 is numerically higher than that used in patients with severe HA without inhibitor in HAVEN 3 (Arm A: 37 unit/kg, Arm B: 27 unit/kg, and Arm D: 46 units/kg with patients who had received FVIII prophylaxis prior to study entry) as well as in HAVEN 4 expansion cohort (25.32 units/kg). The MAH states that such high use of FVIII products in HAVEN 6 was driven by 4 patients who had received higher amounts of short-acting FVIII treatment (cumulative dose >150 units/kg; 27.6%).

Here again, the limitations due to small sample size, high variability, potential confounding factors and biases in estimation of bleeding number, making impossible to draw any conclusion.

Surgeries and Procedures

During the study, 12 patients reported a total of 19 minor and 2 major surgeries. Both major surgeries (i.e. 1 circumcision and 1 inguinal hernia repair) were managed with prophylactic FVIII treatment, 1 of which also required FVIII for a post-operative bleed. 19 minor surgeries were mostly dental surgeries (11/19). 63.2% of minor surgeries (12/19) were managed with FVIII prophylaxis, 3 of which also required FVIII for postoperative bleeds

Overall, under the haemostatic coverage of emicizumab alone in mild and moderate HA, all major surgeries still required FVIII prophylaxis and FVIII for post-operative bleeds in 1 of 2 patients. Almost two-third of minor surgeries were managed with FVIII prophylaxis including 3 postoperative bleeds managed by FVIII.

The MAH analysed surgeries/procedure related bleeds data by separating patients with mild HA and those with moderate HA. At cut-off of the interim analysis (based on snapshot of data performed on 20th December 2021) for HAVEN 6, 13 patients reported 22 surgeries: 2 of 20 patients with mild HA had 1 surgery each (1 minor and 1 major surgery), and 11 of 51 patients with moderate HA had a total of 20 surgeries (1 major and 19 minor surgeries). Overall, only two surgeries were performed in patients with mild HA, 1 tooth extraction resulted in a related bleed. For patients with moderate HA, 6 procedures /surgeries are reported with related bleeding events directly following surgery. The small size makes any comparison difficult.

Supportive studies

The main results of prior HAVEN 1– HAVEN 4 studies have been presented as supportive data.

It must however be acknowledged that:

- the population is different in HAVEN 6 from those HAVEN studies,

- in HAVEN 6, prior study entry ABR was estimated based on a retrospective collection of historic information recalled by patients, the comparator group is lacking.

- HAVEN 6 is a descriptive and exploratory single-arm study in contrast to prior randomised controlled HAVEN studies, the analyses in HAVEN 6 are based on before and after entry study. The reliability of this comparison is questionable.

The ongoing Japan observational TSUBASA study and US research survey ADELPHI study are not considered as sufficiently relevant for supporting this extension of indication.

Overall, the efficacy results observed in severe HA in previous HAVEN studies cannot be easily extrapolated to patients with higher levels of FVIII regardless of the patient's haemophilia severity or inhibitor status, as considered by the ad hoc expert group.

Additional expert consultation

An ad hoc expert group meeting was convened on 22nd September 2022 and were asked to respond to the following efficacy question as agreed by CHMP:

1. Considering that emicizumab has now been used for several years since its approval, is there a clinical need for Hemlibra in the management of patients with mild or moderate congenital haemophilia A without inhibitors to FVIII and what is that need?

The expert group described the current clinical practice, which is based on a broad agreement on the medical need for prophylaxis in patients with *severe* (<1 IU/dL FVIII activity) and *moderate* haemophilia A (1–5 IU/dL activity), across all age groups.

The expert group also agreed that in patients with *mild* haemophilia (> 5 IU/dL– ≤ 40 IU/dL activity), generally, the need for prophylaxis is less clear. However, the expert group recognised that this is not a homogenous group and among mild haemophilia patients there is a small subset of patients for whom there might be a medical need for prophylaxis. Unfortunately, there are no robust data to predict precisely who will most benefit from prophylaxis, apart from those quite rare patients with mild haemophilia who manifest a severe bleeding phenotype. Indeed, as per the current guidelines in *mild* hemophilia A, the treating physician should decide to initiate a regular prophylaxis program after the occurrence of one or more bleeding episodes for which substitutive treatment with factor VIII concentrate was deemed necessary (see WFH Guidelines for the Management of Hemophilia, 2020).

The expert group agreed that clinical decisions and guidelines about the need for prophylaxis likely consider factors like: level of factor VIII activity, with some data in the literature indicating that an

activity between 5 IU/dL and 15 IU/dL might be associated with higher risk of bleeding; history of bleeding; practicing sports with high risk of injury (like football) in some patients. The expert group debated if mucosal bleeding (menorrhagia) in women could be considered as an additional risk factor. No clear conclusion was reached, considering that mucosal bleeding is not clearly related to actual FVIII level and also to the availability of other options such as DDAVP during menses. However, the expert group recognized that this is an area in need of further research in the context of the great impact that women's issues might have in women with haemophilia and haemophilia carriers.

Concerning the choice of prophylaxis treatment, it will be important to consider the harms of different treatment options and any potential risks. In this context, Hemlibra is an additional treatment option for prophylaxis that offers advantages in terms of ease of administration, and consequently, quality of life, in patients with severe and moderate haemophilia. The benefits in prophylaxis for moderate haemophila clearly outweigh the risks given the morbidity and mortality associated with bleedings in this population.

However, in the rare subset of patients with mild haemophilia for whom prophylaxis is clinically indicated, one needs to consider not only the need for prophylaxis but also the known harms and potential risks associated with the product. Unfortunately, given the available data, including from study HAVEN 6, it is difficult to exclude potential thromboembolic risks on the basis of a small database in these patients and pharmacological considerations. Therefore, these potential risks need to be taken into account in individual benefit-risk decisions, and further data should be collected as part of pharmacovigilance efforts to minimise the uncertainties about these risks.

While considering that this small subset of mild haemophilia patients should not be deprived of Hemlibra as prophylaxis option, the expert group also expressed concerns that this should not lead to indiscriminate use of prophylaxis treatment in mild haemophilia, which would result in unnecessary burden for the patients, and worse, could expose patients to the risk of important side-effects. Therefore, there should be clear information for prescribers to carefully consider the need of prophylaxis in mild haemophilia patients and, when considering different options, to balance any potential benefits against the harms and risks of treatment, including the uncertainties about the risk of thrombosis with emicizumab, given the small safety database.

2. Based on the data submitted (i.e. HAVEN 6 clinical study and extrapolation data) to support the extension of indication of Hemlibra in the management of patients with mild or moderate congenital haemophilia A without inhibitors to FVIII; are the data submitted by the company adequate to address the use in this wider patients population?

See above. The expert group strongly recommended that safety and efficacy data collection post-marketing in the form of registries and cohorts should be considered especially for the mild haemophilia population and in children <2 years old.

3. Do you consider that the posology proposed would be adequate for the use in mild and/moderate Haemophilia A without inhibitors?

It is possible that the current dose is not optimised and that lower doses might be equally effective and less likely associated with important risks. No comparison with alternative doses or regimens has been explored for the management of mild and moderate haemophilia A patients. However, it is acknowledged that treatment optimisation is difficult in this rare disease setting. Further research efforts, if feasible, will need to be guided by future findings from pharmacovigilance data about the harms of the product.

4. Do you consider that it is possible, based on the available and upcoming data, in combination with an extrapolation approach, to extrapolate the use in patients < 2 years of age with mild or moderate haemophilia A without inhibitors.

The expert group agreed that extrapolation to patients < 2 years is possible on the basis of pharmacological considerations. The ease of administration (subcutaneous) in this population is considered of critical importance for the patients with *moderate* haemophilia A and their families However, even in this population, the same consideration applies in terms of *mild* haemophilia patients, with careful assessment about the small subset that might need prophylaxis, and considerations about the harms and potential risks of available options.

2.4.3. Conclusions on the clinical efficacy

Efficacy has been demonstrated on the basis of Study HAVEN 6 which is a single-arm, open label, ongoing study with retrospective design. For treated bleeds, the NB regression model based ABR was 0.8 (95% CI: 0.41, 1.46) and the calculated mean ABR 0.7 (95% CI: 0.01, 5.13]). The majority of patients experience 0 treated bleeds while receiving emicizumab prophylaxis (80.3% 57 patients).

Limitations associated with the retrospective design and descriptive nature of the uncontrolled study were observed. However, in line with the outcome of the ad hoc expert group meeting convened on 22nd September 2022, it is agreed that Hemlibra represents an additional treatment option for prophylaxis that offers advantages in terms of ease of administration in patients with severe and moderate haemophilia. The benefits in prophylaxis for moderate haemophilia outweigh the risks given the morbidity and mortality associated with bleedings in this population.

The CHMP agreed with the expert group recommendation that extrapolation to patients < 2 years is possible in this indication on the basis of pharmacological considerations and the clear advantage of the subcutaneous administration in this patients' population. The ongoing HAVEN 7 study will continue to generate efficacy, safety, PK and PD data on the use of emicizumab in young patients with the final CSR expected in 2030 at the conclusion of a 7-year long term follow-up.

Therefore, it was agreed to recommend the extension of indication for patients with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (FVIII $\geq$ 1% and $\leq$ 5%) with severe bleeding phenotype in all age groups.

2.5. Clinical safety

Introduction

The MAH provided the interim Clinical Study Report from Study BO41423 (HAVEN 6) which is a multicentre, open-label, single-arm study designed to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients with mild or moderate haemophilia A without inhibitors against FVIII.

The safety objective is to evaluate the safety profile of emicizumab by the following endpoints:

• Incidence and severity of AEs, with severity determined according to WHO Toxicity Grading Scale

• Incidence of thrombo-embolism, thrombotic microangiopathy and severe hypersensitivity, anaphylaxis, and anaphylactoid events

• Change from baseline in physical, examination findings, vital signs and ECG parameters

• Incidence of laboratory abnormalities

• Incidence and severity of injection-site reactions

• Incidence of AEs leading to drug discontinuation

• Incidence and significance of anti-emicizumab antibodies

• Incidence of de novo development of FVIII inhibitors

Since the Development International Birth Date (DIBD) 28 June 2012, an estimated total of 917 patients have received emicizumab via clinical trial participation.

