31 January 2019
EMA/125963/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hemlibra

International non-proprietary name: emicizumab

Procedure No. EMEA/H/C/004406/II/0002

Note

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

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List of abbreviations

ABR	annualized bleeding rate
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AEGT	adverse event group term
AESI	adverse event of special interest
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AUC	area under the plasma concentration-time curve
BLA	Biologics License Application
BMQ	bleed and medication questionnaire
BR	bleed rate
BTD	breakthrough therapy designation
C_{av}	average concentration
CCOD	clinical cutoff date
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CSR	clinical study report
C_{trough}	trough plasma concentration
$C_{trough, ss}$	steady-state trough plasma concentration
CTD	common technical document
CVAD	central venous access devices
DIL	Dear Investigator Letter
ECG	electrocardiogram
EHL	extended half-life
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Levels
EmiPref	emicizumab preference survey
FEIBA	Factor Eight Inhibitor Bypassing Activity
FVIII	factor VIII
FVIIIa	factor VIII, activated
FIX	factor IX
FIXa	factor IX, activated
F_{rel}	relative bioavailability

FX	factor X
HCP	health care provider
HRQoL	health-related quality of life
ICH	intracranial hemorrhage
IgG	Immunoglobulin
IgG4	Immunoglobulin G4
IQR	interquartile range
ISR	injection site reaction
ISTH	International Society on Thrombosis and Haemostasis
ITT	intent to treat
IV	intravenous
Kd	dissociation constant
MAA	marketing authorization application
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NIS	non-interventional study
NOAEL	no-adverse-effect-level
ODD	orphan drug designation
PDCO	Paediatric Committee
PIP	pediatric investigation plan
PopPK	Population PK
PK	pharmacokinetic
QoL	quality of life
QW	once every week
Q2W	every 2 weeks
Q4W	every 4 weeks
rFVIII	recombinant factor VIII
RTTE	repeated time to event
SAE	serious adverse event
SBP	Summary of Biopharmaceutics
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SQ-ISHI	Satisfaction Questionnaire-Intravenous Subcutaneous Hemophilia Injection
$T_{1/2}$	terminal plasma half-life
$T_{1/2, abs}$	absorption half-life

TE	thromboembolic event
TG	thrombin generation
TMA	thrombotic microangiopathy
USPI	United States Prescribing Information
Vd_{ss}	volume of distribution at steady-state
V/F	volume of distribution

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 10 April 2018 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, IIIA and IIIB

Extension of Indication for Hemlibra to include routine prophylaxis of bleeding episodes in adults and children with haemophilia A with or without factor VIII inhibitors. In addition, two additional posology recommendations for adults and children with haemophilia A with and without factor VIII inhibitors are recommended. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the Risk Management Plan (v.2.0) are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor corrections and editorial changes to sections 4.4, 4.5 and 4.6 of the SmPC.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0196/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0196/2016 was not yet completed as some measures were deferred.

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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

Scientific advice

The applicant 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: Nithyanandan Nagercoil Co-Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	10 April 2018
Start of procedure:	28 April 2018
CHMP Rapporteur Assessment Report	25 June 2018
CHMP Co-Rapporteur Assessment Report	26 June 2018
PRAC Rapporteur Assessment Report	29 June 2018
PRAC members comments	4 July 2018
Updated PRAC Rapporteur Assessment Report	5 July 2018
PRAC Outcome	12 July 2018
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 July 2018
Request for supplementary information (RSI)	26 July 2018
PRAC Rapporteur Assessment Report	24 September 2018
PRAC members comments	24 September 2018
CHMP Rapporteur Assessment Report	4 October 2018
PRAC Outcome	4 October 2018
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	11 October 2018
Request for supplementary information (RSI)	18 October 2018
PRAC Rapporteur Assessment Report	22 November 2018
PRAC members comments	
CHMP Rapporteur Assessment Report	28 November 2018
PRAC Outcome	29 November 2018
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	24 January 2019
Ad hoc expert group meeting	25 January 2019
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Hemlibra in comparison with existing therapies (Appendix 2)	31 January 2019
CHMP Opinion	31 January 2019

2. Scientific discussion

2.1. Introduction

Emicizumab (also known as ACE910, RO5534262, and Hemlibra) is a H2L2 polypeptide structure consisting of two light chains and two heavy chains linked together by disulfide bonds. It is a humanised monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Emicizumab bridges activated factor IX (FIXa) and factor X (FX) to restore the function of missing activated factor VIII (FVIIIa) that is needed for effective haemostasis.

The product is presented as a liquid in a glass vial intended for subcutaneous injection, with the following presentations: 30 mg/1 mL, 60 mg/0.4 mL, 105 mg/0.7 mL and 150 mg/1 mL. The proposed clinical dose is 3 mg/kg once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly.

Hemlibra 30 mg/mL solution for injection and Hemlibra 150 mg/mL solution for injection were approved in the EU on 23 February 2018 and indicated for the routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors.

This application is submitted in accordance with Article 8(3) of Directive 2001/83/EC to extend the indication to the Hemlibra Marketing Authorisation to include the routine prophylaxis of bleeding episodes in adults and children with severe haemophilia A without factor VIII inhibitors. The application also includes data supporting an update of the Summary of Product Characteristics (SmPC) and Package Leaflet with two additional posology recommendations for adults and children with haemophilia A with and without factor VIII inhibitors.

The final indication agreed at the CHMP is:

“Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with

- haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
- severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors.

Hemlibra can be used in all age groups.”

The proposed posology consists of a loading dose of 3 mg/kg once weekly followed by a maintenance dose of either 3 mg/kg every two weeks or 6 mg/kg every 4 weeks, and from week 5 on 3 or 6 mg/kg.

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical pharmacology section of the dossier has been submitted which incorporates a discussion on the evaluation of the prothrombotic potential of emicizumab and bypassing agent interactions. This is presented below along with the studies on the evaluation of the prothrombotic potential of emicizumab and bypassing agent interactions which were reviewed in the initial application. The MAH has made reference to the previous non-clinical development of emicizumab – as assessed in the context of the original MAA for Hemlibra - which included appropriate pharmacology, pharmacokinetics, and toxicology studies and support this application.

2.2.2. Pharmacology

Emicizumab (also known as ACE910, CH5534262, and RO5534262) is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Emicizumab bridges activated factor IX (FIXa) and factor X (FX) to restore the function of missing activated factor VIII (FVIIIa) that is needed for effective haemostasis. In patients with haemophilia A, haemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. The non-clinical pharmacology section of the dossier has been submitted including additional pharmacology information from the evaluations of the pro-thrombotic potential of emicizumab and bypassing agent interactions. This information supplements the previously reviewed studies on the pro-thrombotic potential of emicizumab and bypassing agent interactions.

Pharmacodynamic drug interactions

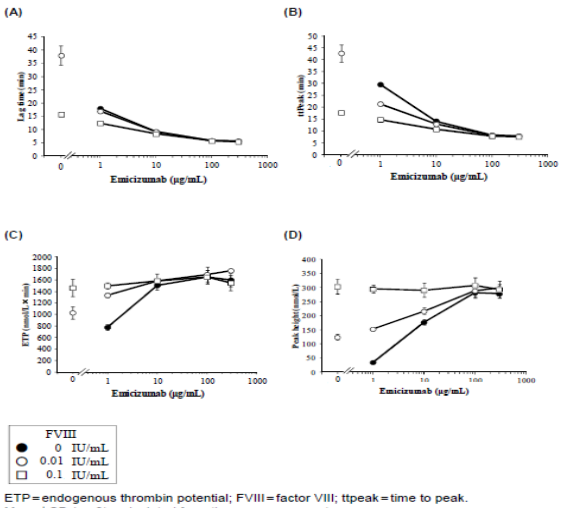
Interactions with FVIII and Bypassing agents

The commercial drugs currently available for treatment of haemophilia A are plasma-derived or recombinant FVIII and bypassing agents, rFVIIa and/or activated prothrombin complex concentrate (aPCC). Due to their mode of action, bypassing agents rFVIIa and aPCC have the potential to interact with emicizumab. As these agents might be given to emicizumab-treated haemophilia A patients as on-demand treatment for bleeding events, the potential pro-coagulant liability of concomitant use of these agents with emicizumab was investigated *in vitro* and *in vivo*.

In vitro effects of emicizumab in combination with FVIII and Bypassing Agents

The effects of emicizumab on the actions of FVIII and bypassing agents were investigated in a thrombin generation assay in human haemophilia A plasma. For the combination of emicizumab and FVIII, thrombin generation was determined via activation of the intrinsic pathway with FXIa as the starting reagent. As the assay is very sensitive to the FVIII concentration, the measurements were performed at either pathologically low-FVIII concentration (0.01 and 0.1 IU/mL) or FVIII-concentration in the normal physiological range (1 IU/mL). Emicizumab alone or at low FVIII concentrations shortened the lag time and ttPeak and increased endogenous thrombin potential (ETP) and peak height (Figure 1).

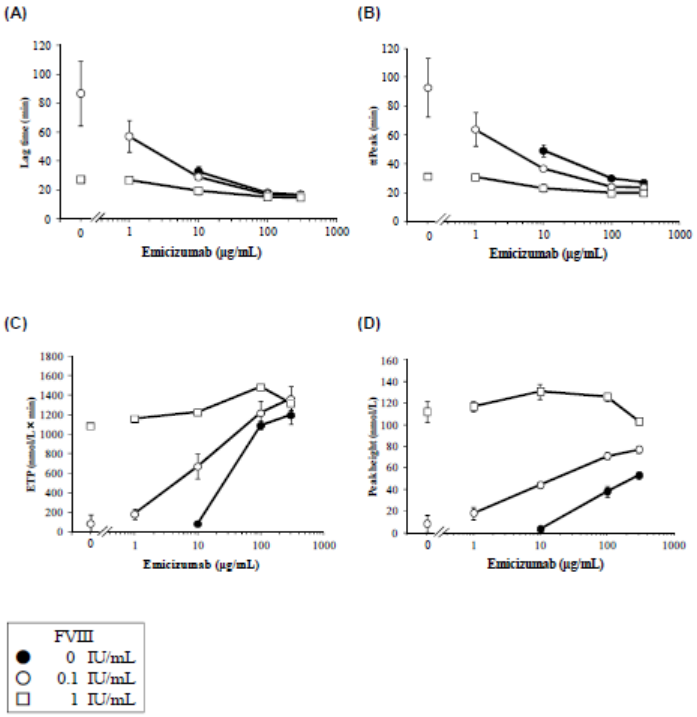
Figure 1 Effect of CH5534262 on thrombin generation in the presence of a low concentration of FVIII in hemophilia A plasma



ETP=endogenous thrombin potential; FVIII=factor VIII; ttpeak=time to peak.
Mean±SD (n=3), calculated from three measurements.
Symbols in the absence of emicizumab indicate blank activity of FVIII.

At FVIII concentrations of 1 IU/mL, emicizumab marginally shortened lag time and ttPeak, showed only weak increase of the endogenous thrombin potential (ETP) and had almost no effect on peak height, indicating that emicizumab competes with FVIII on FIXa-FX binding (Figure 2).

Figure 2 Effect of CH5534262 on thrombin generation in the presence of higher concentrations of FVIII (in the physiological range) in haemophilia A plasma

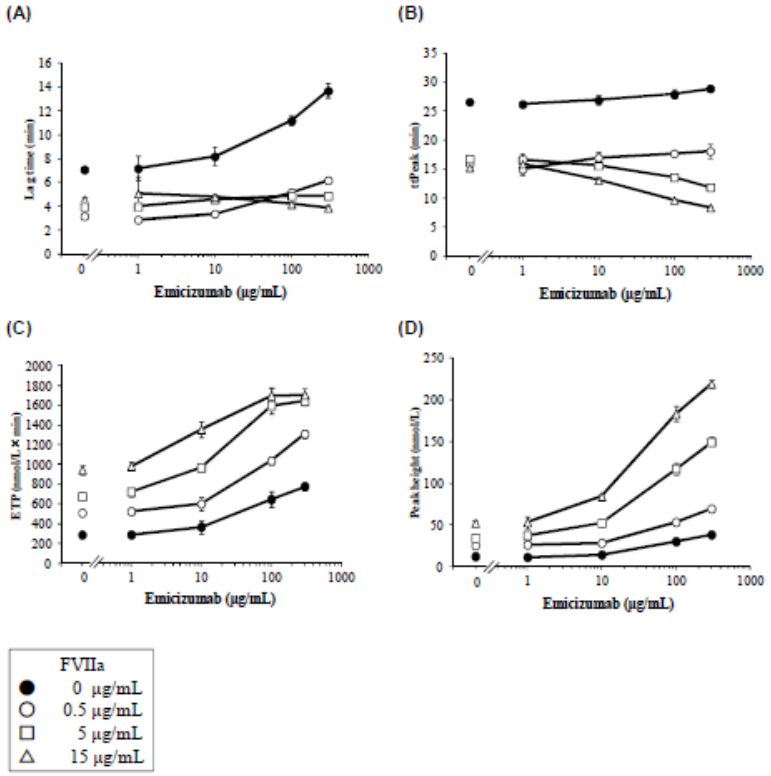


ETP=endogenous thrombin potential; FVIII=factor VIII; ttpeak=time to peak.
Mean±SD (n=3), calculated from three measurements.
Symbols in the absence of emicizumab indicate blank activity of FVIII.

For the combinations of emicizumab and rFVIIa or aPCC, thrombin generation was determined via activation of the extrinsic pathway with very low TF activity as the starting reagent. Under these assay conditions, emicizumab alone in the absence of rFVIIa further prolonged the lag time of haemophila A plasma at concentrations ≥ 100 µg/mL, suggesting that emicizumab itself may delay the thrombin generation starting time of FX-related reactions within the extrinsic coagulation pathway. This effect was also noted in the presence of low rFVIIa concentrations (0.5 µg/mL), while no negative interference with the extrinsic pathway activation of rFVIIa was seen at concentrations of 5 or 15 µg/mL rFVIIa. Although the addition of emicizumab in the presence of 0.5 µg/mL rFVIIa prolonged lag time, it did not affect ttPeak (Figure 3 A & B). However, emicizumab increased the ETP and peak height in the presence of rFVIIa, indicating that concomitant use of rFVIIa and emicizumab further enhanced thrombin generation during the propagation phase (Figure 3C & D). It is noted that the highest recommended dose of 270 µg/kg rFVIIa for on demand treatment of bleeds in haemophilia A inhibitor patients corresponds to a tested *in vitro* concentration of 5 µg/mL rFVIIa.

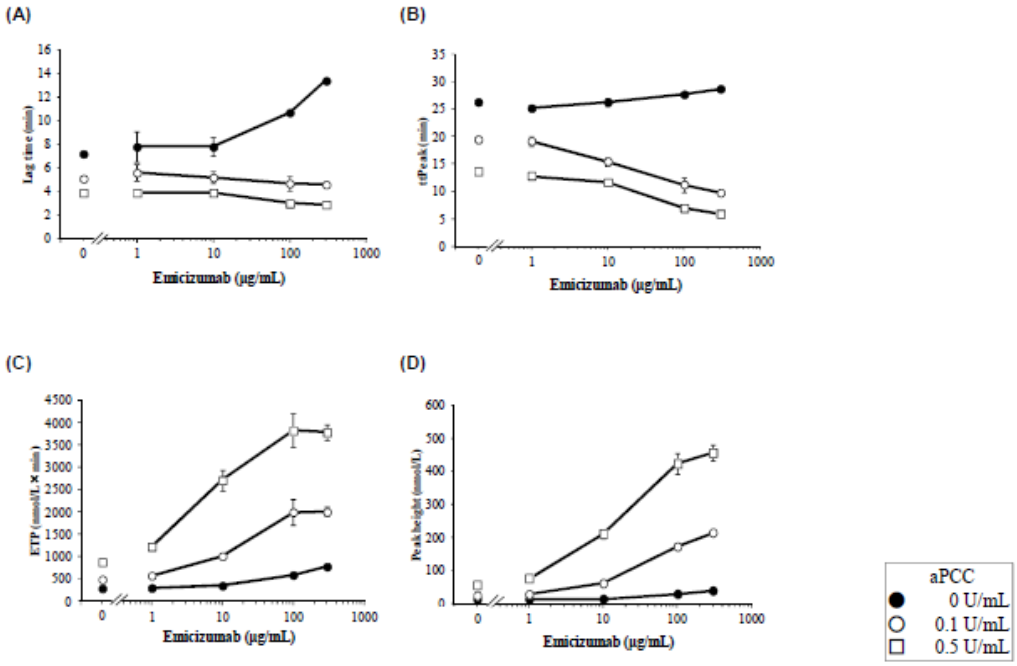
For APCC, the maximum concentration tested, 0.5 IU/mL corresponds to an estimated clinical dose of 25 IU/kg, which is lower than the minimum clinical dose. Emicizumab did not change the lag time, but shortened the ttPeak and increased the ETP and peak height in the presence of aPCC and thus significantly enhanced thrombin generation during the initiation and propagation phase (Figure 4).