In addition to the data from the interim analysis of HAVEN 6, the MAH provided the supportive safety data from ATHN 7 registry in the US.

Patient exposure

Of 72 patients enrolled in Study HAVEN 6, 71 patients started study treatment, and 59 patients (10 with mild disease and 49 with moderate) had completed at least 24 weeks in the study.

Patients were treated with emicizumab 1.5 mg/kg QW (n=24), 3 mg/kg Q2W (n=39), and 6 mg/kg Q4W (n=8), based on patient choice of dosing schedule. In total, patients were exposed to emicizumab prophylaxis for a median duration of 26.14 weeks (range: 4.1 - 61.1). The median number of doses received in the QW group was 27.5, in the Q2W group was 16.0, and in the Q4W group was 10.5.

Demographics

The majority of treated patients were male (69 patients), and 2 were female. The median age was 23.0 years (range: 2−71); 30 patients (42.3%) were <18 years of age and 41 patients (57.7%) were ≥18 years of age.

The median weight of patients at baseline was 75.0 kg (range: 13.5-141.0), and the median BMI was 25.16 kg/m2 (range: 14.1-45.0).

The majority of patients were white (84.5%).

Baseline Haemophilia A characteristics

Of the 71 patients treated, 20 patients (28.2%) had mild haemophilia A and 51 patients (71.8%) had moderate haemophilia A.

At study entry, 37 patients (52.1%) were on prophylactic treatment and 34 patients (47.9%) were on episodic treatment.

Positive FVIII inhibitor titres occurring 5 or more years prior to study entry were reported for 1 patient, which was in line with study inclusion criteria. One patient did not have documentation of a negative inhibitor titre test (performed locally) within 8 weeks prior to enrolment but tested negative for FVIII inhibitor titres on study.

The median number of bleeds in the 24 weeks prior to enrolment was 2.0 (range: 0-60). The overall proportion of patients with target joints (defined as at least 3 bleeds into the same joint over 24 weeks, or an unresolved target joint) was 33.8%. Target joints most frequently included the knee and ankle.

The primary reasons investigators considered prophylaxis warranted for patients was a history of frequent bleeds (54.9%) and/or history of frequent joint bleeds. The two female patients were menarchal and had menstrual bleed history. Neither had heavy bleeding patterns but one had moderate flow and bleeding duration of 8-13 days.

Prior Disease Other than Haemophilia A

The majority of the enrolled patients (71.8%) reported at least one baseline medical condition other than haemophilia. The most frequently reported disorders were haemophilic arthropathy (11.3%), hypertension (9.9%), arthropathy (8.5%), seasonal allergy (7.0%), headache (7.0%), and pain (7%). Other medical disorders were reported infrequently and were typical for the patient population with haemophilia.

Previous Surgeries and Procedures

A total of 43 patients (60.6%) reported surgeries and procedures prior to participating in the study. There wasn't a specific type of surgery/procedure that was commonly reported across patients as each surgery/procedure type was reported in ≤2 patients each.

Previous medications for Haemophilia A:

In the 24 weeks prior to enrolment, 38 treated patients (53.5%) received prophylactic FVIII treatment (57.9% of patients were using FVIII short acting and 42.1% were using FVIII long acting) and 34 patients (46.5%) received episodic FVIII treatment (87.2% receiving FVIII and 15.4% receiving FVIII long acting). Thirty-five patients had received either FVIII or FVIII long-acting in the 7 days prior to first emicizumab dose.

Previous Medication for Conditions Other than Haemophilia A

Previous medications (i.e., those treatments collected outside the Bleed and Medication Questionnaire and stopped before entry into the study) were reported for 12 (16.9%) patients. The most frequently used class of medications was antihemorrhagics, reported in 8 (11.3%) patients (FVIII treatments taken in the week prior to the first dose of emicizumab were recorded on the eCRF page for patients who were continuing their prior FVIII prophylaxis until the second loading dose of emicizumab). All other drugs, by class, were reported for <3% of patients each.

Previous and Concomitant Medication for Conditions Other than Haemophilia A

Previous and concomitant medications were defined as non-haemophilia A treatments that were initiated prior to or at baseline and were continued at study entry (i.e., baseline treatments). The majority of

patients (57.7%) were receiving at least one treatment at baseline, the most common being analgesics, reported for 14 (19.7%) patients.

Concomitant Hemophilia A Treatments

A total of 35 patients (49.3%) received episodically short or long acting FVIII as a treatment for bleeds.

The majority of bleeds (n=29) were treated with short-acting FVIII. The median cumulative dose per bleed was 58.48 units/kg (range: 21.7−902.7), and the duration of treatment was 1 day for the majority (16 bleeds, 55.2%).

High use of FVIII products in HAVEN 6 was driven by 4 patients (all enrolled at one study site) who had received higher amounts of short-acting FVIII treatment and constituted the upper quartile of cumulative dose of short-acting FVIII administered per bleed (cumulative dose >150 units/kg; 27.6%). A high variability of FVIII use between patients in a relatively small sample size of cohorts/arms is observed and the results on FVIII use in HAVEN 6 in part reflect the individual treatment approach of one study site.

The majority of the patients who received short-acting FVIII treatment at any time during the study (n=17 of 21, 81.0%) used a peak dose of < 50 units/kg per treatment administration. The median number of doses administered was 3.0 (range: 1-44).

The majority of patients who received long-acting FVIII treatment at any time during the study (n=12 of 14, 85.7%) used a peak dose of < 50 units/kg per treatment administration. The median number of doses administered was 3.0 (range: 1-7).

Table 16 Treatment with FVIII per Treated Bleed (Treated Population)

Treatment with Factor VIII per Treated Bleed, Before up-titration, All Treated Patients
Protocol: BO41423 Snapshot Date: 26MAY2021 Cutoff Date: 16APR2021

	Emicizumab (N=71)			
	Only Short-Acting FVIII	Only Long-Acting FVIII	Both Short-Acting and Long-Acting FVIII	All Treated Bleeds
Cumulative Dose of Short-Acting FVIII administered per bleed [UNIT/kg]				
n	29	0		29
Mean (SD)	156.18 (224.17)		NE (NE)	156.18 (224.17)
Median	58.48		NE	58.48
IQR	37.31 - 169.97		NE - NE	37.31 - 169.97
Min - Max	21.7 - 902.7		NE - NE	21.7 - 902.7
Cumulative Dose of Long-Acting FVIII administered per bleed [UNIT/kg]				
n		4	0	4
Mean (SD)		53.70 (19.16)	NE (NE)	53.70 (19.16)
Median		46.36	NE	46.36
IQR		42.11 - 65.28	NE - NE	42.11 - 65.28
Min - Max		40.1 - 82.0	NE - NE	40.1 - 82.0
Cumulative Dose of Short-Acting FVIII administered per bleed [UNIT/kg]				
n	29		0	29
<25	3 (10.3%)		0	3 (10.3%)
25-50	10 (34.5%)		0	10 (34.5%)
51-100	4 (13.8%)		0	4 (13.8%)
101-150	4 (13.8%)		0	4 (13.8%)
>150	8 (27.6%)		0	8 (27.6%)
Cumulative Dose of Long-Acting FVIII administered per bleed [UNIT/kg]				
n		4	0	4
<25		0	0	0
25-50		3 (75.0%)	0	3 (75.0%)
51-100		1 (25.0%)	0	1 (25.0%)
101-150		0	0	0
>150		0	0	0
Duration of Short-Acting FVIII per bleed (days)				
n	29		0	29
1	16 (55.2%)		0	16 (55.2%)
2	5 (17.2%)		0	5 (17.2%)
3	3 (10.3%)		0	3 (10.3%)
4	1 (3.4%)		0	1 (3.4%)
>4	4 (13.8%)		0	4 (13.8%)
Duration of Long-Acting FVIII per bleed (days)				
n		4	0	4
1		1 (25.0%)	0	1 (25.0%)
2		2 (50.0%)	0	2 (50.0%)
3		1 (25.0%)	0	1 (25.0%)
4		0	0	0
>4		0	0	0

n is the number of cumulative doses administered to treat a bleed.

Of the 35 patients who received episodic non-emicizumab haemophilia medication, 20 received it after their 2nd loading dose of emicizumab (patients were allowed to continue their haemophilia treatments up to the 2nd loading dose of emicizumab to ensure adequate bleed control until effective emicizumab levels were achieved), 18 of whom used FVIII as treatment for a bleed, 7 of whom used FVIII as preventative for surgery/procedure, and 1 who used FVIII as preventative before activity. The most commonly used non-emicizumab haemophilia medications while on study (after the 2nd loading dose of emicizumab) were FVIII short-acting (12 of 20 patients) and FVIII long-acting (8 of 20 patients).

No other haemophilia treatments (e.g., recombinant FVIIa, PCC, fresh frozen plasma, cryoprecipitate, or DDAVP) were used to treat bleeds in the study.

Concomitant Surgeries and Procedures

Twenty patients (28.2%) reported surgeries and/or procedures during the study. Among 12 patients who reported surgeries, 10 patients had 19 minor surgeries and 2 patients had 2 major surgeries.

Among 19 minor surgeries reported for 10 patients, 12 (63.2%) surgeries were managed with prophylactic hemophilia treatment, 3 of which also required treatment of postoperative bleeds. Both major surgeries were managed with prophylactic hemophilia treatment, 1 of which also required treatment for a post-operative bleed.

All patients who received prophylactic medication for surgery/procedures or treatment for a post-surgical bleed received FVIII (either long or short acting).

Adverse events

A total of 71 patients were included in the safety population. Of these, 49 (69.0%) patients reported 148 AEs in total.

Table 17 Overview of adverse events (treated population):

Safety Summary, Before up-titration, All Treated Patients
Protocol: BO41423 Snapshot Date: 26MAY2021 Cutoff Date: 16APR2021
1

	Emicizumab (N=71)
Total number of patients with at least one AE	49 (69.0%)
Total number of AEs	148
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	4 (5.6%)
AE leading to withdrawal from treatment	0
AE leading to dose modification/interruption	0
Grade >=3 AE	1 (1.4%)
Related AE	11 (15.5%)
Local injection reaction	9 (12.7%)
Confirmed or suspected COVID-19 infection	6 (8.5%)
AE associated with COVID-19	1 (1.4%)
Adverse events of special interest	
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	0
Thromboembolic event (TE)	0
Thrombotic microangiopathy (TMA)	0
Suspected transmission of an infectious agent by the study drug	0
Potential drug-induced liver injury	0

The numbers for systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the Sampson Criteria include only the patients that experienced indicative symptoms identified by the Sampson's Criteria.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.

A total of 69.0% (n=49) of patients experienced at least one AE.

The most common AEs by SOC (≥10% of patients) were Infections and Infestations (23.9%, 17 patients), General Disorders and Administration Site Conditions (19.7%, 14 patients), Musculoskeletal and Connective Tissue Disorders (18.3%, 13 patients), Gastrointestinal Disorders (16.9%, 12 patients), Nervous System Disorders (15.5%, 11 patients), Injury, Poisoning and Procedural Complications (14.1%, 10 patients), Skin and Subcutaneous Tissue Disorders (11.3%, 8 patients).

The most common AEs by SOC with PTs in ≥ 5 % of patients were:

- Infections and Infestations (23.9%, 17 patients): COVID-19 (7%, 5 patients)

- General Disorders and Administration Site Conditions (19.7%, 14 patients): Injection site reaction (5.6%, 4 patients), Injection site erythema (5.6%, 4 patients)

- Musculoskeletal and Connective Tissue Disorders (18.3%, 13 patients): Arthralgia (7%, 5 patients), Pain in extremity (5.6%, 4 patients)

- Nervous System Disorders (15.5%, 11 patients): Headache (14.1%, 10 patients).

All AEs that were reported for the 49 patients were Grades 1-2 with the exception of Grade 3 concussion and Grade 3 hyperglycaemia (both in a single patient).

The safety profile in study HAVEN 6 in the mild / moderate haemophilia A patients without inhibitors was consistent with previous HAVEN Studies (HAVEN 1, HAVEN 2, HAVEN 3 and HAVEN 4) for haemophilia A with or without inhibitors in the primarily severe patient population. There were no new safety signals in HAVEN 6. The MAH provided in the appendices the list of AEs observed within 24 hours after emicizumab administration.

Table 18: AEs reported for HAVEN 6

There were 11 patients with treatment-related AEs. All the treatment-related AEs were non-serious, Grade 1 and 2, and mostly local injection site reactions (9 patients).

MedDRA System Organ Class MedDRA Preferred Term	Emicizumab (N=71)
Total number of patients with at least one adverse event	11 (15.5%)
Overall total number of events	25
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Total number of patients with at least one adverse event	9 (12.7%)
Total number of events	22
INJECTION SITE ERYTHEMA	4 (5.6%)
INJECTION SITE REACTION	4 (5.6%)
FATIGUE	1 (1.4%)
INJECTION SITE PAIN	1 (1.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one adverse event	1 (1.4%)
Total number of events	1
ACCIDENTAL OVERDOSE	1 (1.4%)
INVESTIGATIONS	
Total number of patients with at least one adverse event	1 (1.4%)
Total number of events	1
HEPATIC ENZYME INCREASED	1 (1.4%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one adverse event	1 (1.4%)
Total number of events	1
HEAD DISCOMFORT	1 (1.4%)

Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Table 19: Overview of safety, HAVEN 6, data cut-off 30 October 2021

	Emicizumab (N=72)
Total number of patients with at least one AE	60 (83.3%)
Total number of AEs	248
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	8 (11.1%)
AE leading to withdrawal from treatment	0
AE leading to dose modification/interruption	0
Grade >=3 AE	4 (5.6%)
Related AE	15 (20.8%)
Local injection reaction	12 (16.7%)
Adverse events of special interest	
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	0
Thromboembolic event (TE)	1 (1.4%)
Thrombotic microangiopathy (TMA)	0
Suspected transmission of an infectious agent by the study drug	0
Potential drug-induced liver injury	0

The numbers for systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the Sampson Criteria include only the patients that experienced indicative symptoms identified by the Sampson's Criteria.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.

Serious adverse event/deaths/other significant events

Deaths

There were no deaths reported during the study.

Other Serious Adverse Events

Four patients reported a total of 6 SAEs.

One patient who was using a defective insulin pump reported 3 SAEs (concussion, hyperglycemia and abdominal pain), while the remaining 3 patients reported one each of contusion, diverticulitis and COVID-19 infection.

All SAEs were considered unrelated to study drug by the investigator and were reported to have recovered / resolved. No patients required dose modification due to SAEs. There were no discontinuations from treatment due to SAEs.

Other Significant Adverse Events

None.

Laboratory findings

Haematology

No clinically meaningful post-baseline shifts were observed in haematology parameters (haemoglobin, neutrophils, and platelets).

Chemistry

Overall, there were no clinically meaningful changes in mean chemistry values for any parameter. No trends in shifts from baseline chemistry parameters were observed. Shifts of any magnitude in any parameter were sporadic; shifts from WHO Grade 0-2 at baseline to Grade ≥3 were reported in some patients. The changes were transient and returned to baseline for most patients. In some cases, the laboratory change was reported as an AE. None of the AEs reported for chemistry parameters were considered related to study drug, except one non-serious Grade 1 Hepatic enzyme increased, which resolved. Emicizumab was continued and there was no change in dosage of emicizumab due to this AE.

Coagulation

- Fibrinogen: Treatment with emicizumab had no effect on fibrinogen concentrations, which overall remained stable and generally below the upper limit of normal (4 g/L) throughout the study. Two patients had fibrinogen values over 5 g/L. One of these patients had an SAE of COVID-19 at the time of the high value; the other patient had no AE at the time of the high value. FVIII treatment during the study had generally no effect on fibrinogen concentrations.
- D-Dimer: Treatment with emicizumab had no effect on D-dimer concentrations, which overall remained stable throughout the study duration. The majority of samples contained D-dimer concentrations below the ULN (0.5 µg/mL fibrinogen equivalent units). One patient had high D-dimer (11.05 µg/mL) but there were no AEs reported for this patient around the time of the high D-dimer value. FVIII treatment during the study had generally no effect on D-dimer concentrations.
- Prothrombin Fragment 1+2: Treatment with emicizumab had no effect on concentrations of PF1+2, which overall remained stable and generally within the normal range (2.4 - 7.9 ng/mL) throughout the study duration. Five patients were reported with elevated PF1+2 values; no AEs were reported around the time of these values. FVIII treatment during the study had generally no effect on PF1+2 concentrations.

Theoretical concerns of increased procoagulant risks have been raised with the administration of emicizumab on top of remaining endogenous FVIII activity, as encountered in patients with mild or moderate haemophilia A. However, data on the combination of emicizumab and FVIII on *in vitro* thrombin generation assay indicated that FVIII and emicizumab compete for binding to their targets, FIXa and FX, resulting in non-additive coagulation potential at normal (100 U/dL) FVIII concentrations. Furthermore, there was no indication of prothrombotic effects at high emicizumab exposure on top of the normal endogenous FVIII activity in the repeat-dose toxicity studies in normocoagulative cynomolgus monkeys. In Study HAVEN 6, emicizumab treatment in patients with mild or moderate haemophilia A, i.e. on top of residual endogenous FVIII activity, overall did not increase the peak height of thrombin generation above values seen in normocoagulative individuals. Following treatment with FVIII, immediate increases in FVIII activity reflecting the exogenous FVIII given (up to 176 U/dL) and thrombin generation were observed but TG values remained largely below upper normal limits (400-500 mM for peak height of thrombin generation). Similar investigations were performed for markers of activated coagulation and revealed stable values of D-dimer, PF1+2, and fibrinogen following FVIII administration.

Emicizumab supports the formation of the intrinsic tenase in the absence of sufficient endogenous FVIII. *In vitro* data demonstrate an additive increase of thrombin generation in the presence of 1% or 10% of FVIII, levels representative of patients with moderate or mild haemophilia. Although emicizumab facilitates the intrinsic tenase reaction, its affinity for FIXa or FX is at least 10-fold lower than that of FVIIIa and enzymatic kinetics are not as strong as FVIIIa. These properties of emicizumab safeguard against the risk of a synergistic effect in thrombin generation with FVIIIa.

Vital signs, physical findings and other observations related to safety

Vital signs

No clinically significant changes from baseline in vital signs parameters, including body temperature, pulse rate, respiratory rate, blood pressure (systolic and diastolic) were observed up to the time of the clinical cut-off date.

Electrocardiograms

There were no clinically meaningful changes in any ECG parameters (Heart Rate, PR duration, QRS duration, QT duration, QTcB, QTcF, and RR duration) noted at any study visit. There was no evidence of QT interval shortening or prolongation.

Immunogenicity

Two patients (2.8%) tested positive for ADAs in Study HAVEN 6. Overall, the rate of immunogenicity in this study in patients with mild or moderate haemophilia is consistent with that observed in previous studies. Out of the 2 patients who tested positive for ADA, 1 patient tested positive for the presence of neutralizing anti-emicizumab antibodies (nAbs). The presence of nAbs was not associated with decreased emicizumab concentration.

No bleeding events (treated or all bleed) were reported by the 2 ADA positive patients and there were no reported events of hypersensitivity or anaphylaxis associated with ADA.

A program-wide immunogenicity assessment of emicizumab (including Study HAVEN 6) indicated that 4.9% of patients (36/739 patients) developed ADAs against emicizumab and 2.6% (19/739) developed nAbs. In 4 patients (0.5% of the total population), the presence of nAbs was associated with decreasing emicizumab concentrations. Among these 4 patients, 2 patients withdrew from the respective study (1 patient due to loss of efficacy and the other due to personal preference), 1 patient was still participating in the clinical trial (Study YO39309) as of CCOD and 1 patient completed the study (he was ADA negative at that point and moved to commercial emicizumab).

Overall, the development of anti-emicizumab antibodies did not appear to affect the frequency or type of AEs reported. No SAEs of hypersensitivity or anaphylaxis associated with ADAs were reported, and there was no evidence of a causal relationship between anti-emicizumab antibodies and injection site reactions. While the presence of ADAs was associated with a slightly higher proportion of ISRs, for a majority of ADA-positive patients, ISRs occurred before ADA detection.