Figure 3 Effect of CH5534262 on thrombin generation in the presence of rFVIIa (0.5 to 15 µg/mL) in haemophilia A plasma



ETP = endogenous thrombin potential; FVII = activated factor VII; ttpeak = time to peak.
Mean ± SD (n = 3), calculated from three measurements.
Symbols in the absence of emicizumab indicate blank activity of rFVIIa.

Figure 4 Effect of CH5534262 on thrombin generation in the presence of aPCC (0.1 and 0.5 U/mL) in haemophilia A plasma



The *in vivo* studies carried out in *Cynomologus* monkeys of emicizumab in combination with FVII and bypasssing agents demonstrate that the aPCC-emicizumab combination has a higher potential than rFVIIa-emicizumab to induce thrombosis when aPCC is administered at clinically established high doses and especially when repeat aPCC doses are administered.

Thus, in this study, no thrombosis formation was seen with emicizumab as a single agent. The thrombus formation observed with rVIIa and aPCC alone appeared to be enhanced by the addition of emicizumab and was discussed further in the report submitted.

No non-clinical studies in animal models with mild to moderate haemophilia have been conducted.

2.2.3. Pharmacokinetics

The pharmacokinetics of emicizumab were studied in *Cynomolgus* monkeys. The monkey was identified as the most relevant species as it was shown to cross react with emicizumab.

- ***Methods of analysis***

Concentrations of emicizumab in *Cynomolgus* monkey plasma were determined by an ELISA quantifying dual-binding-competent emicizumab as previously discussed in the initial MAA.

- ***Absorption***

Repeat-dose studies dose studies in monkeys

The toxicokinetics of two studies submitted are summarised below. These studies were submitted in the initial MAA and were therefore previously reviewed. Following once weekly administration to *Cynomolgus* monkeys at 10, 30 and 100 mg/kg (formulated in 20 mmol/L histidine-aspartate buffer (pH 6.0) containing 150 mmol/L arginine aspartate and 0.5 mg/mL poloxamer 188), after the first and fourth dose, the back-extrapolated concentration immediately after IV injection (C0) and AUC0-7 increased in an approximately dose-proportional manner over the investigated dose range. Exposure values are presented in Table 1. C0 and AUC0-7 increased after the 4th dose with accumulation factors of 1.6 to 2.0 and 1.9 to 2.6, respectively. Plasma emicizumab concentrations during the 4-week recovery period decreased gradually in all animals (individual t1/2 at 100 mg/kg: 14.9±18.9 days). No ADAs were detected.

Table 1: 4 week IV study: Mean Pharmacokinetic parameters of emicizumab after once weekly administration (monkey)

Dose (mg/kg)	Sex		C_0 (µg/mL)		AUC_{0-7d} (d*µg/mL)	
			1st dose	4th dose	1st dose	4th dose
10	M	Mean	210	406	668	1810
		SD	24	56	43	250
	F	Mean	267	453	866	1980
		SD	27	37	51	210
30	M	Mean	702	1430	2250	5140
		SD	17	230	180	420
	F	Mean	726	1270	2620	5520
		SD	32	100	260	640
100	M	Mean	2270	3550	7400	14400
		SD	220	460	840	2900
	F	Mean	2160	3560	8120	16400
		SD	300	510	730	3000

ADA=anti-drug antibody; AUC_{0-7d}=area under the plasma concentration-time curve from 0 to 7 days; C_0=initial or back-extrapolated concentration following rapid intravenous injection; SD=standard deviation.
Mean±SD reported. n = 3/sex in each of the 10 and 30 mg/kg groups; n = 5/sex in the 100 mg/kg group.
No ADAs were detected in any of the animals in this study.

Subcutaneous study

Following once weekly SC administration of emicizumab at 1, 6, and 30 mg/kg to *Cynomolgus* monkeys (formulated in 20 mmol/L histidine-aspartate buffer (pH 6.0) containing 150 mmol/L arginine aspartate and 0.5 mg/mL poloxamer 188), plasma emicizumab concentration and PK parameters were comparable to that of the 13-week toxicity study whereby increases in Cmax were approximately dose proportional and exposures increased upon repeated dosing. Exposure values are presented in Table 2. Cmax increased 2.8- to 4.2-fold in Week 13 and 2.8- to 6.0-fold in Week 26 of treatment relative to the first dose. Similarly, AUC0-7d increased 3.0- to 4.5-fold and 2.8- to 6.7-fold compared to Week 1 after the 13th and 26th dose, respectively. The exposure in ADA-negative animals decreased with an apparent t1/2 of 15.7 to 30.8 days.

ADAs were detected in a total of 9 out of 30 (30%) animals treated with emicizumab; in three animals in the 1 mg/kg, two animals in the 6 mg/kg and one animal in the 30 mg/kg dose groups during the treatment period. During the recovery period, one additional animal in each dose group displayed ADAs. ADA-positive animals did exhibit a faster elimination of emicizumab and were therefore excluded from the toxicokinetic evaluation. In four ADA-positive animals, a complete loss of exposure was apparent based on the total dual target binding competent emicizumab assay. Titers ranged from 1 to 100,000, and highest titers were associated with faster emicizumab elimination. ADA-positive animals with an apparent loss of exposure tested positive for neutralising antibodies while samples from other animals could not be assessed for neutralizing activity due to circulating emicizumab concentrations shown to interfere with the characterisation test to determine neutralising activity.

Table 2: 26 week SC study: Mean Pharmacokinetic parameters of emicizumab after once weekly administration (monkey)

Dose (mg/kg)	Sex		C_{max} (µg/mL)			t_{max} (day)			$AUC_{0\text{-}7d}$ (d•µg/mL)		
			1st dose	13th dose	26th dose	1st dose	13th dose	26th dose	1st dose	13th dose	26th dose
1	M	Mean	10.1	44.2[a]	52.0[a]	3.6	1.0[a]	2.8[a]	58.3	260[a]	339[a]
		SD	0.4	4.1	5.6	0.5	0.0	1.3	3.2	23	34
	F	Mean	10.4	38.8[b]	48.2[b]	3.0	1.0[b]	1.0[b]	61.8	253[b]	284[b]
		SD	1.0	7.0	16.4	0.0	0.0	0.0	5.8	48	78
6	M	Mean	59.7	315[a]	358[a]	2.8	1.5[a]	2.8[a]	352	1990[a]	2360[a]
		SD	12.0	43	89	1.1	1.0	1.3	62	350	650
	F	Mean	54.4	196[a]	262[a]	3.2	1.5[a]	2.3[a]	313	1290[a]	1670[a]
		SD	6.1	27	31	0.4	1.0	1.5	38	180	220
30	M	Mean	288	1200[a]	1340[a]	1.8	1.0[a]	3.3[a]	1690	7560[a]	8680[a]
		SD	40	250	240	1.1	0.0	1.5	230	1290	1540
	F	Mean	307	1240	1370	4.2	1.8	1.6	1770	7970	8830
		SD	34	190	310	1.6	1.1	1.3	170	1510	1910

$AUC_{0\text{-}7d}$=area under the plasma concentration-time curve from 0 to 7 days; C_{max}=maximum plasma concentration; SD=standard deviation; t_{max}=time to maximum plasma concentration.

n=5/sex in each dose group; n=4 only for the 26th dose in the 6 mg/kg male group.

Animals with confirmed ADA presence were excluded regardless of neutralizing activity:

[a] One animal excluded.

[b] Two animals excluded.

2.2.4. Toxicology

Repeat dose toxicity

4-week intravenous study

Two toxicity studies have been submitted and are summarised below. These studies were submitted in the initial MAA and therefore previously reviewed.

Emicizumab was administered to *Cynomolgus* monkeys aged 3 to 4 years at 0 (vehicle control), 10, 30, and 100 mg/kg [n=3/sex/group]) QW for 4 weeks (5 times in total). Two additional animals/sex in the control and at 100 mg/kg were monitored for a 4-week recovery period Vehicle solution consisted of 20 mmol/L histidine-aspartate buffer containing 150 mmol/L arginine-aspartate and 0.5 mg/mL poloxamer 188, pH 6.0 (excipients in line with those within the final product). The administration was conducted at a volume of 1.22 mL/kg and at a rate of 4 mL/min with a syringe pump.

No emicizumab-related deaths or moribundity were observed. No emicizumab-related abnormalities were noted in clinical signs, body weight, food consumption, Holter electrocardiography, ophthalmoscopy, urinalysis, blood chemistry, necropsy, organ weight, histopathology, or plasma cytokine analysis in any animals. In addition, no changes in reproductive organs of males and females were noted.

A shortening of aPTT was noted in all groups treated with emicizumab during the treatment and recovery. This was attributed to the pharmacological properties of emicizumab.

In 1 female at 100 mg/kg/week, peri-arteritis in several organs was found histopathologically, suggesting polyarteritis had developed in this animal. Several haematology and blood chemistry changes related to inflammation were also observed. However, these inflammatory markers tended to recover during the dosing period. The cause of the polyarteritis was unclear, but was considered to be incidental and not related to emicizumab based on the following reasons:(1) spontaneous polyarteritis with similar changes have been reported in *Cynomolgus* monkeys; short report summarising historical data which reports incidence of polyarteritis in 2013: 6/841 males and 3/788 females, Porter et al. 2003]; (2) some of the abnormal clinical pathology values improved while emicizumab exposure was maintained; (3) this change only occurred in one female in this study (out of a total of 88 monkeys that received emicizumab in the general toxicity studies).

Immune-mediated vascular injury such as that arising from type III hypersensitivity reaction involving immune complexes, is sometimes seen with biological therapeutics evaluated in *Cynomolgus* monkeys. An antibody response to a test article can result in the deposition of immune complexes, evident as granular deposits in arteries or in kidney glomeruli [Rojko et al. 2014]. No ADAs were detected in this female and there was no evidence for loss of exposure after repeated dosing. However, the possibility that polyarteritis observed in this one female given 100 mg/kg/week IV for 4 weeks is immune-mediated cannot be completely ruled out.

The TK data are presented below. Plasma concentrations of emicizumab decreased gradually during recovery but were still observed until 4 weeks after the last dose. ADAs were not detected in any animals during the dosing or recovery periods.

26-week subcutaneous study

Emicizumab was administered SC to sexually mature (4 to 6 years old at the start of dosing) *Cynomolgus* monkeys at 0 (vehicle control), 1, 6 and 30 mg/kg (n=5 animals/sex/group) QW for 26 weeks (27 times in total). Recovery was assessed in two animals/sex/group over 13 weeks

No emicizumab-related deaths or morbidity were observed during the study. No systemic abnormalities, including disturbed menstrual cycle in females, were observed in the clinical signs, and no emicizumab-related abnormalities were noted in body weight, food consumption, electrocardiography, ophthalmoscopy, urinalysis, haematology, blood chemistry, sperm examination, testes size, or organ weight.

Local injection site reactions were found in several emicizumab administration sites. Subcutis reddish patch at necropsy and haemorrhage/hemosiderin deposition with mononuclear cell infiltration, neutrophil infiltration, eosinophil infiltration, perivascular mononuclear cell/plasma cell infiltration, swelling of endothelium, edema and/or degeneration/necrosis of subcutis were observed histopathologically. These findings were reversible and not dose-related.

In 1 male at 6 mg/kg/week, swelling of the injection sites was observed from Day 135 (after the 20th injection). The swelling was observed at the subsequent injection (21st injection) and treatment was stopped. ADAs were present at an extremely high titre in this animal, and the plasma drug concentration was very low after the third dose and BLQ at later time points. Because the emicizumab plasma concentration was very low/absent, early termination of this animal was not considered to impact the toxicological evaluation. Necropsy at Day 149 revealed subcutis dark reddish patch, edema, reddish change, thickening, and induration. Severe injection site reactions including acute necrotizing vasculitis and chronic vasculitis were noted histopathologically. These findings were consistent with an Arthus reaction, a local immune complex disease classified as type III hypersensitivity. Therefore, the inflammatory reaction at the injection sites was considered to be due to ADA-emicizumab complexes.

ADA analysis showed that ADAs developed in one male and two females at 1 mg/kg/week, one male and one female at 6 mg/kg/week, and one male at 30 mg/kg/week during the treatment period. Plasma concentration of emicizumab decreased to BLQ in three animals at 1 mg/kg/week and one male at 6 mg/kg/week, and ADAs in these four animals were found to have neutralizing activity in an ELISA-based characterization test. Samples from the remaining ADA-positive animals could not be assessed for neutralising capacity because of emicizumab concentrations which have been shown to interfere with the characterisation test. In the recovery period, ADAs newly developed in three additional animals (one male at 1 mg/kg/week, and one female each at 6 and 30 mg/kg/week) after Week 9. The ADA incidence did not impact the overall emicizumab exposure to a relevant degree and thus allowed establishment of the necessary exposure margins for SC administration of emicizumab in this 26-week toxicity study and validity of the study.

Toxicokinetic data

The relevance of the non-clinical no-effect exposures relate to those proposed clinically is summarised below.

In the 26-week study, following the 26th subcutaneous administration of 30 mg/kg/week emicizumab in the monkey, mean exposure Cmax values observed were 1340 and 1370 µg/mL for males and females respectively; 1355 µg/mL combined (see Tables 3, 4 and 5). Mean exposure AUC0-7d values observed were 8680 and 8830 µg/mL for males and females respectively; 8755 d.µg/ml combined (see Tables 3, 4 and 5).

Table 3: No-effect (animal) exposures and exposure margins for 1.5 mg/kg QW dose

Species	Dose (mg/kg/week)	AUC_{0-7d} (d.µg/ml)	AUC_{inf} (d.µg/ml)	Exposure Margin	C_{max} (µg/ml)	Exposure Margin
Monkey	30	8755	NP	22	1355	25

Clinical mean exposures for 1.5 mg/kg QW = $C_{max,SS}$ 54.9 µg/ml and AUC_{ss} τ 375 µg/mL*day. AUC_{ss} τ = area under the concentration time curve at steady-state over the dosing interval (τ = 1, 2, or 4 weeks); $C_{max,SS}$ = maximum concentration at steady-state; Cmax = maximum plasma concentration. NP = Not provided.

Table 4: No-effect (animal) exposures and exposure margins for 3 mg/kg Q2W dose

Species	Dose (mg/kg/week)	AUC_{0-7d} (d.µg/ml)	AUC_{inf} (d.µg/ml)	Exposure Margin	Cmax (µg/ml)	Exposure Margin
Monkey	30	8755	NP	11	1355	23

Clinical mean exposures for 3 mg/kg Q2W = $C_{max,SS}$ 58.1 µg/ml and AUC_{ss} τ 749 µg/mL.day. AUC_{ss} τ = area under the concentration time curve at steady-state over the dosing interval (τ = 1, 2, or 4 weeks); $C_{max,SS}$ = maximum concentration at steady-state; Cmax = maximum plasma concentration. NP = Not provided.

Table 5: No-effect (animal) exposures and exposure margins for 6 mg/kg Q4W dose

Species	Dose (mg/kg/week)	AUC_{0-7d} (d.µg/ml)	AUC_{inf} (d.µg/ml)	Exposure Margin	Cmax (µg/ml)	Exposure Margin
Monkey	30	8755	NP	5	1355	20

Clinical mean exposures for 6 mg/kg Q4W = $C_{max,SS}$ 66.8 µg/ml and AUC_{ss} τ 1499 µg/mL*day.

AUC_{ss} τ = area under the concentration time curve at steady-state over the dosing interval (τ = 1, 2, or 4 weeks); $C_{max,SS}$ = maximum concentration at steady-state; Cmax = maximum plasma concentration. NP = Not provided.

2.2.5. Ecotoxicity/environmental risk assessment

Emicizumab is a recombinant bispecific monoclonal antibody produced by biotechnology. Emicizumab is a large protein with a molecular mass of approximately 146 kDa. Like all monoclonal antibodies, emicizumab is degraded by regular proteolytic mechanisms before excretion, hence no ERA is required (see discussion on non-clinical aspects).