The incidence of patients who tested positive for ADAs remained low as expected for humanized monoclonal antibodies (van Brummelen et al. 2016). Given this low incidence of ADAs, particularly those impacting pharmacokinetics and pharmacodynamics, detection of ADAs, including anti-emicizumab nAbs, has limited effect on clinical management, suggesting that routine laboratory surveillance is not warranted for the clinical use of emicizumab. A progressive loss of efficacy manifested by an increase in breakthrough bleeding events despite compliance with emicizumab dosing regimen, reduced emicizumab concentration, diminished chromogenic FVIII-like activity using an assay with human factors, or prolonged activated partial thromboplastin time could be indicators of the presence of clinically important ADAs.

Anti-Factor VIII Antibody

Emicizumab does not induce inhibitors against FVIII given the lack of sequence or structure homology with FVIII. In most patients with inhibitors against FVIII, titers remained stable or tended to decline. In patients without inhibitors in Studies BH30071 (HAVEN 3) and BO39182 (HAVEN 4), no instance of clinically relevant *de novo* inhibitor development was detected. In line with these findings, there were no instances of inhibitor development in mild or moderate patients from Study HAVEN 6.

Safety in special populations

Adverse Events by Age

Of the overall 71 patients treated with emicizumab in study BO41423 (HAVEN 6), 30 patients were <18 years of age and at least one AE was reported in 18 patients. The remaining 41 patients were ≥18 years of age treated with emicizumab and at least one AE was reported in 31 patients. Overall, the AE profile was similar among all patients, irrespective of age, with however a slightly higher rate of AEs in patients ≥18 years old (75.6%) compared to patients <18 years old (60.0%), although no difference in the severity or seriousness of AEs reported was observed. There were 2 patients ≥ 65 years of age.

Adverse Events by Haemophilia Severity

The AE profile was similar among all patients, irrespective of haemophilia severity (i.e., mild [n=20], moderate [n=51]).

Of the 49 patients with AEs, 14 (70.0%) patients with mild haemophilia had 37 AEs, compared to 35 (68.6%) patients with moderate haemophilia who had 111 AEs. There was no obvious difference in the rates of specific PTs, except 5 patients (9.8%) with moderate haemophilia A reported AEs of COVID-19 compared to 1 patient (5%) with mild haemophilia A. There were no differences in the rates of SAEs between patients with mild or moderate haemophilia: 3 patients (5.9%) with moderate haemophilia had SAEs compared to 1 patient (5%) with mild haemophilia. However, there were a relatively small number of patients with any specific PT in each subgroup. The types of AEs reported in HAVEN 6 were consistent with what has previously been reported for the HAVEN 1 to 4 studies.

Adverse Events by Race

The majority of patients in the study were white (60 [84.5%]). Due to the very low number of patients enrolled in the study who were of other races, the effect of race on AEs is not evaluable.

Phase III clinical trials Haven 1 to 4

The safety profile of emicizumab from previous HAVEN studies (HAVEN 1, CCOD: 8 September 2017, HAVEN 2, CCOD: 5 October 2017, HAVEN 3, CCOD: 15 September 2017 and HAVEN 4, CCOD: 15 December 2017), was used for the pooled analysis of ADRs for the proposed SmPC. The safety profile of emicizumab in mild/moderate haemophilia A patients without inhibitors (Study HAVEN 6) was consistent with previous HAVEN studies in the primarily severe haemophilia A with or without inhibitor patients.

Safety related to drug-drug interactions and other interactions

There is no new information for drug interaction in study HAVEN 6. The prevention and the treatment of breakthrough bleeds having been managed by FVIII in the patients with non-severe haemophilia A without inhibitors included in HAVEN 6 study, no aPCC products have been used and hence there is no new information regarding the interaction between aPCC and emicizumab in this currently investigated subgroup.

Discontinuation due to adverse events

At the time of the CCOD for this interim analysis, 1 patient had discontinued prior to start of study treatment (personal choice) and none had withdrawn from the study after starting treatment.

Among the 71 patients treated in HAVEN 6 study, none was withdrawn for a safety reason.

Post marketing experience

Supportive safety studies from real world data

- Study ATHN7

The ATHN7 (American Thrombosis and Haemostasis Network) study is a longitudinal, natural history cohort study of the safety of the treatments used for people with haemophilia of all severities.

The primary objective of the ATHN7 study is to determine the safety of non-factor products, bypassing agents or clotting factor replacement products when used for patients with haemophilia with or without inhibitors. The ATHN registry examines the use of haemophilia treatment products and their outcomes, which is being conducted at up to 50 ATHN-affiliated sites in the US. The ATHN7 study is part of the wider ATHN Transcends study, which is a natural history study of non-neoplastic hematologic disorders.

In the full ATHN7 study, participants will be followed for 4 years from time of enrolment. The total study duration is 6 years. The current analysis provided by the MAH is a preliminary analysis from the first available emicizumab data until the latest available data up to April 30, 2021.

Results:

There were 35 patients in the emicizumab-treated cohort, of these 27 patients (77%) had mild or moderate haemophilia A without FVIII inhibitors.

Table 20 Baseline characteristics of the people with mild and moderate haemophilia A in the ATHN registry

	No FVIII inhibitors (N=27)	FVIII inhibitors (N=6)	Overall (N=35*)
Current Age			
Mean (SD)	25.4 (19.1)	22.8 (29.1)	25.4 (20.3)
Median [Min, Max]	20.8 [2.66, 81.7]	7.74 [2.33, 77.7]	20.8 [2.33, 81.7]
Age Group			
1 to 18	12 (44.4%)	4 (66.7%)	16 (45.7%)
18 to 65	14 (51.9%)	1 (16.7%)	17 (48.6%)
65 and older	1 (3.7%)	1 (16.7%)	2 (5.7%)
Primary Diagnosis Severity			
Mild	1 (3.7%)	0 (0%)	1 (2.9%)
Moderate	26 (96.3%)	6 (100%)	34 (97.1%)
Sex			
Male	27 (100%)	5 (83.3%)	34 (97.1%)
Female	0 (0%)	1 (16.7%)	1 (2.9%)
Follow-up duration (Patient-days)			
Total	11,240	2,366	13,910
Mean (SD)	416 (197)	394 (243)	397 (206)
Median (Q1,Q3)	436 [29, 744]	459 [36, 661]	399 [29,744]

SD = standard deviation, Q1=lower quartile, Q3=upper quartile,
Baseline characteristics of the people with mild and moderate hemophilia A. *The inhibitor status was not known for 2 cases, these two cases had a total follow-up of 304 days.

Among the 35 patients in the cohort, the mean standard deviation (SD) follow-up time was 397 (206) days, with a median interquartile range (IQR) of 399 (29, 744) days. The total follow-up was 13,910 patient days or 38.08 years. The mean (SD) follow-up time among the 27 patients without FVIII inhibitors was 416 (197) days, with a median (IQR) of 436 (29, 744) days.

One serious adverse event was recorded in the mild and moderate population over the 38.08 patient-years. The serious AE rate was 0.026 per patient year. This was a case reported with traumatic hemorrhage (chronic subdural hematoma) assessed unlikely to be related to emicizumab by the treating physician. The ICH event likely occurred during the loading phase of emicizumab when therapeutic levels of emicizumab would not have been achieved. In the literature, a substantial proportion of ICH occur in older adults and patients with milder forms of hemophilia (Ljung, R.C.R., 2008).

There were no cases of TMA or anaphylaxis. This analysis was limited by the small sample of patients with mild or moderate hemophilia A treated with emicizumab, a targeted list of AE categories, and relatively

short exposure time to emicizumab. At this interim analysis of real-world data, these AEs are consistent with the safety profile of emicizumab observed in clinical trials.

TSUBASA

The MAH provided, in the clinical summary of efficacy, interim data on the TSUBASA study, an observational study conducted in Japan, claiming that these data provide supportive safety data for the use of emicizumab in patients with hemophilia A without FVIII inhibitors.

- Post-marketing data

Since the DIBD 28 June 2012 and until the DLP of the PBRER (15 November 2020), an estimated total of 917 patients have received emicizumab via clinical trial participation. In addition an estimated cumulative total of 10,787 patients have received emicizumab from marketing experience.

Safety data from the clinical trials:

A total of 223 SAEs were cumulatively retrieved for all company-sponsored interventional studies using emicizumab as an investigational drug. Review of these data did not identify any new safety concerns that could impact the safety profile of emicizumab.

Safety data from Postmarketing data Sources:

A total of 998 SAEs were cumulatively retrieved from post-authorization sources (Spontaneous, including health authority (worldwide), literature, non-interventional postmarketing study and reports from other solicited sources). Review of interval data did not identify any new safety concerns that could impact the well-known safety profile of emicizumab. A summary of the SOC under which AEs were most frequently reported from post-authorisation sources is shown below.

Table 21 Total numbers of AEs and SOCs of the most frequently reported AEs from Post-authorization Sources

SOC	Spontaneous, including health authority (worldwide) and literature				Non-interventional post-marketing study and reports from other solicited sources [b]	
	Serious		Non-serious		Serious	
	interval	cum.	interval	cum.	interval	cum.
Total no. of AEs (all SOCs)	191	691	585	1857	76	307
SOCs of the most frequently reported AEs in the reporting interval						
Injury, poisoning and procedural complications	36	108	197	506	6	39
General disorders and administration site conditions	9	43	162	530	3	35
Vascular disorders	25	108	44	151	19	54
Musculoskeletal and connective tissue disorders	34	121	34	149	6	48
SOCs of the most frequently reported AEs cumulatively						
Injury, poisoning and procedural complications	36	108	197	506	6	39
General disorders and administration site conditions	9	43	162	530	3	35
Musculoskeletal and connective tissue disorders	34	121	34	149	6	48
Vascular disorders	25	108	44	151	19	54

cum. = cumulative; SOC = System Organ Class.

Source: Appendix 2b (Cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources) from the latest PBRER (15 November 2020), Report Number 1104302.