A Manometric Respirometry Test according to OECD 301F under GLP quality assurance showed that formulated Emicizumab (including excipients) is readily biodegradable [Straub, 2010]. The biochemical oxygen demand (BOD) in the test, compared to the theoretical oxygen demand (ThOD) for emicizumab and all excipients, corresponded to a minimum of 90% mineralisation at the end of the 10-day window. The total mineralisation for the active substance emicizumab (deducting the BOD for the excipients, which with the exception of Poloxamer 188 were shown to be readily biodegradable themselves [Straub, 2010) corresponded to a minimum of 98% by day 28. In addition, the calculated removal determined as the decrease in dissolved organic carbon (DOC) for formulated emicizumab was 99% by day 28. Comparing the removal percentages by BOD with the very similar figures obtained by reduction in DOC and chemical oxygen demand, strongly supports mineralisation by biodegradation of emicizumab as the removal mechanism [Straub, 2010].

Therefore, while emicizumab may normally be expected to be degraded by regular human protein metabolism, 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. In addition, an inhibition control in the OECD 301F test, with sodium benzoate as a readily biodegradable reference substrate in addition to formulated emicizumab, showed no inhibition of biodegradation [Straub, 2010], hence no significant toxicity to activated sludge micro-organisms.

Acute ecotoxicity limit tests with green algae (Desmodesmus subspicatus) 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. While these tests are only acute (except for the algae), they do underpin a low risk for unexpected aquatic ecotoxicity of emicizumab, particularly considering the rapid, far-reaching removal expected through biodegradation in sewage treatment.

2.2.6. Discussion on non-clinical aspects

Pharmacology

The effects of emicizumab in combination with FVIII, rFVIIa or aPCC have been studied in in vitro thrombin generation assays in human haemophilia A plasma and in vivo in a model of venous stasis in normocoagulative Cynomolgus monkeys and in a venous stasis model of provoked thrombosis in FVIII-neutralised (haemophilia A model) Cynomolgus monkeys.

For the combinations of emicizumab and rFVIIa or aPCC, thrombin generation was determined via activation of the extrinsic pathway with very low tissue factor activity as the starting reagent. Under these assay conditions, in the absence or in the presence of low concentrations of rFVIIa (0.5 µg/mL), emicizumab at ≥ 100 µg/mL, delayed the thrombin generation starting time of FX-related reactions within the extrinsic coagulation pathway. However, emicizumab increased the ETP and peak height in the presence of rFVIIa (≤15 µg/mL), indicating that concomitant use of rFVIIa and emicizumab further enhanced thrombin generation during the propagation phase.

Emicizumab did not change the lag time, but shortened the ttPeak and increased the ETP and peak height in the presence of aPCC and thus significantly enhanced thrombin generation during the initiation and propagation phase. In haemophilia A, the rate of FIX-catalysed FX activation is extremely low. It is increased in the presence of emicizumab, but the reaction rate is even further increased in the presence of elevated plasma concentrations of the aPCC components, thus promoting disproportionate haemostatic activity (a 2.6 and 5-fold increase in peak height and endogenous thrombin potential, respectively). Such an increased haemostatic potency for combinations of emicizumab with rFVIIa or aPCC versus emicizumab alone has also been suggested by the in vivo data generated in the Cynomolgus monkey: In a haemophilia A venous stasis model, no thrombosis formation was seen when emicizumab was administered alone as a single agent; however, the thrombus formation observed with rVIIa and aPCC alone appeared to be enhanced by the addition of emicizumab. It is noted that statistical analysis was not performed and in addition, the study was unable to completely address the differences in thrombosis risk given the slow clearance of aPCC. Nevertheless, it has been established that aPCC in combination with emicizumab has the highest interaction potential in terms of thrombin generation and thrombogenic risk; this has been reflected in section 4.4 of the SmPC.

The MAH identified that emicizumab has the potential to interact with aPTT diagnostic tests but has also highlighted a series of diagnostic tests that are not affected. Such assays should therefore not be used for monitoring patients treated with emicizumab. This has also been reflected in section 4.4 of the SmPC.

The MAH stated that FVIII, or the bypassing agents rFVIIa and aPCC, may be given to emicizumab-treated haemophilia A patients, depending on their FVIII inhibitors status (or titer), as on-demand treatment for bleeding events. In an in vitro thrombin generation assay, the combination of emicizumab and low (0.01 or 0.1 IU/mL) FVIII showed greater peak height of thrombin than either agent alone, but emicizumab caused little to no increase in peak height above that seen with 1 IU/mL FVIII alone. rFVIIa in combination with emicizumab had a relatively small additive effect on thrombin generation, while in contrast, a disproportionate synergistic increase in thrombin generation with steep exposure-response curves was seen with aPCC-emicizumab combinations, indicating that increasing aPCC plasma concentrations significantly increase net haemostatic potency at clinical exposure levels of emicizumab.

In a normo-coagulative Cynomolgus monkey venous-stasis model, a similar degree of thrombus formation was seen with single agent administration of emicizumab, rFVIIa, or FVIII, indicating that the addition of emicizumab to normal levels of endogenous FVIII has a similar potential for increased net haemostatic potential as the addition of FVIII. However, as mentioned previously, no evidence of spontaneous thrombosis has been observed during any of the toxicology studies in normocoagulative Cynomolgus monkeys.

Pharmacokinetics

In a 4-week toxicity study, following the intravenous administration of up to 100 mg/kg/week emicizumab in the monkey, the mean exposure values C0 and AUC0-7d observed were up to 3555 µg/mL and 15400 d.µg/ml, respectively.

In a 26-week toxicity study, following the subcutaneous administration of 30 mg/kg/week emicizumab in the monkey, the mean exposure values Cmax and AUC0-7d observed were up to 1355 µg/mL and 8755 d.µg/ml, respectively.

Toxicology

In the 4-week intravenous toxicity study in Cynomolgus monkeys, polyarteritis in the liver, pancreas, stomach, and spleen and related abnormal clinical pathology test results were observed in one female in the 100 mg/kg group after the third dose. The pathomechanism of the polyarteritis remained unclear and the finding was considered to be a spontaneous case of polyarteritis was based on reports of spontaneous onset of polyarteritis in monkeys in published literature and the fact that no similar finding was noted in any other monkey after treatment with emicizumab. The affected animal tested ADA negative and exposure assessment did not indicate an ADA response either. However, the possibility that the polyarteritis was immune-mediated cannot be completely discounted. The shortening of aPTT in all emicizumab-treated groups was attributed to the pharmacological action of emicizumab.

In conclusion, no adverse effects were induced when emicizumab was intravenously administered once a week for 4 weeks up to 100 mg/kg. Therefore, the no observed adverse effect level (NOAEL) was considered to be 100 mg/kg or more in males and females under the condition of this study.

In the 26-week subcutaneous toxicity study, one male Cynomolgus monkey dosed with 6 mg/kg once weekly developed swelling/haemorrhage/vasculitis at the administration site and was prematurely necropsied on the day after the 22nd dose. Anti-emicizumab antibodies were detected in this animal prior to the third dose and reached very high titres from the seventh dose onward to the extent that plasma emicizumab concentrations were sometimes below the level of quantification. Histopathological examination of the administration site revealed acute necrotising vasculitis and chronic vasculitis associated with severe haemorrhagic changes. Based on the course of the swelling and the histopathological findings, the cause of the administration site swelling was deemed to be an Arthus

reaction (type III hypersensitivity) triggered by administration of a heteroprotein. In this study, the NOAEL of emicizumab was considered to be 30 mg/kg.

A comparison was made between the exposure values (Cmax and AUC) obtained at the no observed adverse effect level (NOAEL) in the 26-week toxicity study in monkeys subcutaneously administered 30 mg/kg/week emicizumab and the clinical exposures in humans treated with doses of 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W. For the Cmax values, the safety margins for the 1.5 mg/kg QW, 3 mg/kg Q2W and 6 mg/kg Q4W doses were 25, 23 and 20, respectively. For the AUC values, the safety margins for the 1.5 mg/kg QW, 3 mg/kg Q2W and 6 mg/kg Q4W doses were 22, 11 and 5, respectively.

Amendments were provided for the 4- week intravenous and 26-week subcutaneous toxicity studies in monkeys relating to error calculations. These amendments do not appear to alter the safety profile of emicizumab and are considered to be of minor importance.

In accordance with the CHMP guideline for Environmental risk assessment of medicinal products for human use" [EMEA/CHMP/SWP/4447/00 corr 2], as the proposed product falls within the classification of a products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an environmental risk assessment (ERA) is not required. The experimental assessment of emicizumab confirms the general finding that biologics (protein and peptide) active pharmaceutical ingredients are biodegradable, show low acute ecotoxicity and therefore present no significant risk to the environment. Based on the above considerations, no formal ERA was submitted for the emicizumab Type II Variation which is considered to be acceptable.

2.2.7. Conclusion on the non-clinical aspects

The non-clinical data support the extension of indication of emicizumab (Hemlibra) for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors and severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors.

2.3. Clinical aspects

2.3.1. Introduction

The currently approved indication in adult and paediatric patients with haemophilia A with FVIII inhibitors was supported by results from Study BH29884 in patients ≥ 12 years of age and interim results from Study BH29992 in children < 12 years of age, plus supporting data from the Phase I and I/II studies (ACE001JP, ACE002JP, and JP29574) and the non-interventional study (NIS) BH29768.

The current application includes clinical efficacy data from two new pivotal Phase III Studies BH30071 and BO39182 and updated results from Studies BH29992, BH29884, and ACE002JP.

- Primary analysis of Study BH30071 in 152 adult and adolescent patients with haemophilia A without FVIII inhibitors (QW and Q2W dosing regimens).
- Interim analysis of Study BO39182 in 48 adult and adolescent patients with haemophilia A with or without FVIII inhibitors (Q4W dosing regimen). Patient enrolment is complete.
- Updated interim analysis of Study BH29992 in 63 paediatric patients <12 years old or 12 to 17 years old weighing < 40 kg, with FVIII inhibitors, including 10 patients ≤ 2 years of age (QW dosing regimen). Patient enrolment is complete, pre-specified follow-up period for the primary analysis not yet reached.

- Updated, long term efficacy and safety analyses from Study BH29884 in 113 adults and adolescents ≥ 12 years of age with FVIII inhibitors (QW dosing regimen).
- Updated, long term efficacy and safety analyses from the open-label extension Study ACE002JP in 16 patients aged ≥ 12 and < 60 years (2 patients from Study ACE001JP Part C did not enter extension Study ACE002JP).

In addition, data from NIS BH29768 (n = 226) are also included, to allow for evaluation of efficacy in Studies BH30071, BH29992, and BH29884 through intra-patient comparisons where patients act as their own control.

GCP

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

The applicant 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**

Patient Population	Dosing Regimen(s)	Objectives	Analysis/Clinical Cutoff Date (*No. of patients*)/ Exposure Time (weeks)
Pivotal Phase III Studies			
BH30071: Open-label, multicenter, global, randomized study			
Patients aged ≥12 years with severe hemophilia A (intrinsic FVIII level <1%) without FVIII inhibitors **Arm A, Arm B, and Arm C:** patients (previously on episodic FVIII) randomized 2:2:1 to receive emicizumab prophylaxis QW (Arm A), Q2W (Arm B), or no prophylaxis (Arm $C_{control}$). **Arm D:** Non-randomized arm for patients previously on prophylactic FVIII who received QW emicizumab prophylaxis.	Arm A, B, and D: Patients receive loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 1.5 mg/kg QW (Arm A)[a], 3 mg/kg Q2W (Arm B)[a], or 1.5 mg/kg QW (Arm D)[b]. Arm $C_{control}$: Patients receive no prophylaxis, allowed to switch to receive emicizumab prophylaxis after at least 24 weeks on no prophylaxis[a] referred as Arm C_{emi} (loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 3 mg/kg Q2W).	Primary Bleed rate (with bleeds defined as those treated with coagulation factors) in Arm A and Arm B compared to Arm $C_{control}$. Secondary Comparison of Arm A and B with Arm $C_{control}$ for the following parameters: all bleed rate (bleeds treated and not treated with coagulation factors), treated spontaneous bleed rate, treated joint bleed rate, treated target joint bleed rate; HRQoL (Haem-A-QoL, Haemo-QoL-SF), health status (EQ-5D-5L) and EmiPref. Arm A, Arm B, and Arm D intra-patient comparisons with data from NIS BH29768 for treated and all bleeds. Other • Safety • PK	**Primary analysis (Study ongoing)** Data cutoff: 15 Sep 2017 Enrolled: N = 152 Randomized: Arm A: N = 36 Arm B: N = 35 Arm C: N = 18 Non-randomized: Arm D: N = 63 (48 from NIS BH29768) **Exposure Time** Median = 29.0 weeks (range: 0.1–50.1) (N = 150)

Patient Population	Dosing Regimen(s)	Objectives	Analysis/Clinical Cutoff Date (*No. of patients*)/ Exposure Time (*weeks*)
BO39182: Open-label, multicenter, global, non-randomized study			
Patients aged ≥12 years with hemophilia A with or without FVIII inhibitors.	Expansion Part: Patients receive a loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 6 mg/kg Q4W[a]. PK run-in part: Patients receive a dose of 6 mg/kg Q4W[a]. No loading dose was given in PK run-in part[a].	To investigate the efficacy (treated and all bleeds [bleeds treated and not treated with FVIII or BPA]), treated spontaneous bleed rate, treated joint bleed rate, treated target joint bleed rate; as well as HRQoL (Haem-A-QoL, Haemo-QoL-SF),health status (EQ-5D-5L), EmiPref without any formal statistical hypothesis testing. Other • Safety • PK	**Interim Analysis (Study ongoing)** Data cutoff: 18 Oct 2017 Enrolled: N =48 (41 in expansion part, 7 in PK run-in)[c] **Exposure time** Expansion Part: Median = 16.1 weeks (range: 12.1 – 20.1) (N = 41) PK Run-in Part: Median = 32.1 weeks (range: 32.1–36.3) (N = 7)

Patient Population	Dosing Regimen(s)	Objectives	Analysis/Clinical Cutoff Date (*No. of patients*)/ Exposure Time (*weeks*)
BH29992: Open-label, multicenter, global, single-arm study			
Pediatric patients with inhibitors from birth to <12 years of age, with allowance of patients 12–17 years of age who weigh <40 kg[d].	Patients receive loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 1.5 mg/kg QW[e].	To evaluate the efficacy (treated and all bleeds [bleeds treated and not treated with BPA]), treated spontaneous bleed rate, treated joint bleed rate, treated target joint bleed rate; HRQoL, aspects of caregiver burden without any formal statistical hypothesis testing. Other • Safety • PK	**Interim Analysis (Study ongoing)** Data cutoff: 05 Oct 2017 Enrolled: N=63 < 12 years N=60 (including 10 patients ≤ 2 years of which 5 patients <2 years) ≥ 12 years and <40kg: N=3 **Exposure Time** Median = 29.1 weeks (range: 8.3–63.0) (N = 63)