[a] Non-interventional studies (including post-authorisation safety studies), reports from other solicited sources, and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, health authorities [worldwide], and scientific literature).

[b] This does not include interventional clinical trials.

The MAH has assessed the relevant data that became available during the reporting interval of the most recent PBRER, including data from clinical trials, post-marketing, published literature, and other safety risk management sources. Based on the evaluation of these data, no new safety concerns were identified and all newly available information that became available during the reporting interval did not alter the known benefit-risk profile of emicizumab.

2.5.1. Discussion on clinical safety

The MAH provided the interim safety results from Study BO41423 (HAVEN 6) in patients with mild or moderate haemophilia A without inhibitors against FVIII, according to the EMA's request following the previous application for this extension of indication. It was indeed concluded in the frame of the first application assessment that the very limited data that had been provided on non-severe haemophilia A patients were not sufficient to assess, among other concerns, the safety profile of emicizumab in this population, due to the hypothetical risk of thromboembolism associated to the administration of emicizumab in patients having an endogenous FVIII activity ≥ 1% and potentially receiving additional FVIII doses as part of bleeding management (the risk of elevated thrombin generation already being a concern in severe haemophilia patients only treated by emicizumab or by emicizumab in association to FVIII products).

In total, 71 patients (20 with mild haemophilia A and 51 with moderate HA) in study HAVEN 6 were exposed to emicizumab prophylaxis for a median duration of 26.14 weeks. 59 patients (only 10 with mild disease and 49 with moderate) had completed at least 24 weeks in the study. A total of 35 patients (49.3%) received episodically short or long acting FVIII as a treatment for bleeds. No other haemophilia treatments than FVIII (e.g., recombinant FVIIa, aPCC, fresh frozen plasma, cryoprecipitate, or DDAVP) were used to treat bleeds in the study which is a reassuring information (it is however to note that tranexamic acid was reported to be used in stomatological preparations in 11 patients concomitantly emicizumab exposure). Out of the 35 patients who received episodic non-emicizumab haemophilia medication, 20 received it after their 2nd loading dose of emicizumab. Among 19 minor surgeries reported for 10 patients, 12 were managed with prophylactic haemophilia treatment (either short or long acting FVIII), 3 of which also required treatment of postoperative bleeds. Two major surgeries were managed with prophylactic haemophilia treatment, 1 of which also required treatment for a post-operative bleed.

49 out of the 71 patients reported 148 AEs in total as of 16 April 2021. There were no deaths, AEs of special interest (including thrombotic microangiopathy, thromboembolism, systemic hypersensitivity / anaphylactic / anaphylactoid reaction) or AEs that led to withdrawal from treatment, AEs leading to dose modification, or AEs leading to study drug interruption that were reported. The AEs ventilation through the SOCs was consistent with the events that can be observed for the disease and consistent with the safety data observed in the previous studies of the clinical development of emicizumab.

Eleven patients had 24 non-serious adverse reactions. Most of the ADRs were injection site reactions (injection site erythema (5 patients), injection site pain (1 patient) and injection site reaction (14 in 4 patients, 1 patient having reported this ADR in 10 different occurrences). Also, one patient who reported an injection site erythema also had fatigue and a head discomfort, one patient had an increase of hepatic enzymes and there was one accidental overdose reported in one patient.

The MAH compared the safety data retrieved in study HAVEN 6 between patients with mild haemophilia and patients with moderate haemophilia. No major difference between the two groups of patients was seen but the MAH acknowledges that the relatively small number of patients with any specific PT in each subgroup did not allow an adequate comparison.

Based on the available data, the safety profile in the paediatric population did not appear to be different to that in adults.

The vital signs and physical findings were not of concern within the interim results.

Regarding clinical laboratory parameters, there were no meaningful observations in hematology parameters, but some meaningful changes of chemistry values were reported as AEs at different time points for some patients. In one case the AE of hepatic enzyme increase was assessed as an adverse reaction by the investigator. The coagulation parameters were tested throughout the study, and emicizumab exposure, associated or not to FVIII treatment, did not have a major effect on the levels of fibrinogen, D-dimer and

PF1+2 concentrations. For some patients at different time points, elevated values were observed, but no AE that could be associated to a thromboembolic event was observed when these values were elevated.

Even though the AEs and ADRs observed in HAVEN 6 study did not bring any new safety information considering the currently known safety profile of emicizumab, these data are not considered as sufficient to conclude as the amount of exposed patients, the median duration of exposure and the median number of emicizumab doses are considered too low for the mild haemophilia subgroup. The number of patients having received a FVIII product concomitantly to emicizumab is also considered too small to appropriately assess and conclude on the safety consequences of such treatment associations in patients with a non-severe congenital haemophilia A.

An update to the interim analysis has been provided as part of this procedure. The clinical cut-off date of the primary analysis was 30 October 2021 resulting in a median emicizumab exposure of 54.29 weeks, which is more than double the median follow-up time of the interim analysis (16 April 2021). Overall, the safety results in patients with mild and moderate HA without FVIII inhibitors are consistent with data previously observed at interim analysis. The pharmacodynamic and safety biomarkers assessed in the 72 included patients did not show abnormal signs of interaction between emicizumab and endogenous FVIII and no safety biomarker that could signal a thrombotic event. One case of interest of anal vein thrombosis was observed but this case is not considered to add new information to the safety profile of emicizumab as the event was not considered as related to study treatment by the investigator but a potential triggering role of emicizumab cannot be fully excluded.

Two patients (2.8%) tested positive for ADAs, 1 out of the 2 patients having tested positive for the presence of neutralizing ADAs (nAbs) (without decreased emicizumab concentration or clinical consequence associated). Regarding this issue, since the beginning of the MA for Hemlibra, there has been no available commercially validated assay for testing the ADA/nAb status in clinical use setting, as testing is only possible in the clinical trials held by the MAH, using a company validated assay. Therefore in case of increase in breakthrough bleeding events or evocative sign of loss of efficacy, evaluation is currently based on PK and clinical assessment. The treatment decision-making can only rely on the experience and practices of specialized centres. This likely raises a concern for accurate assessment of etiologic factors in case of increase in bleeding events. It is therefore needed that the MAH develops tests to measure neutralising antibodies outside clinical trials in order to investigate the etiology of loss of efficacy and to allow physicians to adapt Hemlibra treatment if necessary.

The MAH provided, as supportive information, interim results for the ATHN7 study conducted in the US. Within this study 27 patients with non-severe haemophilia A without inhibitors have been included, which is very limited, and no adverse reaction was observed. The MAH also provided interim analysis of TSUBASA study, conducted in Japan, but no patients with mild haemophilia A were recruited, 15 patients with moderate haemophilia A were recruited and no safety data have been made available yet. These data do not bring any new information.

The safety of emicizumab in the post-marketing setting is regularly assessed throughout the PBRER and the PSUSA procedures. In addition to spontaneous reporting, the safety of emicizumab is monitored in two PASS (European registries EUHASS and PedNET). No particular safety concern was raised from the post-marketing / clinical trial studies in patients with mild or moderate HA. Two thrombotic events were reported from post-marketing use and the potential facilitating role of emicizumab cannot theoretically be excluded but the patients' medical history and multiple risk factors do not allow to draw any conclusion.

Based on available data, the safety profile in the paediatric population does not appear to be different to that in adults.

2.5.2. Conclusions on clinical safety

Section 4.4 of the SmPC already mentioned that treatment with bypassing agents should be discontinued the day before starting Hemlibra therapy. In addition, the SmPC also recommends that patients receiving Hemlibra prophylaxis should be monitored for the development of thromboembolism when administering aPCC. The physician should immediately discontinue aPCC and interrupt Hemlibra therapy if clinical symptoms, imaging, and/or laboratory findings consistent with thrombotic events occur and manage as clinically indicated.

Thrombo-embolic events will be further assessed in a PASS based on data from national registries (please see RMP).

Based on the safety data submitted, the CHMP agree not to recommend an indication in routine prophylaxis of bleeding episodes in patients with Haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitor who have mild disease considering the small safety database in this patients' population, the potential risk of thromboembolic events which would not outweigh the need for prophylactic treatment.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submittedan updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.7 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.7 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• **Thromboembolic events (associated with emicizumab and aPCC)** • **Thrombotic microangiopathy (associated with emicizumab and aPCC)** • **Loss of efficacy due to anti-emicizumab antibodies**
Important potential risks	• **Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab** • **Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions** • **Thromboembolic events not associated with concomitant aPCC**
Missing information	• **Use in Neonates and Infants**

aPCC = activated prothrombin complex concentrate

Pharmacovigilance plan

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 27 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
This section is not applicable because there are no specific requirements.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
This section is not applicable because there are no specific requirements.				
Category 3 - Required additional pharmacovigilance activities				
PASS based on the EUHASS registry Ongoing	To assess the incidence of thromboembolism, thrombotic microangiopathy, and anaphylaxis in real-world conditions, in patients exposed to emicizumab and treated at centers participating to the European Haemophilia Safety Surveillance System (EUHASS) in all disease severities.	• Thromboembolic events (associated with emicizumab and aPCC) • Thrombotic microangiopathy (associated with emicizumab and aPCC) • Thromboembolic events not associated with concomitant use of aPCC • Systemic hypersensitivity, anaphylaxis, and anaphylactoid events • Loss of efficacy due to anti-emicizumab antibodies	PASS annual report (generated by Roche, based on the emicizumab -specific annual report from EUHASS) Submission of First PASS annual report Submission of annual reports yearly thereafter (final data collection Dec 2024) Submission of Final study report	 January 2021 January 2026

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
PASS based on the PedNet registry Ongoing	Evaluation of the incidence of thromboembolic events, TMA, and anaphylaxis in the pediatric population in the post-authorization setting in all disease severities.	• Thromboembolic events (associated with emicizumab and aPCC) • Thrombotic microangiopathy (associated with emicizumab and aPCC) • Thromboembolic events not associated with concomitant use of aPCC • Systemic hypersensitivity, anaphylaxis, and anaphylactoid events • Use in Neonates and Infants • Loss of efficacy due to anti-emicizumab antibodies	PASS annual report (generated by Roche, based on the emicizumab -specific annual report from PedNet) Submission of First PASS annual report Submission of annual reports yearly thereafter (final data collection Dec 2024) Submission of Final study report	January 2021 January 2026
PASS based on national disease registries and ongoing multi-country registries (BO44691) Planned	To evaluate the long-term safety of emicizumab treatment in patients with moderate hemophilia A and severe bleeding phenotype.	• Thromboembolic events (associated with emicizumab and aPCC) • Thromboembolic events not associated with concomitant use of aPCC • Thrombotic microangiopathy (associated with emicizumab and aPCC) • Systemic hypersensitivity, anaphylaxis, and anaphylactoid events	Following initiation of the study, an update on recruitment status will be provided yearly. The first interim study report will be provided once 100 patients have been reports will be submitted yearly thereafter until study completion.	Final Study Report expected January 2029

aPCC = activated prothrombin complex concentrate; EUHASS = European Haemophilia Safety Surveillance; HCP = healthcare professional; *EUHASS/PedNet data collection may be extended further, depending on reimbursement timelines for moderate HA.

Risk minimisation measures

V.3 SUMMARY TABLE OF PHARMACOVIGILANCE AND RISK MINIMIZATION ACTIVITIES BY SAFETY CONCERN

Table 30 Summary table of Pharmacovigilance and Risk Minimization activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified risks		
Thromboembolic events (associated with emicizumab and aPCC)	Routine risk minimization measures: • SmPC section 4.4: Special warnings and precautions for use • SmPC section 4.5: Interaction with other medicinal products and other forms of interaction section • SmPC section 4.8: Undesirable effects • Package Leaflet Section 2 What you need to know before you use Hemlibra and Section 4 Possible side effects • Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders Additional risk minimization measures: • Guide for Healthcare Professionals • Patient Card • Patient/Carer Guide	Routine pharmacovigilance activities: • Specific guided questionnaires • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry • PASS based on multinational registry study BO44691
Thrombotic microangiopathy (associated with emicizumab and aPCC)	Routine risk minimization measures: • SmPC section 4.4: Special warnings and precautions for use • SmPC section 4.5: Interaction with other medicinal products and other forms of interaction section • SmPC section 4.8: Undesirable effects • Package Leaflet Section 2 What you need to know before you use Hemlibra and Section 4 Possible side effects • Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders Additional risk minimization measures: • Guide for Healthcare Professionals • Patient Card • Patient/Carer Guide	Routine pharmacovigilance activities: • Specific guided questionnaires • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry • PASS based on multinational registry study BO44691

Safety concern	Risk minimization measures	Pharmacovigilance activities
Loss of efficacy due to anti-emicizumab antibodies	Routine risk minimization measures: • SmPC section 4.4: Special warnings and precautions for use • SmPC section 4.8: Undesirable effects • SmPC section 5.1: Pharmacodynamic properties • Package Leaflet section 2: What you need to know before you use Hemlibra • Package Leaflet section 4: Possible side effects with Hemlibra	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry • PASS based on multinational registry study BO44691
Important Potential risks		
Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab	Routine risk minimization measures: • SmPC section 4.4: Special warnings and precautions for use • SmPC section 4.5: Interaction with other medicinal products and other forms of interaction section • Package Leaflet section 2 What you need to know before you use Hemlibra • Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders Additional risk minimization measures: • Guide for Healthcare Professionals • Patient Card • Patient/Carer Guide • Guide for Laboratory Professionals	Additional pharmacovigilance activities: N/A

Safety concern	Risk minimization measures	Pharmacovigilance activities
Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions	Routine risk minimization measures: • SmPC section 4.3: Contraindications • SmPC section 4.8: Undesirable effects • Package Leaflet section 2 What you need to know before you use Hemlibra • Package Leaflet section 4: Possible side effects with Hemlibra *No additional measures*	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry • PASS based on multinational registry study BO44691
Thromboembolic events not associated with concomitant aPCC	Routine risk minimization measures: • No specific text in the SmPC • Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders *No additional measures*	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNet registry • PASS based on multinational registry study BO44691
Missing Information		
Use in neonates and infants	• SmPC section 4.2: Posology and method of administration (special populations) *No additional measures*	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: PASS based on the PedNET registry

aPCC = activated prothrombin complex concentrate; EUHASS = European Haemophilia Safety Surveillance; SmPC = Summary of Product Characteristics

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, of the SmPC have been updated. The Package Leaflet has been updated accordingly. The additional monitoring (black triangle) has also been removed.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- No significant changes affecting the readability of the package leaflet have been made;
- User consultation was carried out in the context of the initial MAA; the target group of users is similar between the initial approval indication and the proposed extension of indication, with no age difference;
- The safety profile remains consistent with that observed in approved indication, with no new safety signals seen in mild or moderate HA patients without FVIII inhibitors.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH seeks to extend the currently approved indication statement for emicizumab to include adult and paediatric patients with HA without FVIII inhibitors who have mild or moderate disease for whom prophylaxis is clinically indicated.

3.1.2. Available therapies and unmet medical need

The standard treatment for HA patients with severe bleeding phenotype is FVIII replacement therapy either episodic or prophylactic. Prophylactic therapy has been recognised as beneficial. However, due to the high treatment burden of FVIII prophylaxis, a substantial fraction of patients is only treated episodically in response to the occurrence of bleeding symptoms.

Although standard definitions of HA severity are based upon laboratory FVIII activity and the residual plasma level of clotting factor is considered to be the most critical predictor of spontaneous bleeding, the determinants of clinical bleeding phenotype may be complex.

For patients with HA with a severe phenotype (note that this may include patients with moderate HA with a severe phenotype), international organisations recommend regular long-term prophylaxis as the standard of care to prevent hemarthrosis and other spontaneous or breakthrough bleeding, maintain musculoskeletal health and promote quality of life.

Prophylactic regimen varies between individuals according to differences in clinical and lifestyle characteristics. Reflecting this, it is becoming increasingly accepted that prophylactic regimen for non-severe HA should be individualized and tailored to prevent bleeding for an individual level by taking into consideration his bleeding phenotype, joint status, clinical conditions (i.e. need for surgery), inter-patient

PK variability, physical activities (daily and sporting), lifestyle, adhesion to therapy etc. This is of the most importance for young patients given that their physical activities and lifestyle are changing, as well as for mild HA patients (FVIII may up to 40%) who may not necessarily have abnormal or prolonged bleeding problems until they experience serious trauma or undergo surgery.

For these reasons, the WFH recommends considering desmopressin as an option for treatment which is effective for the treatment of minor bleeding episodes in most patients with mild HA. Antifibrinolytic therapy such as tranexamic acid is also a valuable alternative particularly in controlling muco-cutaneous bleeding or for dental/oral procedures. In those mild HA patients unresponsive to DDAVP, replacement therapy with FVIII is the treatment of choice for bleeding episodes. To our knowledge, there is not any international organisation recommending the consideration of routine prophylaxis in mild HA without inhibitors.

Given the wide intra- and inter-individual variability and in the context of concomitant use of several procoagulant drugs, individualised tailoring of prophylaxis treatment including flexibility of dosing is known as key to achieve optimal protection by adjusting for physical activity, lifestyle, individual PK without inducing hypercoagulability responsible for thrombotic complications.

Emicizumab is designed as prophylactic agents to be used according to fixed dosing schedules, therefore, individualised tailoring of such treatment to meet the physical needs of the patient is not possible.

According to the advice of the ad-hoc expert group (SAG), there are different views on the subgroup of non-severe haemophilia patients who might benefit from prophylaxis treatment. There is general agreement that currently, routine prophylaxis to be investigated for emicizumab would include moderate haemophilia patients with FVIII levels ≤5%:

• who had a first spontaneous intra-articular bleed before the age of 5 years or

• who were already started on a prophylaxis regimen with a long-term prophylaxis intention

This SAG's advice is in line with the recommendation of the WFH i.e. "Prophylaxis is the standard of care for people with severe haemophilia, and for some people with moderate haemophilia, or for those with another congenital bleeding disorder that is associated with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding". It is also consistent with recently published expert opinion (Valentino LA et al Expert Rev Hematol. 2020 Jul;13:731-743) highlighting that early prophylaxis may also be appropriate for children with moderate haemophilia A who experience joint bleeding prior to age 5 years and have a more severe bleeding pattern. Indeed, as discussed by experts, hemarthrosis accounts for more than 90% of all serious bleeding events, this hallmark typically begins early in childhood and one paramount benefit of long-term prophylaxis is joint protection. According to this expert opinion, although the subcutaneous administration with long-effect of emicizumab is an undeniably appealing prophylactic option for haemophilia, a major challenge to the widespread use of emicizumab and other pro-coagulant therapies is a lack of data regarding the overlap between the therapeutic window, where bleeding is prevented, and the toxicity window, where the risk of thrombosis increases. Large, multicenter studies are needed comparing ABR/AJBR in patients receiving FVIII versus emicizumab prophylaxis to justify the higher cost of this nonfactor therapy.

3.1.3. Main clinical studies

The current application includes data from the Phase III Study BO41423 (HAVEN 6), which is a single-arm, open label, ongoing, multicentre study evaluating the safety and efficacy of emicizumab. Patients of all ages with mild (FVIII > 5% and < 40%) and moderate HA (FVIII ≥ 1% and ≤ 5%) without FVIII inhibitors who warrant prophylactic treatment were enrolled. Furthermore, subjects should be able to provide documentation of the details of prophylactic or episodic FVIII treatment and of number of

bleeding episodes during the last 24 weeks prior to enrolment for generating retrospective baseline data. Both patients on prophylactic and episodic FVIII treatment were enrolled.

The sample size and timing for this specific interim analyses (IA) were not defined in the study protocol, and potential additional IAs were left undefined. There is no formal hypothesis testing in this study whose primary endpoint was safety. Primary efficacy endpoint was number of treated bleeds over time (i.e. bleed rate). All efficacy analyses are of descriptive / exploratory nature in this study.

The emicizumab dosing regimen was 4 loading doses of emicizumab 3 mg/kg SC QW for 4 weeks followed by a maintenance dose of either 1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W based on patient preference in this single-arm study. For the treatment of breakthrough bleeds, FVIII should be used at the lowest dose expected to achieve haemostasis. Other drugs intended to control bleeds e.g., bypassing agents, DDAVP, or antifibrinolytics were permitted.