Supportive Studies			
BH29884: Open-label, multicenter, global, randomized study			
Patients ≥ 12 years of age with inhibitors to FVIII **Arms A and B**: patients previously on episodic BPA randomized 2:1 to receive emicizumab prophylaxis (Arm A) vs. no prophylaxis (Arm $B_{control}$). **Arm C**: Non-randomized emicizumab arm for patients previously on BPA prophylaxis. **Arm D**: Non-randomized emicizumab arm for patients previously on episodic or prophylactic BPA who participated in NIS BH29768 but were unable to enroll before closure of enrolment in Arms A, B, and C.	Arm A, C, and D: Patients receive loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 1.5 mg/kg QW[3]. Arm $B_{control}$: Patients receive no prophylaxis, allowed to switch to receive emicizumab prophylaxis after at least 24 weeks on no prophylaxis, referred as Arm B_{emi} (loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 1.5 mg/kg QW)[3].	Primary Bleed rate (with bleeds defined as those treated with BPA) in Arm A compared to Arm $B_{control}$. Secondary Comparison of Arm A with Arm $B_{control}$ for the following parameters: all bleed rate (bleeds treated and not treated with BPA), treated spontaneous bleed rate, treated joint bleed rate, treated target joint bleed rate; HRQoL (Haem-A-QoL, Haemo-QoL-SF), health status (EQ-5D-5L). Arm A and Arm C intra-patient comparisons with data from NIS BH29768 for the following parameters: treated and all bleeds. Other • Safety • PK	**Updated analysis (Study ongoing)** Data cutoff: 08 Sep 2017 Enrolled: N = 113 Randomized: Arm A: N = 35 Arm B: N = 18 Non-randomized: Arm C: N = 49 Arm D: N = 11 **Exposure Time** Median = 60.5 weeks (range: 3.3 – 94.2) (N = 112)
ACE002JP: conducted in Japan, Phase I/II, open-label extension study of patients from Study ACE001JP Part C with possible dose up-titration to other treatment groups *Results of ACE001JP Part C were analyzed with its extension Study ACE002JP. All references to "Study ACE002JP" in this document should be understood to mean ACE001JP Part C and ACE002JP collectively.*			
Patients with hemophilia A with and without inhibitors from Part C of Study ACE001JP.	Group 1: patients receive loading dose of emicizumab 1 mg/kg prior to starting maintenance of 0.3 mg/kg QW maintenance dose[7] Group 2: patients receive loading dose of emicizumab 3 mg/kg loading dose prior to starting maintenance of 1 mg/kg QW maintenance dose[7] Group 3: patients receive no loading dose prior to starting maintenance of 3 mg/kg QW maintenance dose[7]	To investigate the safety and, in an exploratory manner, the inhibitory effect of emicizumab on bleeding during long-term treatment in patients with hemophilia A who have participated in Study ACE001JP.	**Interim Analysis (Study ongoing)** Data cutoff: 31 Aug 2017 (includes data from ACE001JP Part C) N = 18 (3 groups of 6 patients each)[2] **Exposure Time** 0.3 mg/kg/week: Median = 222 weeks (range: 220 – 225 weeks), 1 mg/kg/week: Median = 197 weeks (range: 4.1 – 204 weeks) 3 mg/kg/week: Median = 174 weeks (range: 12.1 – 178 weeks)

Patient Population	Dosing Regimen(s)	Objectives	Analysis/Clinical Cutoff Date (*No. of patients*)/ Follow-up Efficacy Period (*weeks*)
Non-interventional Study			
BH29768: Non-interventional, multi-cohort, multicenter study			
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.	Coagulation factors regimens were not specified in this non-interventional study. Dosing and duration of routine treatment with coagulation factors were at the discretion of investigators in accordance with local clinical practice and local labeling. This study did not include emicizumab	To document the number and type of treated bleeds, all bleeds(treated and untreated with coagulation factors), treated spontaneous bleeds, treated joint bleeds, treated traumatic bleeds, to estimate the number of bleeds over time; as well as HRQoL (Haem-A-QoL, Haemo-QoL-SF, Adapted Inhib-QoL), health status (EQ-5D-5L); and safety; under routine clinical practice in patients with hemophilia A with and without FVIII inhibitors.	**Final Analysis** Data cutoff: 31 March 2017 Cohort A: N=103; Cohort B: N=25 Cohort C: N=98 **Follow-up Cohort A** Episodic group: Median=25.4 weeks (range: 4.1–69.6) Prophylactic group: Median=26.9 weeks (range: 8.1–49.3) **Follow-up Cohort B** Episodic group: Median=31.2 weeks (range: 21.3–41.1) Prophylactic group: Median=17.9 weeks (range: 8.7–36.4) **Follow-up Cohort C** Episodic group: Median=27.7 weeks (range: 15.4–47.7) Prophylactic group: Median=30.4 weeks (range: 12.4–45.1)

AE=adverse event; EQ-5D-5L=EuroQoL-Five Dimension-Five Levels; FVIII=factor VIII; Haem-A-QoL=hemophilia-specific quality of life index for adults; Haemo-QoL SF=hemophilia-specific quality of life index for adolescents Short Form; HRQoL=health-related quality of life; NIS=non-interventional study; PK=pharmacokinetics; SC=subcutaneous.

[a] Patients had the opportunity to increase their dose to 3 mg/kg QW if they had completed at least 24 weeks on study drug, met the specific criteria, and received approval from the Medical Monitor.

[b] Patients had the opportunity to increase their dose to 3 mg/kg QW after the second qualifying bleed, with approval from the Medical Monitor.

[c] Only safety and PK assessment of Q4W emicizumab regimen was performed in the PK run-in part (n=7). These patients were not included in efficacy assessment. Safety and efficacy was assessed in expansion part consisting of 41 patients.

[d] Two new cohorts in patients <12 years of age have been added to the study (protocol amendment 3) to investigate 3.0 mg/kg Q2W and 6.0 mg/kg Q4W dosing regimens. The enrollment to these additional cohorts took place after the cut-off of the analysis of the Interim CSR.

[e] Patients had the opportunity to increase their dose to 2.25 mg/kg QW in first instance followed by 3 mg/kg QW if they experienced more than two spontaneous bleeding events during a 12-week treatment period at a given dose.

[f] Patients in Group 1 and Group 2 had the opportunity to increase their dose to 1 mg/kg/week and 3 mg/kg/week, respectively, following approval by the study's Efficacy and Safety Evaluation Committee based on evaluation of laboratory test values, vital signs, 12-lead ECG results, adverse events, pharmacokinetics, pharmacodynamic response, serum cytokine concentrations, and number of bleeding episodes during a treatment period of at least 12 weeks (12 consecutive administrations) at the subject's maximum dose. The same evaluation process was used to determine whether any patient in Group 1 having been escalated to 1 mg/kg/week (Group 2), may subsequently be escalated to 3 mg/kg/week (Group 3).

[g] Results include 2 patients from Study ACE001JP Part C who did not enter extension Study ACE002JP.

2.3.2. Pharmacokinetics

PK characteristics in adult/adolescent patients and patients < 12 years of age with haemophilia A from Studies BH29992, BH29884, and ACE002JP were submitted with in addition results from two new pivotal studies (BH30071 and BO39182) in haemophilia A patients with or without FVIII inhibitors. The clinical PK of emicizumab was analysed using both descriptive, NCA, and a population PK based compartmental analysis.

Study BH30071

Study BH30071 (also known as HAVEN 3) is an ongoing randomized, multicenter, open label,Phase III clinical study in adult and adolescent patients (age ≥ 12 years) with severe haemophilia A (intrinsic FVIII level < 1%) without inhibitors against FVIII who previously received either episodic or prophylactic treatment with FVIII. The study was similar in design to Study BH29884.

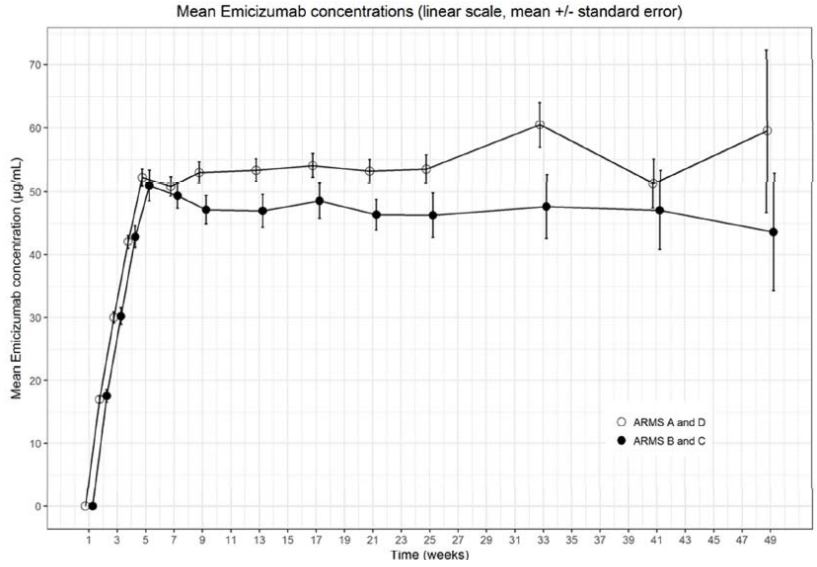
For all patients, pre-dose (trough) plasma concentrations of emicizumab were analysed descriptively by treatment arm, including arithmetic and geometric means, median, range, standard deviations, standard errors, and coefficients of variation. Since patients in treatment Arms A and D, and Arms B and C_{emi} received the same dosing regimen (i.e., loading doses of emicizumab at 3 mg/kg QW for 4 weeks followed by maintenance doses of 1.5 mg/kg QW (Arms A and D) or 3 mg/kg Q2W (Arms B and C), mean PK profiles are presented as two dose regimens (QW or Q2W).

With the QW dosing regimen (Arms A and D), mean trough plasma emicizumab concentrations increased with weekly doses of 3 mg/kg to achieve 52.2 µg/mL at Week 5 (Table 3). Mean trough plasma concentrations between 50.8 and 60.5 µg/mL were maintained from Week 7 to Week 41 with weekly doses of 1.5 mg/kg. The mean concentration observed at Week 49 (59.5 µg/mL) was based on data collected in 3 patients only.

With the Q2W dosing regimen (Arms B and Cemi), mean trough plasma concentrations of emicizumab increased with weekly doses of 3 mg/kg to achieve 50.9 µg/mL at Week 5. Mean trough concentrations of approximately 48 µg/mL were maintained from Week 7 to Week 41 with bi-weekly doses of 3 mg/kg.

Overall, the variability was moderate (coefficient of variations of approximately 30 - 40%), with a range of individual trough plasma concentrations after Week 5 between 16.8 and 128 µg/mL after 1.5 mg/kg QW (Table 3) and between 12.0 and 103 µg/mL after doses of 3 mg/kg Q2W.

Figure 5: Mean plasma emicizumab concentrations vs. time profiles by dosing regimens:



Study BO39182

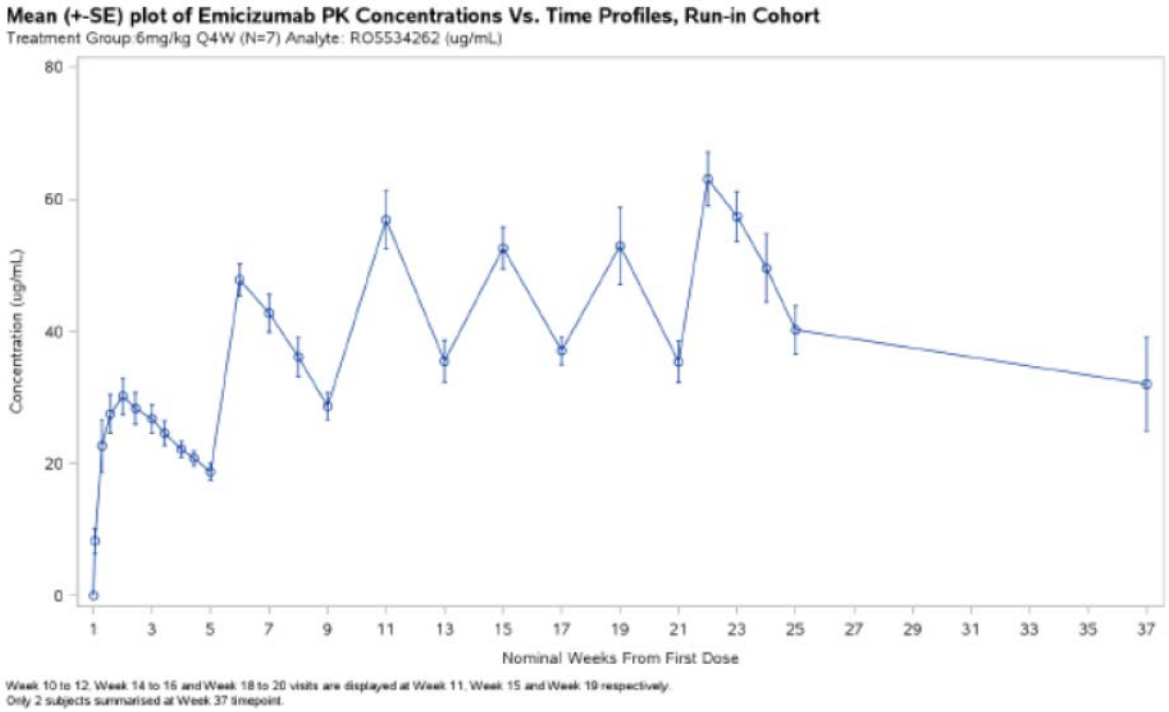
Study BO39182 (also known as HAVEN 4) is a non-randomized, multicenter, open-label, Phase III clinical study evaluating the efficacy, safety, PK, and PD of emicizumab (6 mg/kg) administered Q4W in adult/adolescent patients with haemophilia A with or without inhibitors against FVIII.

The study consists of two parts: a PK run-in part followed by an expansion part.

In the PK run-in part, a full PK profile was measured in the first 6 enrolled patients during their first 4 weeks of treatment to characterise the pharmacokinetics of dosing with emicizumab Q4W at an SC dose of 6 mg/kg. Intense PK sampling was performed after the first and second emicizumab dose administration, followed by a reduced PK sampling schedule from Week 9 to Week 21. After Week 21, sampling frequency was increased to characterise steady-state PK.

The arithmetic mean plasma emicizumab concentration-time profile based on all samples collected up to the time of the CCOD (18 October 2017) is shown below.

Figure 6: Mean plasma emicizumab concentration-time profile (PK run-in cohort)



After administration of the first SC dose of emicizumab at 6 mg/kg, an arithmetic mean peak plasma emicizumab concentration (Cmax) of 32.3 µg/mL was reached at a median time of 6.95 days. The time to maximum concentration (Tmax) in individual patients ranged from approximately 4 to 7 days. Subsequently, emicizumab plasma concentrations declined in a mono-exponential manner with an arithmetic mean apparent terminal T1/2 of 31.3 days. Of note, estimates of lambda z (λz) dependent PK parameters (i.e., T1/2 , area under the concentration-time curve from time 0, extrapolated to infinity [AUC0-inf] and CL/F) were approximate and should be interpreted with caution as the sampling and dosing schedules did not allow a proper estimation of λz.

Table 6: Summary of pharmacokinetics parameters of emicizumab in plasma after the first and the sixth emicizumab administration (PK run-in cohort)

PK Parameters [a]	After the first emicizumab dose (Week 1 to Week5)	After the sixth emicizumab dose (Week 21 to Week 25)
T_{max} (day)	6.95 (3.99-7.18)	6.98 (6.90-14.03)
C_{max} (µg/mL)	31.8 (19.3)	62.7 (17.3)
AUC_{τ} (day*µg/mL)	663 (19.6)	1420 (20.7)
$t_{1/2}$ [b] (day)	29.5 (38.5)	ND
AUC_{0-inf} [b] (day*µg/mL)	1490 (27.2)	ND
CL/F [b] (mL/h)	10.7 (23.9)	11.1 (20.8) [c]

ND: not determined

[a] Median (range) for T_{max}; geometric mean (CV%) for all other parameters.

[b] $t_{1/2}$ not properly estimated after the first dose; hence dependent PK parameters are not well estimated.

[c] CL_{ss}/F is reported.

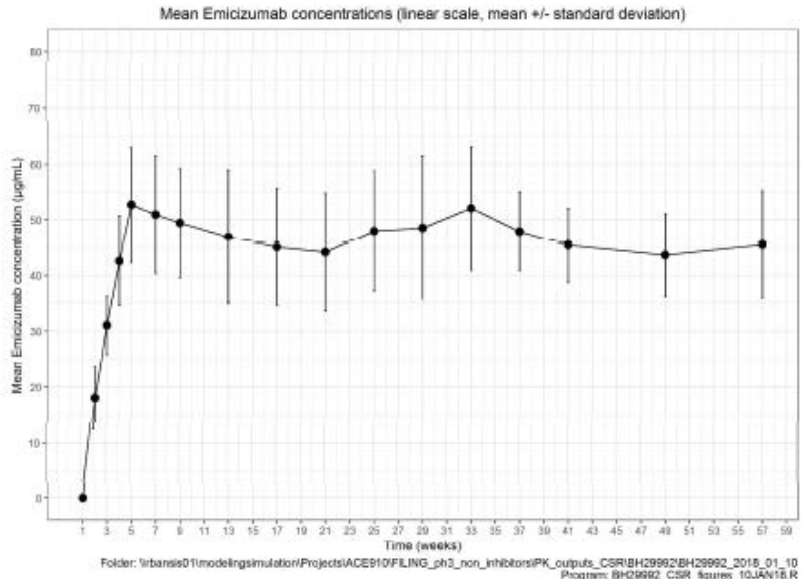
Study BH29992

Study BH29992 (also known as HAVEN 2) is a multicenter, open-label clinical study in paediatric patients (< 12 years old or 12 - 17 years old and < 40 kg) with haemophilia A with FVIII inhibitors. Patients received emicizumab prophylaxis at a loading dose of 3 mg/kg SC QW for the first 4 weeks, followed by maintenance doses of 1.5 mg/kg QW thereafter.