3.2. Favourable effects

The primary (treated bleeds) and secondary efficacy analyses were based on the treated population, by excluding all bleeds due to surgery/ procedure and by implementing 72 hour-rule:

Follow up for a median of 27.5 weeks, the interim results indicated that:

- For treated bleeds, the NB regression model based ABR was 0.8 (95% CI: 0.41, 1.46) and the calculated mean ABR 0.7 (95% CI: 0.01, 5.13]). The majority of patients experience 0 treated bleeds while receiving emicizumab prophylaxis (80.3% 57 patients).

- For all bleeds (those treated and untreated with coagulation factors, the model based ABR was 2.3 (95% CI: 1.63, 3.10) and the calculated mean ABR was 2.2 (95% CI: 0.31, 7.53).

A total of 38 (53.5%) patients experienced all bleeds during the study by excluding bleeds due to surgery/ procedure and by implementing 72 hour-rule.

A total of 33 treated bleeds (primary endpoint) were reported in 14 (19.7%) of 71 patients; 90.9% (30 of 33 bleeds) were traumatic bleeds while the rest 9.1% (3/33 bleeds) were spontaneous bleeds (excluding bleeds due to surgery/procedure). Treated bleeds occurred most frequently in the joints (48.5%, 16/33 bleeds) reported in 7 patients (9.9%) including 4 (5.6%) patients with treated target joint bleeds.

- For treated joint bleeds and for treated spontaneous bleeds, the model-based ABR was 0.3 (95% CI: 0.12, 0.65) and 0.1 (95% CI: 0.02, 0.23) respectively.

- For treated target joint bleeds (including unresolved target joints), the model-based ABR did not converge due to a low number of bleeds with short follow-up times. The calculated mean ABR was 0.1 (95% CI: 0.00, 3.93).

Exploratory analyses by including bleeds due to surgery/procedure and irrespective of the 72-hour rule: a total of 109 bleeds occurred in 71 treated patients; 67.9% (74/109 bleeds) were traumatic bleeds, 22.9% (25/109 bleeds) were spontaneous bleeds, and 9.2% (10/109 bleeds) were due to surgery/procedure. Locations other than joints or muscle such as nose, mouth, and fingers/thumb represent 70.6% (77 of 109 bleeds) reported in 28 patients.

A post-hoc analysis was performed to compare ABR for All bleeds retrospectively collected by the patients in the 24 weeks prior to study entry with ABR collected during the efficacy period of this study. This analysis showed that the median estimated ABR prior to study entry was 4.3 (0.0-8.7) and the median calculated ABR for All Bleeds (72h-rule) was 1.5 (0.0-3.4).

Updated data (cut-off date 30 October 2021) with a median emicizumab exposure of 54.29 weeks (range: 8.1- 89.1), showed that the safety and efficacy profile of emicizumab in patients with mild and moderate HA without FVIII inhibitors are consistent with data previously observed at interim analysis (cut-off date 16 April 2021).

At the cut off for primary analysis on 30 October 2021, none of the 38 participants who experienced one or more bleeding events tested positive for ADA, and no bleeding events were reported by the 2 participants who were identified as ADA positive.

3.3. Uncertainties and limitations about favourable effects

The pivotal trial is an ongoing, single arm, open-label study, the absence of a comparator is a clear limitation for the interpretation of study data.

All efficacy analyses are of descriptive nature in this study, without formal hypothesis testing nor adjustment for multiplicity. So all analyses should be viewed as exploratory.

The number of bleeds in the last 24 weeks before study entry has been collected retrospectively based on historic information collected by patients, which limits the interpretation of baseline bleeds in comparison with post-baseline data and makes questionable the accuracy and completeness of baseline data. Additional analyses were performed by the MAH to assess the potential bias in the retrospective collection of bleed data. However bias cannot be excluded nor quantified based on these exploratory analyses. It is still of concern due to the retrospective nature of pre-study data, and the comparability between baseline and post-baseline data remains doubtful.

At the approved dosing, emicizumab does not completely restore normal haemostasis in mild/moderate patients enrolled in this study and more than half of treated patients (38/71, 53.5%) still experience on-study bleeds by excluding bleeds due to surgery/ procedure and by implementing 72 hour-rule. Development of neutralising anti emicizumab antibodies with decreasing emicizumab concentration leading to loss of efficacy has been observed during clinical trials. At this stage of knowledge, in absence of a commercially validated assay specific for assessing the antidrug antibody status with emicizumab, treatment decision-making can only rely on the experience and practices in place in specialised centres according to scientific guidelines.

A post-hoc analysis was performed to compare ABR for All bleeds retrospectively collected by the patients in the 24 weeks prior to study entry with ABR collected during the efficacy period of this study. During emicizumab treatment, the ABR increased in 13 patients compared to their pre-study estimated ABR, 20 patients with stable ABR and 38 patients with decreased ABR respectively. Of the 24 patients who presented target joint bleeds prior to study, 7 had bleeds in their target joints and of those 4 required additional treatment for target joint bleeds during the efficacy period.

A total of 35 patients (49.3%) received a FVIII medication during the study. The median cumulative dose per bleed was 58.48 units/kg (range: 21.7-902.7) and the median number of doses administered was 3.0 (range: 1-44). This median cumulative dose of short-acting FVIII per bleed administered in HAVEN 6 is numerically higher than that used in patients with severe HA without inhibitor in HAVEN 3 (Arm A: 37 unit/kg, Arm B: 27 unit/kg, and Arm D: 46 units/kg with patients who had received FVIII prophylaxis prior to study entry) as well as in HAVEN 4 expansion cohort (25.32 units/kg).

12 patients reported a total of 19 minor and 2 major surgeries. All major surgeries still required FVIII prophylaxis and FVIII substitution for post-operative bleeds in 1 of 2 patients. Almost two-third of minor surgeries were managed with FVIII prophylaxis including 3 postoperative bleeds managed by FVIII.

The baseline bleeding characteristics (treated or not, spontaneous or trauma/surgery related, location, severity…) were not collected, thus cannot be taken into account into analysis.

The rate of major protocol deviations is high: 117 major protocol deviations reported in 48 of 71 patients (67.6%).

In the clinical study report, the 72-hour rule as well as bleed exclusion rule (when due to surgery/procedure) were not consistently used across both baseline and post-baseline periods. Both rules were only applied for on-study bleeds calculation but not for estimation of retrospective baseline bleeds, thus potentially leading to misleading interpretation of baseline versus post-baseline bleeds. The MAH has now conducted a sensitivity analysis where ABR statistics are derived for on-study ABR and prior study ABR, both without and with the 72 hour rule. It is noted that ABR model-based estimates are slightly lower when applying the 72 hour rule, for on-study ABR as well as for prior study ABR. On-study ABR model-based estimates are numerically smaller than prior study ABR, and a larger proportion of patients with zero bleeds is observed for post-baseline bleeds, with and without the 72 hour rule. As mentioned above, concerns remain regarding bias and the comparability of baseline and post-baseline periods, due to the retrospective nature of pre-study data.

The studied population is highly heterogeneous: a half on FVIII prophylaxis and another half on episodic treatment at study entry. Regarding patients receiving prophylaxis at inclusion, the reasons why patients warrant prophylaxis do not seem consistent with the patient's bleeding history.

The need for prophylaxis at inclusion was only based on investigator's individual decision. The analysis of the haemophilia history data from HAVEN 6 demonstrated the heterogeneity of reasons for warranting prophylaxis in the study participants.

No patient younger than 2 years was enrolled. One of the biggest problems at an early stage after birth is how to avoid the occurrence of intracranial haemorrhage (ICH). However, considering the PK of subcutaneous emicizumab, it might not be expected to exert a haemostatic effect immediately even if administered at an early stage after birth. After 1 or 2 years, bleeding frequency increases due to an increase in activity associated with normal growth and development of infants, trauma, and patients most often experience initial joint bleeding. Hence, in response to an increase in the bleeding risk, this stage is generally the time to introduce prophylactic replacement therapy. Therefore, it should be discussed carefully in the clinical situation where early administration of emicizumab after birth is warranted. Experts from the ad hoc expert group expressed their views on the clear advantage of Hemlibra being administered subcutaneously for this age group and that the efficacy can be based on the pharmacological considerations. The ongoing HAVEN 7 study will continue to generate efficacy, safety, PK and PD data on the use of emicizumab in young patients with the final CSR expected in 2030 at the conclusion of a 7-year long term follow-up.

3.4. Unfavourable effects

In the current clinical use setting in the authorised indication:

The known safety profile for Hemlibra depicts mostly injection site reactions, arthralgia and headache.

Emicizumab interferes with some laboratory coagulation tests.

The association of emicizumab with aPCC products should be avoided or used with caution due to the risk of thromboembolic events and thrombotic microangiopathy.

The increased risk of thrombosis in patients not concomitantly treated by aPCC is a potential safety concern (important potential risk in the RMP).

Interim safety results from HAVEN 6 study did not bring any new information on the safety profile of emicizumab, therefore the limited available data on this study does not modify the currently known safety profile and does not raise issue in the investigated population. In addition safety data from post-marketing use and post-marketing safety studies did not raise concern within the subgroup with non-severe haemophilia A.

3.5. Uncertainties and limitations about unfavourable effects

Of the 71 exposed patients, 20 had mild haemophilia A and 51 had moderate haemophilia. Only 59 patients (including only 10 with mild disease) had completed at least 24 weeks in the study. Globally the amount of patients, the median duration of exposure, the median number of emicizumab doses and the amount of concomitant exposure to FVIII are considered as not sufficient to conclude on the safety profile.

While it is not associated with strong evidence, a higher risk of elevated thrombin generation increasing the risk of thromboembolic event in severe haemophilia patients only treated by emicizumab or by emicizumab in association to FVIII products is viewed as a possibility that cannot be excluded at the moment. A PASS based on multinational registries is requested as part of the RMP. An additional uncertainty is raised in non-severe HA patients who have endogenous FVIII activity levels ≥ 1% and who would moreover need to receive additional FVIII dosing for bleeding treatment.