Sixty - three patients received emicizumab prophylaxis at a loading dose of 3 mg/kg QW for 4 weeks followed by maintenance doses of 1.5 mg/kg QW. Mean trough plasma concentrations of emicizumab increased with QW administration to reach 52.7 µg/mL at Week 5.

Thereafter, mean trough concentrations were maintained between 43.7 and 52.1 µg/mL with QW administrations of 1.5 mg/kg from Week 7 to Week 57. Overall, the inter-individual variability was moderate, with individual trough plasma concentrations in the range of 19.2 to 88.7 µg/mL at steady-state (from Week 7 to Week 57).

Figure 7: Mean plasma emicizumab concentration-time profile (PK population)



Mean plasma concentration-time profiles by patient age and body weight are shown in Figure 8 and Figure 9, respectively. Descriptive summary statistics by age and body weight, and the corresponding PK profiles

in individual patients have been provided. Among the 63 patients included in the analysis, no effects of age or body weight on emicizumab exposure (mean trough concentration) were identified.

Table 7: Summary statistics of emicizumab plasma concentration (µg/mL) by scheduled time (PK population)

	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 7	WEEK 9	WEEK 13	WEEK 17
Scheduled day	1	8	15	22	29	43	57	85	113
N	62	62	62	62	61	63	62	61	62
Mean	.	18.0	31.1	42.6	52.7	50.9	49.5	46.9	45.1
SD	.	5.5	5.2	8.1	10.3	10.6	9.9	12.1	10.5
SE	.	0.7	0.7	1.0	1.3	1.3	1.3	1.5	1.3
Min	.	8.2	20.0	28.5	23.5	27.9	29.1	25.9	22.8
Median	.	17.3	30.1	42.6	52.6	50.4	47.7	43.6	44.4
Max	.	39.2	44.2	64.5	87.4	80.0	75.8	83.9	72.9
Geom mean	.	17.2	30.6	41.9	51.7	49.8	48.5	45.5	43.9
CV of geom mean	.	28.9	16.9	19.0	20.9	21.7	20.7	25.6	24.7

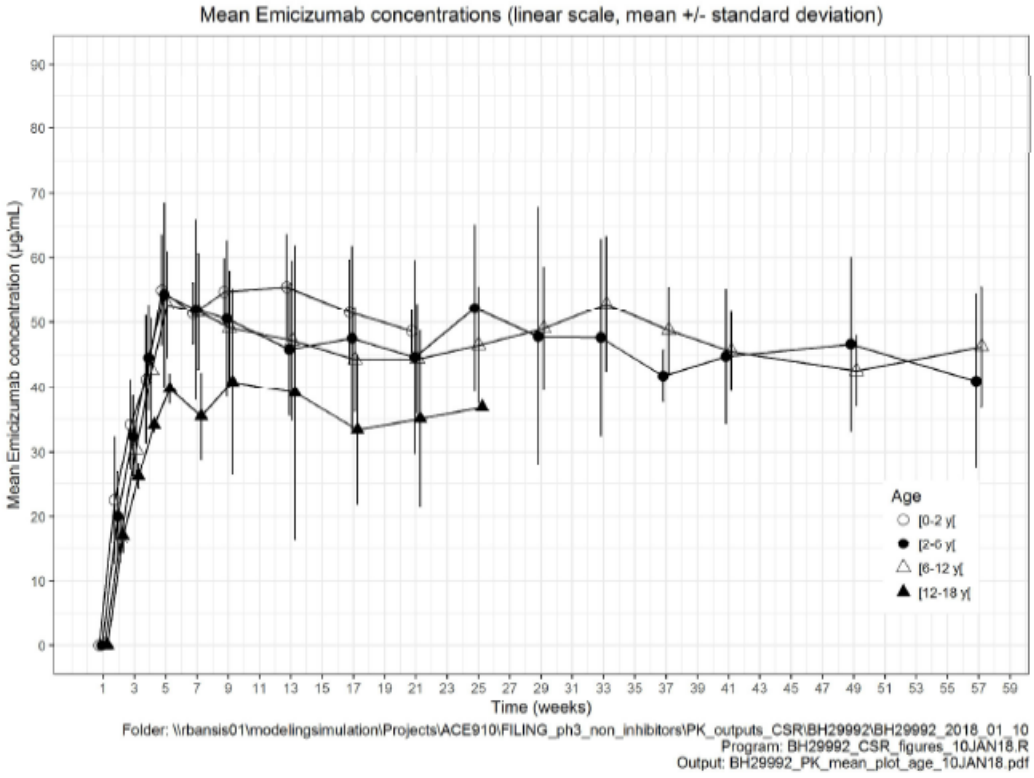
	WEEK 21	WEEK 25	WEEK 29	WEEK 33	WEEK 37	WEEK 41	WEEK 49	WEEK 57
Scheduled day	141	169	197	225	253	281	337	393
N	60	49	35	27	21	20	20	18
Mean	44.2	48.0	48.6	52.1	47.9	45.4	43.7	45.5
SD	10.6	10.8	12.9	11.1	7.1	6.6	7.4	9.6
SE	1.4	1.5	2.2	2.1	1.5	1.5	1.7	2.3
Min	19.2	23.1	23.6	28.8	34.1	30.9	35.0	28.7
Median	43.8	48.5	47.0	48.9	47.5	46.1	41.3	44.6
Max	88.7	68.0	83.8	72.7	61.8	56.9	63.6	62.1
Geom mean	43.0	46.8	46.9	50.9	47.4	45.0	43.1	44.5
CV of geom mean	24.5	23.8	27.6	22.4	15.2	15.4	16.2	21.8

CV=coefficient of variation; Geom mean=geometric mean; Max=maximum; Min=minimum; N=number of patients evaluated; SD=standard deviation; SE=standard error.

Notes: All 63 patients are included in the PK population. PK samples were missing at various visits for individual patients.

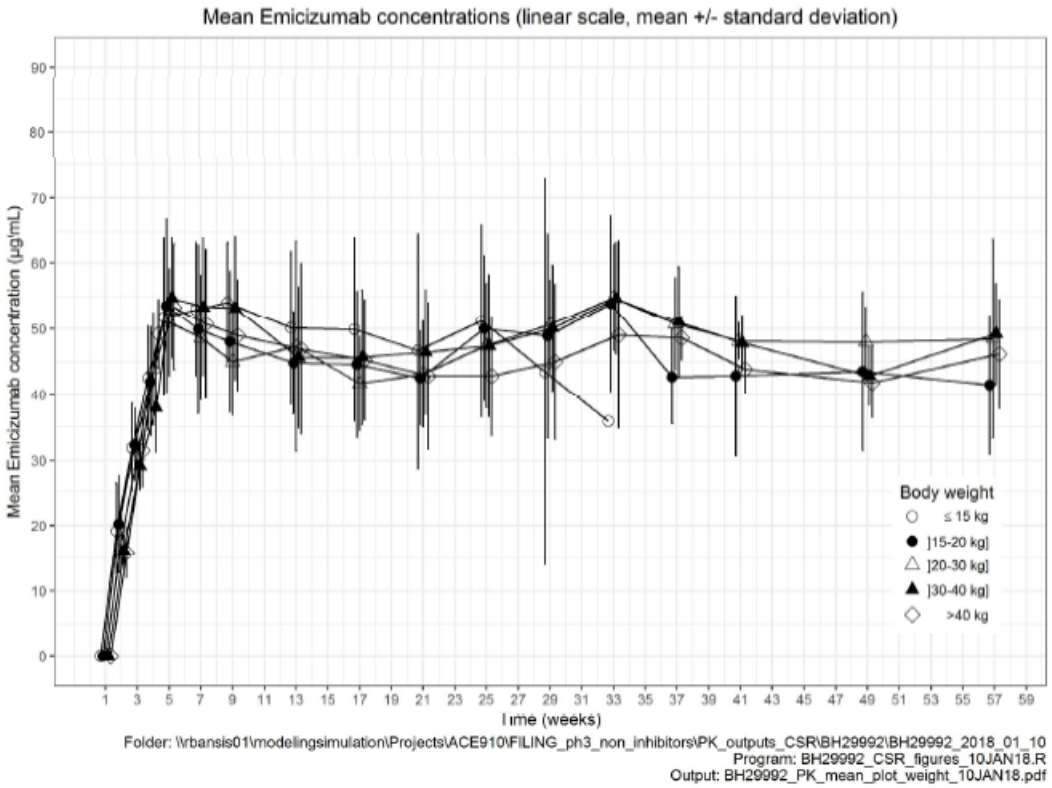
Patient (N) numbers decrease over time due to the differential enrollment dates and consequent follow-up periods at the time of the clinical cutoff date.

Figure 8: Mean plasma emicizumab concentration-time profiles by age group (PK population)



n values: [0–2 y[: n=5 ; [2–6 y[: n=17 ; [6–12 y[: n=38 ; [12–18y[: n=3

Figure 9: Mean plasma emicizumab concentration-time profiles by body weight group (PK population)



n values: BW ≤15 kg: n=13 ;]15–20]: n=13;]20–30 kg] : n=17 ;]30–40 kg] : n=12 ; BW > 40 kg: n=8

Study BH29884

Study BH29884 (also known as HAVEN 1) is a randomized, multicenter, open-label, Phase III clinical study enrolling patients aged 12 years or older with haemophilia A with inhibitors who previously received either episodic or prophylactic treatment with bypassing agents. The study evaluated prophylactic treatment with emicizumab at a loading dose of 3 mg/kg QW SC for 4 weeks, followed by maintenance doses of 1.5 mg/kg QW SC thereafter. The study was similar in design to Study BH30071.

In the 4 treatment arms, all patients treated with emicizumab received the same dosing regimen (i.e., 4 doses of emicizumab 3 mg/kg QW, followed by a maintenance dose of 1.5 mg/kg QW). As the PK profiles were similar across treatment arms, results are presented for all arms together as a single dose group.

Mean trough plasma concentrations of emicizumab increased following 3 mg/kg QW administration to achieve 54.1 µg/mL at Week 5. Mean trough concentrations slightly above 50 µg/mL were maintained thereafter with weekly doses of 1.5 mg/kg. The apparent decline of mean trough concentration at Week 85 is likely related to the small number of patients (n = 8) at this time point.

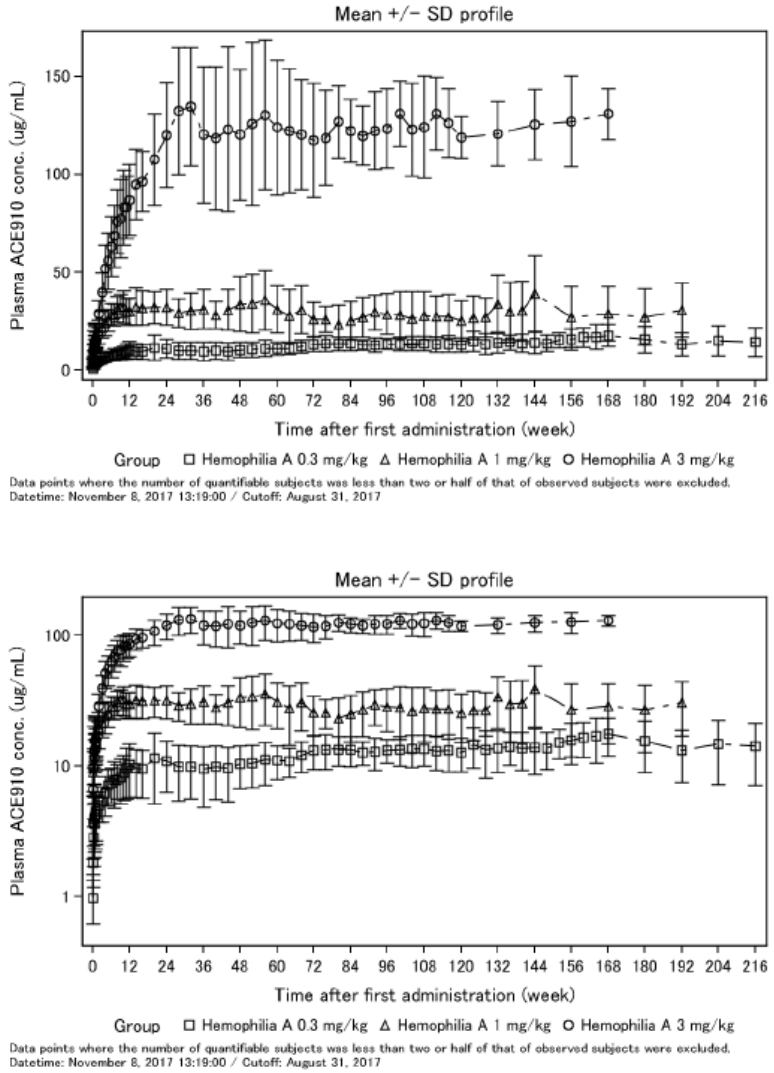
The variability was moderate (coefficient of variations of approx. 30 - 40%); however, the range of individual trough plasma concentrations after Week 5 was 2.8 - 148 µg/mL.

Study ACE002JP

Study ACE002JP is an ongoing Phase I/II open-label extension study in male Japanese patients aged ≥ 12 years and < 60 years with severe congenital haemophilia A who completed Part C of Study ACE001JP. In Part C of Study ACE001JP, a total of 18 Japanese patients with haemophilia A (11 patients with inhibitors, 7 patients without inhibitors) were enrolled.

Plasma emicizumab concentrations increased over time with weekly administration in all groups. The time to plateau in plasma emicizumab Ctrough levels (steady-state) was approximately 12 weeks where an initial loading dose was given at the approximately 3-fold maintenance dose (0.3 and 1 mg/kg/week groups), and approximately 24 weeks where no initial loading dose was given (3 mg/kg/week group). Plasma emicizumab Ctrough levels at steady-state increased in a dose-proportional manner with mean (SD) of 10.3 (4.54) µg/mL and 29.9 (6.88) µg/mL at 12 weeks for the 0.3 and 1 mg/kg/week dose groups, respectively, and 120 (26.8) µg/mL at 24 weeks for the 3 mg/kg/week group.

Figure 10: Mean time course of plasma ACE910 concentration following multiple subcutaneous administrations



Upper: normal scale, lower: semi-logarithmic scale

Table 8: Summary statistics of pharmacokinetic parameters of ACE910 following multiple subcutaneous administration

Analyte: Pharmacokinetic parameters of ACE910
Group: Hemophilia A
Subset: Both subjects tested positive and negative for anti-ACE910 antibodies

PK parameter	Unit	Dose (mg/kg)	N	n	Mean	SD	CV (%)	Median	Minimum	Maximum	Geomet. mean	Geomet. CV (%)
t1/2	day	-	3	3	24.3	3.49	14.3	26.0	20.3	26.7	24.2	15.1
kel	1/day	-	3	3	0.0289	0.00450	15.6	0.0267	0.0259	0.0341	0.0287	15.1
Ctrough,ss	ug/mL	0.3	6	6	10.3	4.54	44.1	8.90	4.75	15.9	9.45	48.9
		1	5	5	29.9	6.88	23.0	31.0	18.9	37.9	29.1	26.3
		3	5	5	120	26.8	22.3	109	97.0	158	118	21.8

"N" means the number of observed subjects. "n" means the number of calculable subjects.
Datetime: November 8, 2017 13:50:00 / Cutoff: August 31, 2017

$C_{trough,ss}$ was defined as the C_{trough} at the time of steady state achievement for each dosing group (12, 12, and 24 weeks post-dose for the 0.3, 1, and 3 mg/kg/week groups, respectively).

The results of power model analysis on dose - proportionality confirmed dose linearity.

Table 9: Regression coefficient for dose-proportionality

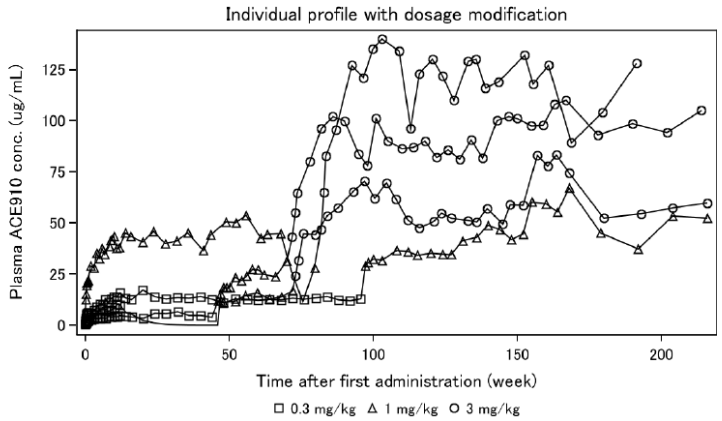
Power model analysis on dose-proportionality
Regression coefficient on log-transformed dose

Group	PK parameter	The number of subjects included in the analysis	Point estimates	95% confidence interval
Hemophilia A	Ctrough,ss	15	1.076	0.866 - 1.286

Ctrough,ss for subjects tested positive for anti-ACE910 antibodies by the time of steady state achievement were excluded.
Datetime: November 8, 2017 13:50:00 / Cutoff: August 31, 2017

In 4 patients who received dose escalation, plasma emicizumab concentrations increased with higher doses. In 3 patients, after the multiple administrations were stopped, plasma emicizumab concentrations decreased exhibiting a monophasic time course regardless of dose. In these patients, the mean (SD) T1/2 after last administration was 24.3 (3.49) days.

Figure 11: Individual time course of plasma ACE910 concentration following multiple subcutaneous administrations with dose modification



0.05 ug/mL was assigned if below the lower limit of quantification.
Squares, triangles and circles represent the data observed during continuously receiving maintenance doses of 0.3, 1 and 3 mg/kg (or the corresponding loading dose if any), respectively.
Datetime: November 8, 2017 13:19:00 / Cutoff: August 31, 2017

2.3.3. PK/PD modelling

The population PK and exposure-efficacy/safety analyses are based on data from Phase I/II Study ACE001JP Part C/ACE002JP and Phase III Studies BH30071, BO39182, BH29884, and BH29992.

Table 10: NONMEM parameter estimates for the final PK model

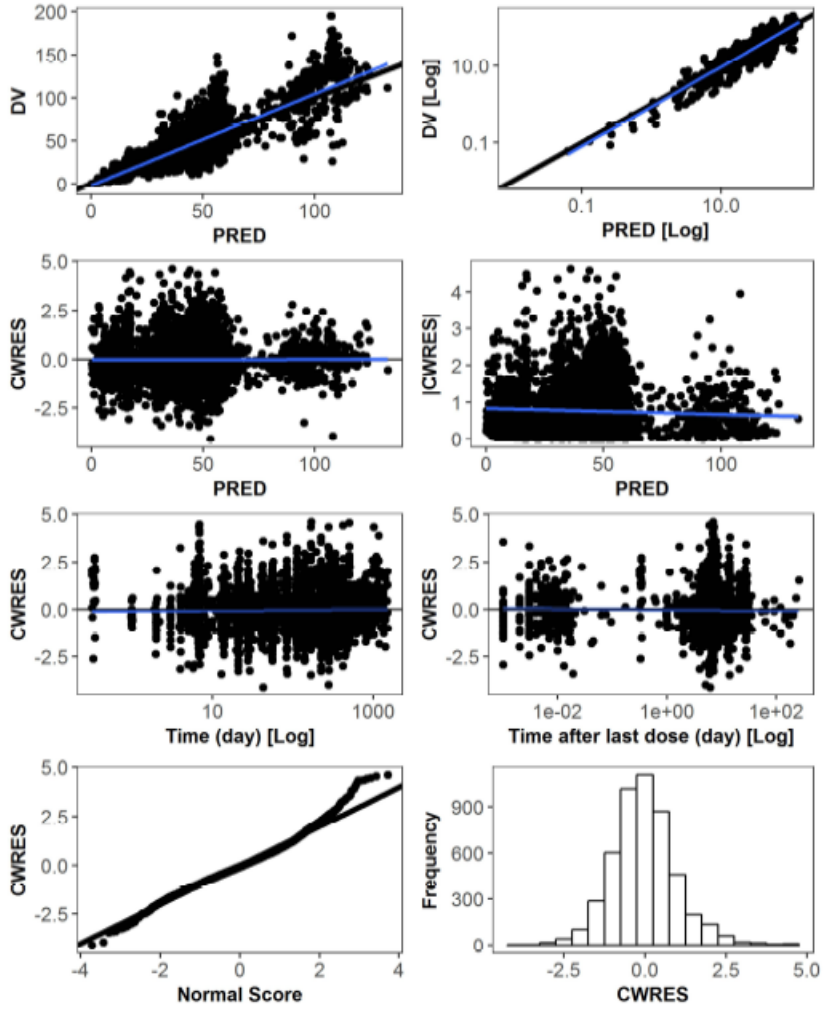
Parameter	Unit	Estimate	RSE (%)	95% CI (lower, upper)	Shrinkage (%)
Fixed Effects					
CL/F	L/day	0.272	1.9	(0.262, 0.282)	
V/F	L	10.4	1.9	(10.0, 10.8)	
KA	1/day	0.536	7.1	(0.462, 0.610)	
Random Effects BPV					
CL/F	CV%	28.7	8.6[a]		3.7
V/F	CV%	25.9	8.9[a]		10.3
KA	CV%	72.5	14.7[a]		40.6
Correlation CL/F-V/F	-	0.217	31.8[b]		
Correlation CL/F-KA	-	-0.341	25.0[b]		
Covariate Effects					
Effect of BW on CL/F	-	0.911	3.2	(0.854, 0.968)	
Effect of ALB on CL/F	-	1.57	28.4	(0.696, 2.44)	
Effect of BW on V/F	-	1.00	3.0	(0.941, 1.06)	
Effect of Black or African American on V/F	-	−0.215	19.7	(−0.298, −0.132)	
Effect of AGE>30 years on F_{rel}	-	6.51×10^{-1}	16.3	$(4.43\times10^{-1}, 8.59\times10^{-1})$	
Error Model					
σ_1 (additive)	µg/mL	0.025 F	-		
σ_2 (proportional)	%	14.6	2.0	(14.0, 15.2)	
RUNID: RUN8_32, OFV: 24264.001					

ALB=albumin; BPV=between-patient variability; BW= body weight; σ=residual error; RSE=relative standard error of estimate; CI=Confidence interval; CV=coefficient of variation; OFV=objective function value; F=Fixed.

[a] RSE computed for the corresponding variance.

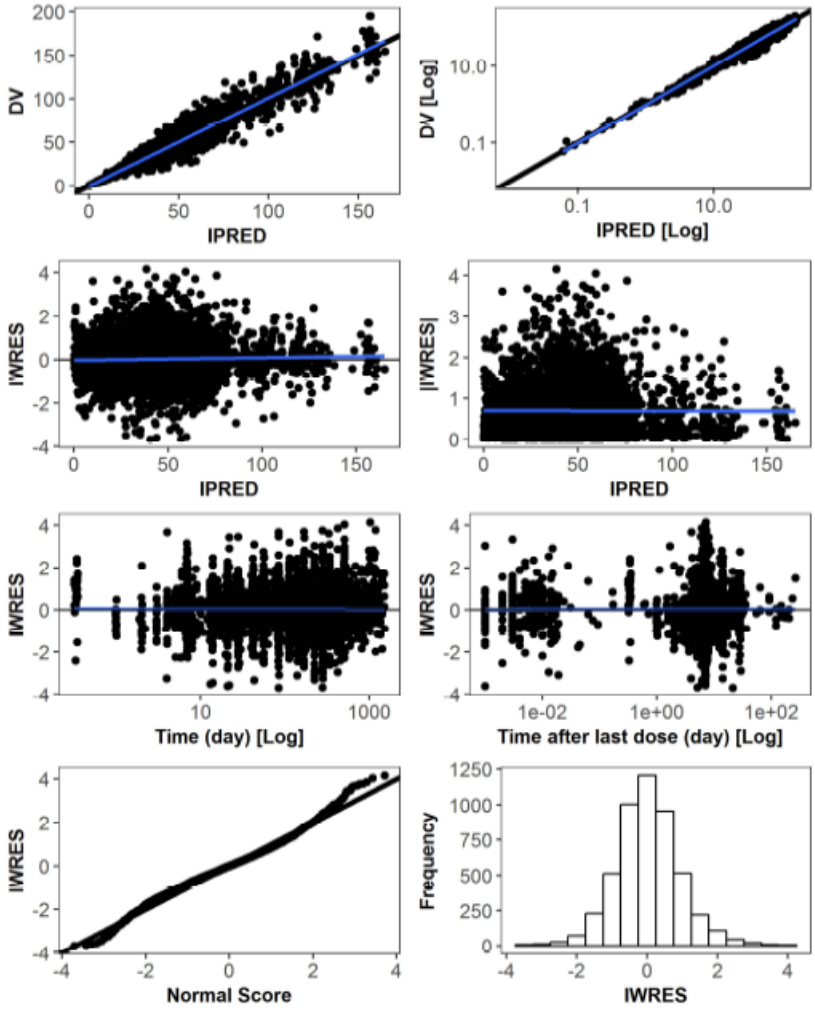
[b] RSE computed for the corresponding covariance.

Figure 12: Goodness-of-fit plots for the final PK model for emicizumab – I:



DV – Observed emicizumab concentrations [µg/mL], PRED (IPRED) – NONMEM predicted emicizumab concentrations [µg/mL] based on population (individual) PK parameters, TIME – time after first drug intake [days], CWRES (IWRES) – Conditional (Individual) weighted residual values.

Figure 13: Goodness-of-fit plots for the final PK model for emicizumab -II



DV – Observed emicizumab concentrations [µg/mL], PRED (IPRED) – NONMEM predicted emicizumab concentrations [µg/mL] based on population (individual) PK parameters, TIME – time after first drug intake [days], CWRES (IWRES) – Conditional (Individual) weighted residual values.

The empirical Bayesian estimates from the final PK model per type of patient status (inhibitors or non-inhibitors) and per type of dosing regimens, respectively were presented which further confirm the absence of residual effects in the final model with respect to those covariates and their lack of impact on the primary PK parameters of Emicizumab.

Results of the Visual Predictive Check (VPC) for the studies are presented in Figures 11-16.

Figure 11 Visual Posterior Predictive Check for Emicizumab for Adults and Adolescents Inhibitor Patients receiving 3 mg/kg QW SC for 4 weeks followed by 1.5 mg/kg QW SC (Study BH29884)

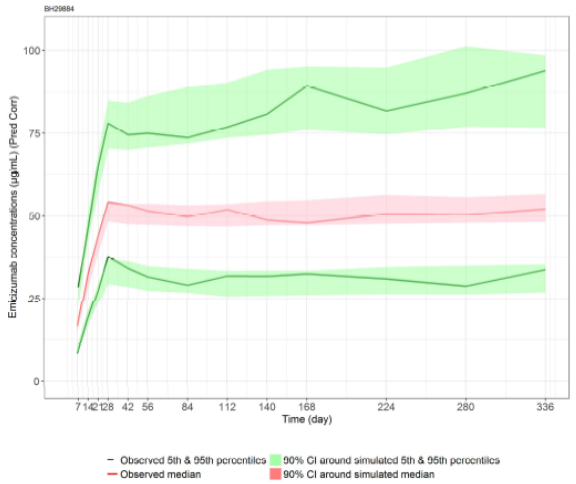


Figure 12 Visual Posterior Predictive Check for Emicizumab for Adults and Adolescents Non-Inhibitor Patients receiving 3 mg/kg QW SC for 4 weeks followed by 1.5 mg/kg QW SC (Study BH30071 Arms A and D)

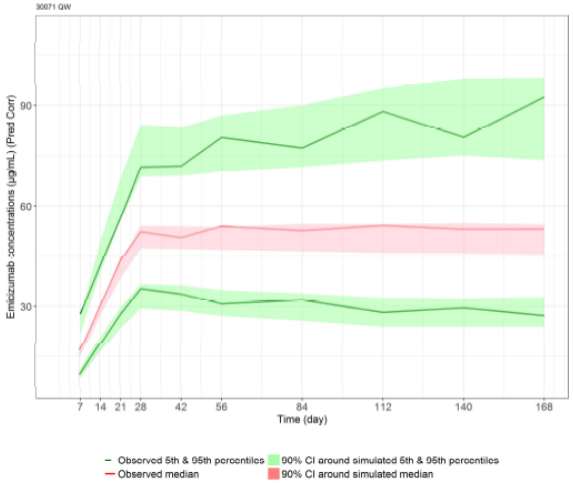


Figure 13 Visual Posterior Predictive Check for Emicizumab for Adults and Adolescents Non-Inhibitor Patients receiving 3 mg/kg QW SC for 4 weeks followed by 3 mg/kg Q2W SC (Study BH30071 Arms B and C_{emi})

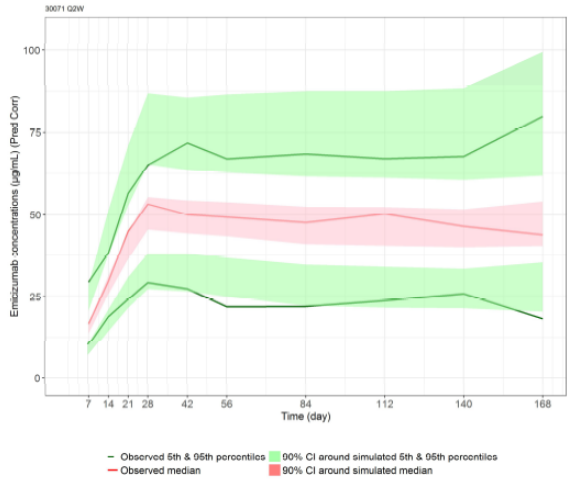


Figure 14 Visual Posterior Predictive Check for Emicizumab for Pediatric Inhibitor Patients ≥ 1 to < 6 years (left, N = 22) and ≥ 6 years (left N = 39), receiving 3 mg/kg QW SC for 4 weeks followed by 1.5 mg/kg QW SC (Study BH29992)

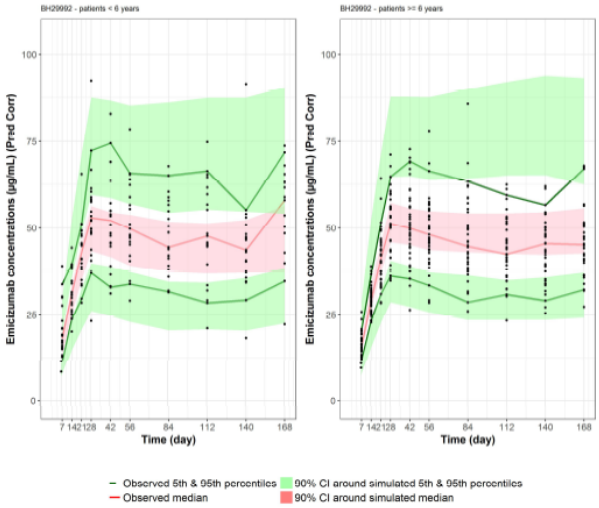


Figure 15 Visual Posterior Predictive Check for Emicizumab for Adults and Adolescents Patients with or without FVIII inhibitors receiving 6 mg/kg Q4W SC (Study BO39182 [PK Run-in])

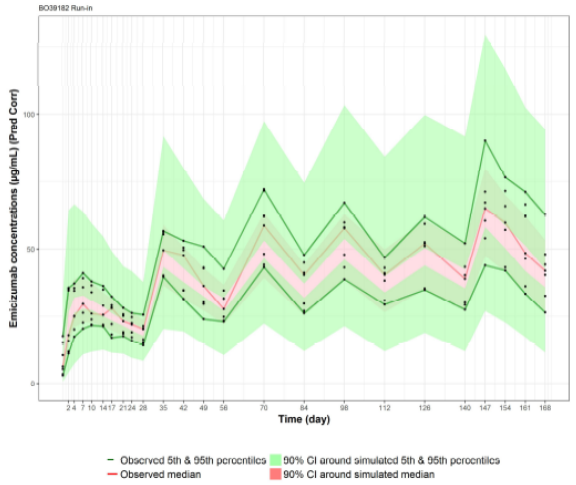
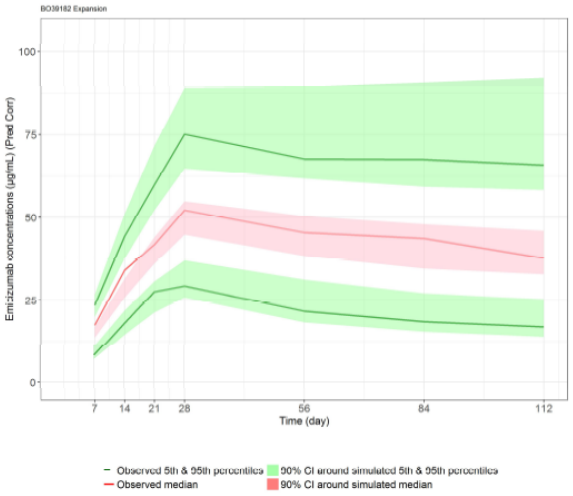