Since the MAH did not provide any non-clinical testing results to further support the claimed indication, the clinical data are the only source of information for this particular subgroup and therefore need to rely on a substantial amount of exposure data, even more so considering the MAH's assertion on the absence or the low additive coagulation potential of emicizumab associated to FVIII.

An update to the interim analysis has been provided in response to RSI D120. The clinical cut-off date of the primary analysis was 30 October 2021 resulting in a median emicizumab exposure of 54.29 weeks, which is more than double the median follow-up time of the interim analysis (16 April 2021). Overall, the safety results in patients with mild and moderate HA without FVIII inhibitors are consistent with data previously observed at interim analysis. The pharmacodynamic and safety biomarkers assessed in the 72 included patients did not show abnormal signs of interaction between emicizumab and endogenous FVIII and no safety biomarker that could signal a thrombotic event.

In addition, no particular safety concern was raised from the post-marketing / clinical trial studies in patients with mild or moderate HA.

Considering the low patients number included in the mild haemophilia subgroup and the potential safety risk of thrombo-embolic events, it was agreed only to include the routine prophylaxis of bleeding episodes in adult and paediatric patients with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype.

3.6. Effects Table

Table 22: Effects Table for emicizumab and in adult and pediatric patients with mild or moderate haemophilia A without inhibitor (data cut-off 16 April 2021 in the treated population)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ABR treated bleeds (72h-rule, exclusion bleeds due to surgery/ procedures)	ABR 0.8 (95% CI: 0.41, 1.46).	Negative binomial regression model based Bleeds per year	emicizumab	NA	Single arm, ongoing descriptive, open-label Retrospective design No formal hypothesis testing, primary endpoint is safety 72-hour rule and exclusion of surgery/procedure related bleeds were not consistently used across both baseline and post-baseline periods High rate of major protocol deviation No patient younger than 2 years of age was enrolled The study population was highly heterogeneous. Some trends of improvement, but given the sample size and study design, no conclusion can be drawn.	
ABR All bleeds (72h-rule, exclusion bleeds due to surgery/ procedures)	ABR 2.3 (95% CI: 1.63, 3.10)	NB regression model based Bleeds per year	emicizumab	NA		
ABR Treated Joint bleeds	ABR 0.3 (95% CI: 0.12, 0.65)	Model based Bleeds per year	emicizumab	NA		
ABR treated spontaneous bleeds	ABR ratio 0.1 (95% CI: 0.02, 0.23)	Model based Bleeds per year/	emicizumab	NA		
Post-hoc analysis by comparing ABR for all bleeds	Estimated ABR prior to study entry: Median (IQR) 4.3 (0.00-8.69) Calculated ABR for All Bleeds in the study: 1.5 (0.00-3.79)	Model based Bleeds per year	emicizumab	NA		
QoL measures	CATCH questionnaire EmiPref HJHS DSC MBQ EQ-5D-5L VAS score EQ-5D-5L Index Utility Score					
Unfavourable Effects						
Currently known safety profile	Interference with coagulation laboratory parameters, interaction with aPCC causing risk of TMA and TE		Emicizumab		The limited set of interim data in HAVEN 6 did not allow to assess whether the safety profile remains unchanged or is modified in the investigated subgroup of patients	HAVEN 6 study interim csr, Hemlibra SmPC
Potential risk of thrombosis in patients not treated by aPCC			Emicizumab		The limited exposure in study HAVEN 6 did not allow to conclude on the hypothetical higher risk of hypercoagulation and thrombosis in non-severe HA patients, treated or not by FVIII for bleeding management but not treated by aPCC	HAVEN 6 study interim csr
Post-marketing data	The MAH asserts that no safety concern was raised from post-marketing exposure		Emicizumab		No detailed data have been presented by the MAH on patients with non-severe HA	Last PBRER (DLP nov 2020)

Abbreviations: CATCH Comprehensive Assessment Tool of Challenges in Haemophilia; EmiPref Emicizumab Preference Survey; HJHS Haemophilia Joint Health Survey; DSC daily step count; MBQ Menstruation Heaviness and Menstruation-Related Quality of Life

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

With this application, the MAH is submitting interim analyses of an ongoing, single-arm, open label study (HAVEN 6).

Efficacy has been demonstrated on the basis of Study HAVEN 6 which is a single-arm, open label, ongoing study with retrospective design. For treated bleeds, the NB regression model based ABR was 0.8 (95% CI: 0.41, 1.46) and the calculated mean ABR 0.7 (95% CI: 0.01, 5.13]). The majority of patients experience 0 treated bleeds while receiving emicizumab prophylaxis (80.3% 57 patients).

However, it has to be noted that some limitations are noted for HAVEN 6 study:

The efficacy observed in patients with inhibitors or severe HA cannot be easily extrapolated to patients with possible almost adequate residual endogenous FVIII activity (up to 40%). The accuracy for the estimation of baseline bleeds collected in a retrospective manner, as well as the comparability and potential bias between baseline *versus* post-baseline ABR are questionable, making impossible to draw any reliable conclusion from all analyses of Study HAVEN 6 due to its descriptive and exploratory nature.

HAVEN 6 enrolled both patients receiving prophylactic and episodic FVIII treatment prior to study entry. The reasons why patients warrant prophylaxis do not seem to consist with patient's bleeding history. Indeed, half of patients with minor disease received FVIII prophylaxis prior to study, while they had not experienced any bleed in the last 24 weeks. In contrast, half of patients with minor disease received only episodic treatment, while they all had a history of severe bleeding and/or frequent (joint) bleeding in the last 24 weeks. HAVEN 6 was designed to be inclusive of the full spectrum of reasons why a patient with m/m HA without inhibitor warrants prophylaxis irrespective of their prior treatment (PUT or PTP, episodic or prophylactic). A major challenge to the widespread use of emicizumab and other pro-coagulant therapies is a lack of data regarding the overlap between the therapeutic window, where bleeding is prevented, and the toxicity window, where the risk of thrombosis increases.

At the approved dosing, emicizumab does not completely restore normal haemostasis in mild/moderate patients enrolled in this study. A total of 109 bleeds occurred in 71 treated patients irrespective of 72-hour rule and bleeds exclusion rule (when related to surgery/procedure). During emicizumab treatment, the ABR increased in 13 patients compared to their pre-study estimated ABR, 20 patients with stable ABR and 38 patients with decreased ABR respectively. Of the 24 patients who presented target joint bleeds prior to study, 7 had bleeds in their target joints and of those 4 required additional treatment for target joint bleeds during the efficacy period. A total of 35 patients (49.3%) received a FVIII medication during the study. Of these 35 patients, 20 patients received a FVIII after their 2nd loading dose of emicizumab.

During the study, 12 patients reported a total of 19 minor and 2 major surgeries. Under the haemostatic coverage of emicizumab alone in mild and moderate HA, all major surgeries still required FVIII prophylaxis and FVIII for post-operative bleeds in 1 of 2 patients. Almost two-third of minor surgeries were managed with FVIII prophylaxis including 3 postoperative bleeds managed by FVIII.

Data are missing in patients < 2 years with m/m HA without inhibitors. It should be noted that Emicizumab binds to FIXa and FX, both factors are comparatively low in neonates and their level depends also on prematurity, hepatic immaturity and vitamin K deficiency. The FXI gradually increases to adult normal values possibly beyond 2 years of age. Of note, in a mouse model the efficacy of emicizumab was significantly altered when human FIX and FX levels were low. The ongoing HAVEN 7 study will continue to generate efficacy, safety, PK and PD data on the use of emicizumab in young patients with the final CSR expected in 2030 at the conclusion of a 7-year long term follow-up.

In line with the recommendations of the ad hoc expert group meeting, it is agreed that Hemlibra is an additional treatment option for prophylaxis that offers advantages in terms of ease of administration, and consequently, quality of life, in patients with severe and moderate haemophilia. The benefits in prophylaxis for moderate haemophilia clearly outweigh the risks given the morbidity and mortality associated with bleedings in this population.

With regards to safety; the safety results in patients with mild and moderate HA without FVIII inhibitors are consistent with data previously observed at interim analysis. The pharmacodynamic and safety biomarkers assessed in the 72 included patients did not show abnormal signs of interaction between emicizumab and endogenous FVIII and no safety biomarker that could signal a thrombotic event. While the available interim safety data from study HAVEN 6 did not show a difference in the safety profile of emicizumab compared to the identified risks observed throughout the clinical development and are listed in the SmPC. A total of 148 AEs were observed but no concern involving thrombosis or thrombotic microangiopathy was reported. The monitoring of coagulation laboratory parameters did not detect a pattern of abnormal results (some elevated values were observed but without any associated AE).

3.7.2. Balance of benefits and risks

Despite several methodological limitations, efficacy has been demonstrated on the basis of Study HAVEN 6 which is a single-arm, open label, ongoing study with retrospective design.

No specific safety issues were reported in the HAVEN 6 study. Considering that patients with thrombo-embolic risk factors were excluded from the study, a PASS based on data from multi-national registries have been requested in order to investigate any potential risk of thrombosis when Hemlibra is given in a real life setting (please see RMP).

Consequently, the CHMP agrees with this extension of indication to include routine prophylaxis of bleeding episodes in adult and paediatric patients with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (FVIII $\geq$ 1% and $\leq$ 5%) with severe bleeding phenotype. Hemlibra can be used in all age groups.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Hemlibra in the extended indication to include the routine prophylaxis of bleeding episodes in adult and paediatric patients with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (FVIII $\geqslant$ 1% and $\leqslant$ 5%) with severe bleeding phenotype in all age groups is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include routine prophylaxis of bleeding episodes in adult and paediatric patients with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (FVIII $\geqslant$ 1% and $\leqslant$ 5%) with severe bleeding phenotype. Hemlibra can be used in all age groups. Consequently, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC and Section 1 of the package leaflet are updated. In addition, Section 4.2 is updated to make it clear that the maintenance dose for Hemlibra applies from week 5 of dosing. The PIL is updated accordingly. Version 4.7 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0196/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

No significant studies in the agreed paediatric investigation plan P/0196/2016 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Hemlibra is not similar to Roctavian within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.