Figure 16 Visual Posterior Predictive Check for Emicizumab for Adults and Adolescents Patients with or without FVIII inhibitors receiving 3 mg/kg QW SC for 4 weeks followed by 6 mg/kg Q4W SC (Study BO39182 [Expansion Part])



Model based simulations were used to derive individual secondary PK parameters, summarised in the following table:

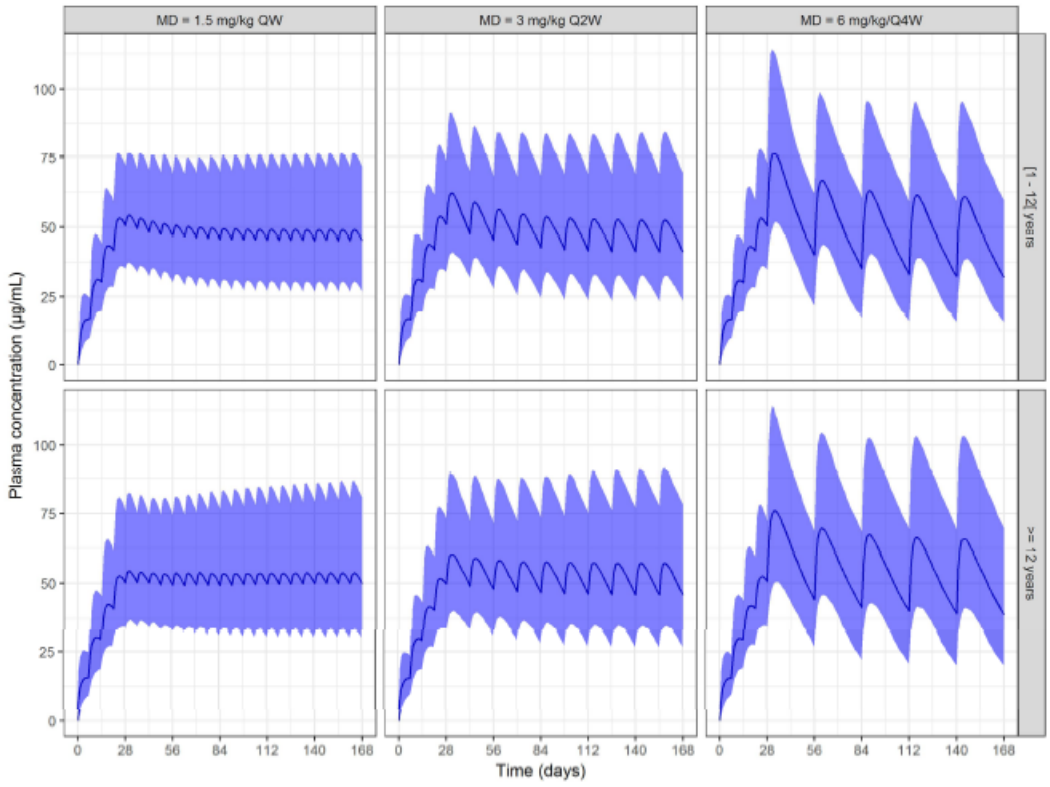
Table 11: secondary PK parameter derived for emicizumab per considered dosing regimens using the primary individual PK parameters obtained by the final population pharmacokinetic model

Secondary PK Parameters	1.5 mg/kg QW		3 mg/kg Q2W		6 mg/kg Q4W	
	Mean (SD)	Median [5th – 95th] percentiles	Mean (SD)	Median [5th – 95th] percentiles	Mean (SD)	Median [5th – 95th] percentiles
$T_{1/2}$ (day)	26.8 (9.16)	25.1 [13.9– 41.4]	26.8 (9.16)	25.1 [13.9– 41.4]	26.8 (9.16)	25.1 [13.9– 41.4]
$T_{1/2,abs}$ (day)	1.61 (0.957)	1.27 [0.897-3.80]	1.61 (0.957)	1.27 [0.897 - 3.80]	1.61 (0.957)	1.27 [0.897 -3.80]
$C_{max,SS}$ (µg/mL)	54.9 (15.9)	53.9 [30.9-82.4]	58.1 (16.5)	57.0 [33.6 - 85.9]	66.8 (17.7)	65.9 [40.4-97.7]
$C_{trough,SS}$ (µg/mL)	51.1 (15.3)	49.9 [28.4 - 78.7]	46.7 (14.9)	45.6 [24.9 - 75.0]	38.3 (14.3)	36.5 [17.7 - 64.7]
$C_{max,SS}$ / $C_{trough,SS}$ (–)	1.08 (0.03)	1.07 [1.03 - 1.15]	1.26 (0.12)	1.24 [1.12 - 1.49]	1.85 (0.46)	1.74 [1.36- 2.85]
$AUC_{ss,\tau}$ (µg × day/mL)	375 (108)	366 [211 - 568]	749 (219)	733 [423 -1135]	1499 (439)	1465 [845 - 2271]
$C_{av,SS}$ (µg/mL)	53.5 (15.7)	52.3 [30.2 - 81.1]	53.5 (15.7)	52.3 [30.2 - 81.1]	53.5 (15.7)	52.3 [30.2 - 81.1]

$T_{1/2}$=elimination half-life; $T_{1/2,abs}$=absorption half-life; $C_{max,SS}$=maximum concentration at steady-state; $C_{trough,SS}$= trough/minimum concentration at steady state; AUCss, τ =steady-state AUC over dosing interval τ, with τ =1, 2 or 4 weeks; $C_{av,SS}$=steady-state average concentrations; SD=standard deviation; N=381.

Figure 18 illustrates the predicted PK profile with respect to paediatric patients ≥ 1 to < 12 years and adolescent and adult patients (≥12 years) for the 3 different dosing regimens (3 mg/kg QW for 4 weeks followed by a maintenance dose of either 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W) over a period of 6 months of emicizumab.

Figure 14: Predicted PK time course in patients (1-12 (years of ≥ 12 years with respect to the three different maintenance doses: 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W.



Blue curve: median of predictions; Blue area: 90% prediction intervals.MD= maintenance dose

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Relationship between plasma concentration and effect

Exploratory Graphical Analysis of Exposure-Efficacy

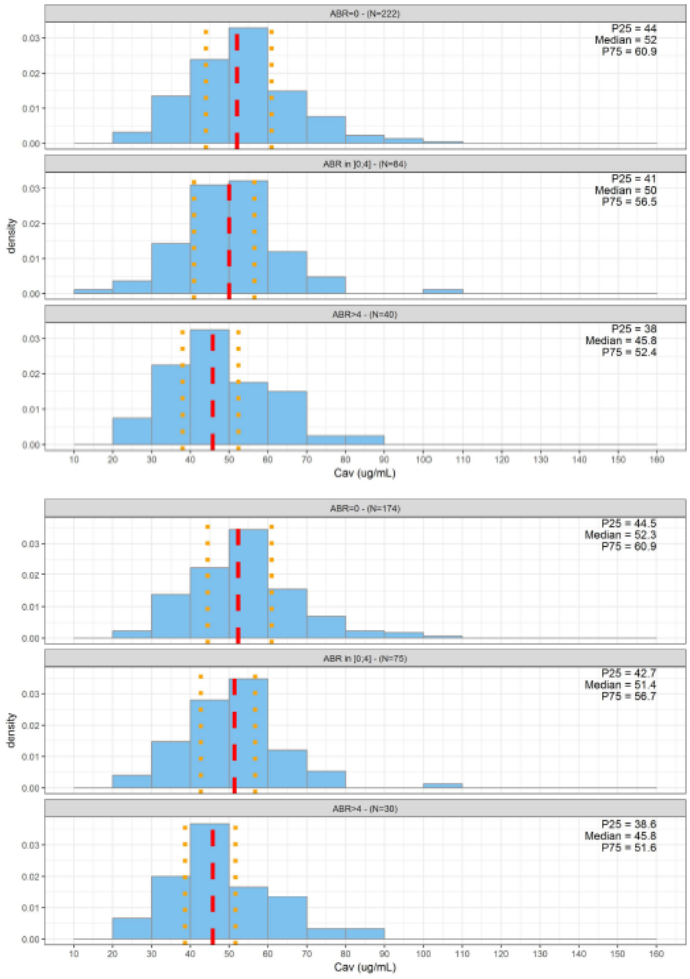
Methods: Since the patients in Studies BH29884, BH29992, BH30071, and BO39182 were not treated for the same duration at the time of the data cut-off, two different categories of patients were defined for these graphical exposure-efficacy analyses: those who were treated for at least 12 weeks of treatment (N = 346) and those who were treated for at least 24 weeks of treatment (N = 279).

Using the final population PK model, individual average concentrations (Cav) computed over the treatment period and individual predicted average trough concentrations over the period of maintenance doses (Ctrough,mean) were used as exposure metrics for the efficacy analyses.

Results: The variability in exposure following the doses of 1.5 mg/kg QW, 3 mg/kg Q2W and 6 mg/kg Q4W, was found to contribute marginally to the variability in response.

These data indicate that the dose of 3 mg/kg QW SC during 4 weeks followed by 1.5 mg/kg QW SC or 3 mg/kg Q2W or 6 mg/kg Q4W provides emicizumab exposure that results in effective control of bleeding in a large majority of patients and that a lower dose might potentially lead to lower reduction.

Figure 15: Distribution of estimated average concentrations (Cav) by Category of ABR for patients from Studies BH30071, BO39182 (expansion part), BH29884 and BH29992 who received at least 12 weeks (top) or at least 24 weeks (bottom) of emicizumab treatment



Dotted red line represents the median of the C_{av} and the orange dotted lines the 25th (P25) and 75th (P75) percentiles of observation respectively. Distributions are represented as density histograms so that the area of each rectangle equals the relative frequency of the corresponding class, and the area of the entire histogram equals 1.

Exploratory Graphical Analysis of Pharmacokinetics-Pharmacodynamics Relationships

Methods: Graphical analyses were performed to explore the relationships between emicizumab plasma concentrations and the following pharmacodynamic (PD) markers:

- activated partial thromboplastin time (aPTT)
- Thrombin generation (peak height)
- FVIII activity (chromogenic assay)
- FIX and FX antigen concentrations

Results: Pharmacodynamic markers of coagulation were correlated with emicizumab plasma concentration:

- aPTT was normalized at low concentrations (~ 5 ug/mL)

- Thrombin generation and chromogenic FVIII activity increased with increased emicizumab concentration
- PK/PD relationships of emicizumab were not impacted by the amount of FIX or FX, as well as by age, inhibitor status, or dosing regimen

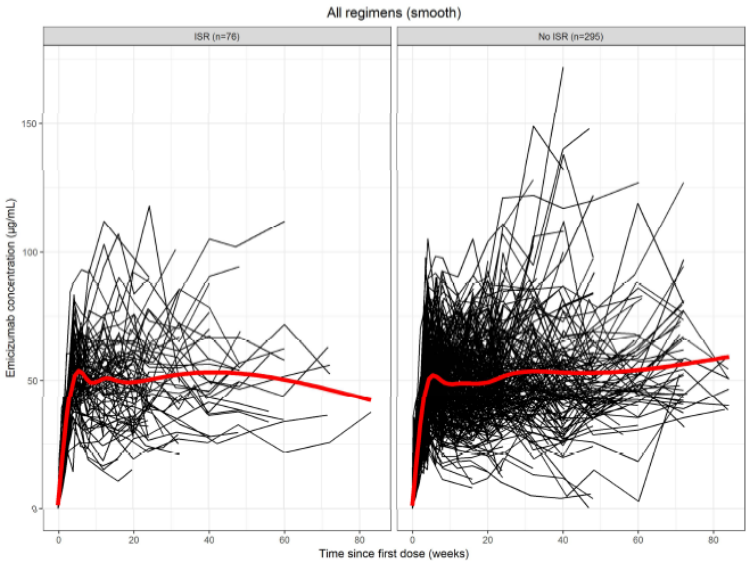
Median profiles of D-dimer and prothrombin fragment 1 and 2 appeared similar across categories of emicizumab exposure.

Exploratory Graphical Analysis of Exposure-Safety Relationship

Methods: Graphical analyses were performed to investigate whether the occurrence of safety events could be attributed to the variability in emicizumab exposure at the dose of 3 mg/kg QW SC for 4 weeks followed by 1.5 mg/kg QW SC, 3 mg/kg Q2W SC, or 6 mg/kg Q4W SC.

Results: Results from the exposure-safety graphical analyses did not show any evidence of relationship between exposure and ISRs, or between exposure and the occurrence of thrombotic microangiopathy or thromboembolic events.

Figure 16: Emicizumab concentration time course per group of patients with at least one injection site reaction (N=76, left) or without any injection site reaction (N=295, right) over the entire profile of administration (studies BH29884, BH29992, BH30071 and BO39182)



Black lines represent the individual emicizumab concentration-time profiles. Red lines represent smooth lines.

Exposure-Response Modeling of Bleeding Counts

Methods: Six clinical studies were included in the analysis: ACE001JP(Part C)/ACE002JP, BH29768, BH29884, BH29992, BH30071 and BO39182. The study population consisted of 445 males in the age range from 1.22 to 77 years, and weights ranging from 9.5 to 156 kg.

This report reflects an analysis of the population pharmacokinetic pharmacodynamic (PopPKPD) of emicizumab via non-linear mixed effects methods while treating the bleeding event data as count data. Different distributions were considered to describe the count data, as well as different PKPD models to characterise the relationship between daily emicizumab concentration and the bleed frequency. Patient covariate relationships on the model parameters were examined in a stepwise procedure. Episodic/prophylactic treatment during observation period, patient type (with or without factor VIII (FVIII) inhibitors), body surface area (BSA), body mass index (BMI), body weight, factor IX (FIX) and

factor X (FX) concentrations, dosing regimen (once a week (QW), Q2W, Q4W) and baseline bleed frequency (where available) were included in the search procedure. The final model was qualified by numerical and graphical goodness of _t (GOF) checks, including visual predictive check (VPC). Simulations were performed using the final model in order to illustrate the estimated exposure-response relationship.

Results: The patients receiving prophylactic FVIII before emicizumab had a lower baseline bleeding rate (i.e.: λ = 0.00515, relative standard error (RSE)=16.9 %) than the other patients (i.e: λ = 0.0258, RSE=8.6%).As a consequence of effective treatment with FVIII prophylaxis, the analysis consisted in consecutively characterizing two PKPD relationships for emicizumab: one to evaluate the additional effect of emicizumab in patients previously receiving prophylactic FVIII and another one to evaluate the genuine PKPD relationship of emicizumab in patients having baseline bleeding rate barely, or even not at all impacted by, previous treatment. In those patients, no statistically or clinically significant differences with regards to inhibitor and non-inhibitor, to episodic and prophylactic treatment and to the dosing frequency (QW, Q2W and Q4W) were found.

Run3138 was defined to be the final model and its parameter estimates are summarised in the following table:

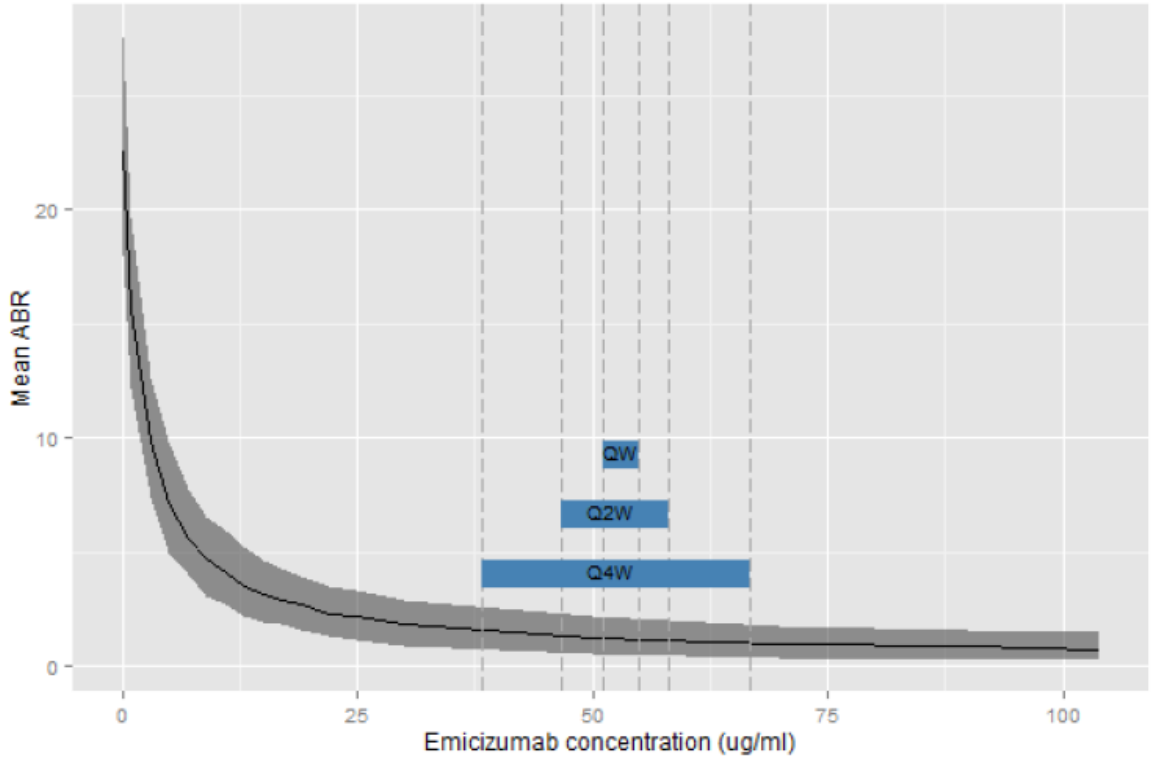
Table 12: Parameters estimated for final model

Parameter	Alias	Estimate	RSE (%)	95% CI
θ_1	λ - Non-Inhibitors, Episodic and all Inhibitors	0.0258	8.6	(0.0214 - 0.0301)
θ_2	δ	0.0247	17.6	(0.0162 - 0.0331)
θ_3	E_{max}	0.987	0.8	(0.971 - 1)
θ_4	EC_{50} - Other Patients ($ug{\cdot}\mathrm{ml}^{-1}$)	2.28	21.5	(1.32 - 3.24)
θ_5	λ Non-Inhibitors - Prophylactic	0.00515	16.9	(0.00344 - 0.00685)
θ_6	EC_{50} - Non-Inhibitors, Prophylactic ($ug{\cdot}\mathrm{ml}^{-1}$)	49.8	21.1	(29.2 - 70.3)
$\omega_{1.1}$	ω^2_{lambda}	1.70	11.4	(1.32 - 2.08)

VPCs: As the observation time varies by patient, the total number of observations decreases with time and bin widths are adjusted accordingly.

Dose-response simulations: The results of the simulation of the genuine exposure-response of emicizumab characterized in haemophilia A patients with baseline bleeding rate barely, if at all impacted by previous treatment (i.e. λ=0.0258) is given in Figure 15. A clinically meaningful bleeding control is expected to be reached at plasma emicizumab concentrations above approximately 30 _g/mL, and the benefit of higher concentrations appears to be limited. The mean concentration ranges under different regimens are also indicated.

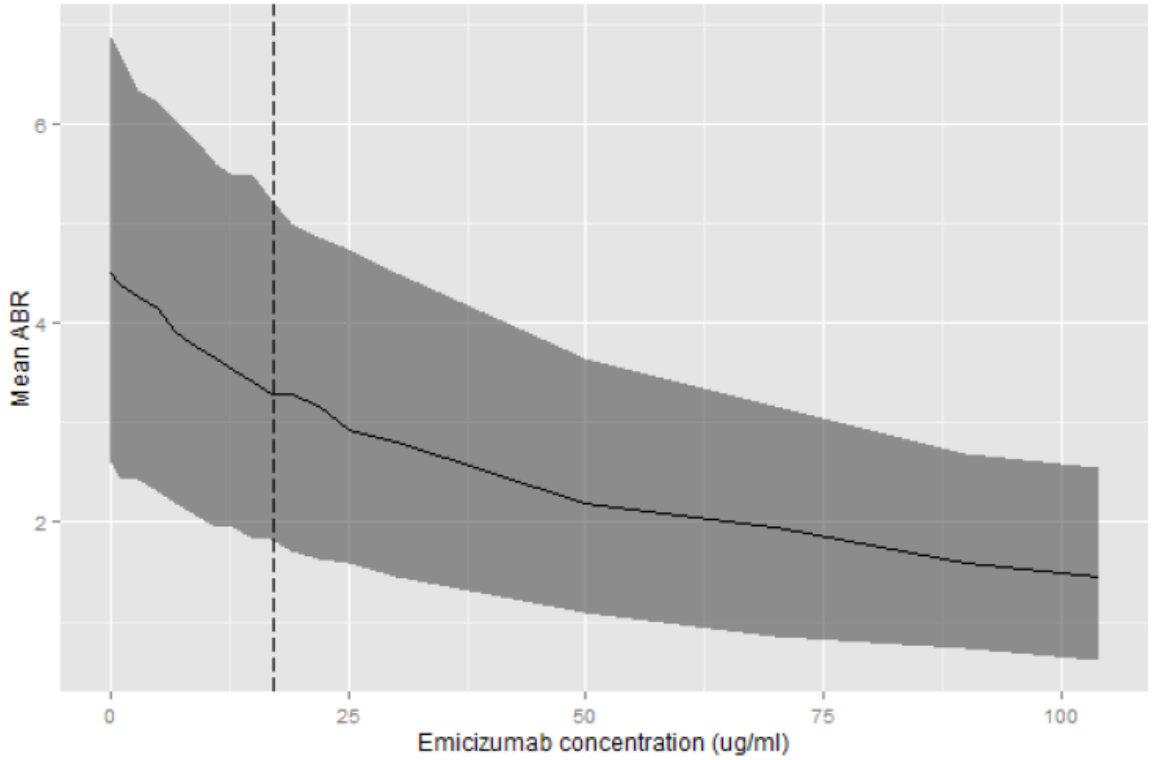
Figure 17: Simulated specific exposure-response of emicizumab



Envelopes around the simulated means indicate 2.5^{th} and 97.5^{th} percent bounds of the prediction intervals. Stippled drop lines indicate observed range of mean concentrations at maintenance doses of 1.5 mg/kg QW, 3 mg/kg Q2W and 6 mg/kg Q4W, also indicated using droplines.

The PK/PD relationship in non-inhibitor patients with a low baseline bleeding rate due to their FVIII prophylactic (i.e. _=0.00515) is presented in Figure 16. This relationship does not reflect the genuine exposure response of emicizumab but the additional effect of emicizumab when the patients shifted from their previous efficacious FVIII treatment to emicizumab. Since the FVIII prophylaxis treatment continued during the first week after the start of emicizumab, there is an overlap in the efficacy when the concentration of emicizumab are still relatively low (i.e.: below the median emicizumab concentration at the end of the first week - 17.2 µg/mL). Above this value, indicated in Figure 16, the PKPD relationship of emicizumab becomes superimposable to the genuine one for emicizumab concentrations.

Figure 18: Simulated exposure-response of emicizumab following previous and overlapping effective FVIII prophylaxis



Envelopes around the simulated means indicate 2.5^{th} and 97.5^{th} percent bounds of the prediction intervals. A stippled drop line indicates observed median trough concentrations at the end of the first week of Emicizumab treatment.

2.3.4. Discussion on clinical pharmacology

The MAH has included data from data from studies ACE001JP Part C/ACE002JP, BH30071, BO39182, BH29884, and BH29992 in the population PK model. The base model and covariates have both been re-assessed. The final population PK model is a one-compartment model with first-order absorption and elimination processes. Variability was minimal with the goodness-of-fit plots and VPCs being acceptable. Patient status (inhibitors or non-inhibitors) or type of dosing regimen (QW, Q2W and Q4W) were not significant covariates in the final population PK model. Body weight, age, race (White vs Black patients) and albumin were identified as retained covariates in the final model. Race and weight had minimal impact on steady state exposure. The model confirms that there are lower exposures in older (elderly) patients. Low albumin concentrations of 33 g/L (low) and 57 g/L (high) were associated with a Cav,ss reduction of 31% and increase of 23%, respectively. Body weight dosing appears to be appropriate for adults, adolescents (≥12 to <18 years) and children (<12 years) patients with haemophilia. The PK of emicizumab has been simulated for the different dosing regimens (QW,Q2W and Q4W) in paediatrics with steady state concentrations appearing comparable with the adult exposures.

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The final Emax model appears fit for purpose with the different dosing regimens (1 .5 mg/kg QW, 3 mg/kg/Q2W and 6.0 mg/kg Q4W) resulting in mean trough emicizumab concentrations being above 30 µg/mL; this was similar for both inhibitor and non-inhibitor patients.

Simulations from the population PK model suggest that the mean range of trough emicizumab concentrations are within the therapeutic window however the simulations based on the population model suggests that the lower limit of the 90% CI may be <25 µg/mL.

Results from Study BH29884 and Study BH29992 demonstrate that emicizumab trough plasma concentrations are consistent across different ages. In healthy individuals, FVIII levels remain constant from birth through adulthood (Andrew et al. 1988; 1992), so in this respect the emicizumab levels are consistent with the physiologic lack of change of FVIII activity levels with age. The early physiologic maturation of FVIII levels (Kuhle et al. 2003) suggests that a given FVIII activity is expected to provide a similar safety and efficacy in adults and in children.

Since the average dose is identical, each individual dose administered Q2W or Q4W is 2 or 4 times higher than each weekly dose, respectively (3 mg/kg or 6 mg/kg versus 1.5 mg/kg). Hypothetically, a resulting higher Cmax may be associated with safety concerns.However, due to the slow absorption of emicizumab, the higher individual doses result in only modestly higher peak concentrations (Cmax). Modelling of emicizumab plasma-time concentration profiles shows that the 95th percentile of emicizumab concentrations at Cmax is estimated to be approximately 82.4, 85.9, and 97.7 µg/mL in the Q1W, Q2W and Q4W regimens, respectively. Thus, since the various regimens result in comparable Cmax and total exposures, the safety profile of QW emicizumab maintenance (as observed in Study BH29992) is representative of the safety profile in children receiving Q2W or Q4W emicizumab maintenance (see also Discussion on Clinical Safety).

Further, it is of interest to consider the relative concentrations of emicizumab and its substrates FIX and FX whose plasma levels are approximately 90 and 150 nM, respectively. At Cmax, emicizumab concentrations correspond to 560 nM in the Q1W and to 700 nM in the Q4W regimens representing a 4-6 or 5-7 fold higher molar concentration of emicizumab over its targets in the QW or Q4W regimens, respectively. Hence, the modestly higher emicizumab Cmax in the Q4W regimen results in a stoichiometrically inconsequential excess of emicizumab. In addition, given the weak binding affinities of emicizumab to FIX and FX and the corresponding Kd values that are higher than the Cmax at even the Q4W regimen, the peak emicizumab concentration has no physiologic impact on antigen blockade.

2.3.5. Conclusions on clinical pharmacology

The pharmacokinetics of emicizumab have been further described in the patients with haemophilia A, namely investigating the impact of Q2W and Q4W dosing with compared with QW dosing . Followed by 1.5 mg/kg/week sc. each following a loading regimen of 3 mg/kg/week s.c. for 4 weeks. Furthermore, the pharmacokinetics of emicizumab has been investigated in paediatric and adult patients with and without

FVIII inhibitors. Results support comparable PK properties of the different maintenance dosing regimens. Simulations of the different proposed dosing regimens have been simulated in paediatrics and appear comparable with the adult exposures.

2.4. Clinical efficacy

2.4.1. Main studies

Methods

Overall Design Features of Pivotal and Supporting Studies

Two new pivotal Phase III Studies BH30071 (HAVEN-3) and BO39182 (HAVEN-4) assessing the efficacy, safety, pharmacokinetics and pharmacodynamics of emicizumab prophylaxis in adults and adolescents ≥ 12 years of age with haemophilia A are included in the current application:

- Study BH30071 is a randomized, controlled, open-label study in patients with severe haemophilia A aged ≥ 12yrs and without FVIII inhibitors, who previously received either episodic or prophylactic treatment with FVIII.
- Study BO39182 is a single-arm study in patients with haemophilia A aged ≥ 12yrs with or without FVIII inhibitors who previously received either episodic or prophylactic treatment with FVIII or bypassing agents.

Updated information is provided from the 2 studies which supported the initial MA and which assess the efficacy, safety, pharmacokinetics and pharmacodynamics of emicizumab prophylaxis:

- Study BH29884 (HAVEN -1) is a randomized, open-label Phase III study in patients aged ≥ 12 with haemophilia A with FVIII inhibitors who previously received either episodic or prophylactic treatment with bypassing agents.
- Study BH29992 (HAVEN-2) is a single-arm Phase III study, in children < 12 years of age, with haemophilia A with FVIII inhibitors who previously received either episodic or prophylactic treatment with bypassing agents.

Additionally, updated analyses from Study ACE002JP (an extension Phase I/II study to multiple-ascending dose Study ACE001JP) in Japanese patients with and without FVIII inhibitors, which provides long-term emicizumab efficacy and safety data is included.

In addition, the MAH submitted during the evaluation of this application:

- An update to study BO39182 (HAVEN-4)
- Initial data from an extra 33 paediatric subjects enrolled in to study BH29992 (HAVEN-2) and Japanese study JO39881

Despite the above differences in study populations (adult and adolescent patients aged ≥ 12 years vs. paediatric patients < 12 years of age), previous haemophilia A treatment regimens (bypassing agents vs. FVIII), and differing emicizumab dosing regimens (QW, Q2W, and Q4W), the studies share important features. These include similar eligibility criteria; collection, definitions, and analyses of bleed data and bleed-related endpoints, as well as other efficacy endpoints, which allow for assessment of efficacy across these studies.

Study participants

Inclusion criteria are summarised:

Table 13: Haemophilia – related inclusion criteria for all studies in the efficacy population

BH30071	BO39182	BH29992	BH29884
Diagnosis of severe congenital hemophilia A (intrinsic FVIII level < 1%) without inhibitors against FVIII	Diagnosis of severe congenital hemophilia A (intrinsic FVIII level < 1%) or hemophilia A with FVIII inhibitors	Diagnosis of congenital hemophilia A with high-titer inhibitor (i.e., ≥ 5 BU) against FVIII	Diagnosis of congenital hemophilia A with high-titer inhibitor (i.e., ≥ 5 BU) against FVIII
Documented history of prophylactic or episodic FVIII treatment	PK run-in part: Current episodic treatment (FVIII or bypassing agents) at the study entry and documented history of episodic treatment for at least 24 weeks prior to study entry Expansion part: Documented history of prophylactic or episodic treatment (FVIII or bypassing agents)	Required treatment with bypassing agents	Documentation of treatment with episodic or prophylactic bypassing agents for at least the last 24 weeks
For patients on episodic treatment pre-study: ≥ 5 bleeds in the last 24 weeks prior to study entry No requirement of number of bleeds for patients on FVIII prophylaxis during 24 weeks prior to the study entry	Expansion part: For patients on an episodic regimen, ≥ 5 bleeds in the prior 24 weeks, regardless of inhibitor status No requirement of number of bleeds for patients in PK run-in part	For patients ≥ 2 years of age *on an episodic bypassing agent regimen:* ≥3 bleeds in the last 24 weeks (ABR of ≥ 6) *on a prophylactic bypassing agent regimen:* inadequately controlled (e.g., 2 bleeds since starting prophylaxis or 1 life-threatening bleed) or CVAD placement medically not feasible or deemed unsafe For patients < 2 years of age determined by investigator to be in high unmet medical need	For patients on episodic treatment pre-study: ≥ 6 bleeds in the last 24 weeks prior to screening) For patients on prophylactic bypassing agent regimen pre-study: ≥ 2 bleeds in the last 24 weeks prior to screening (if on a prophylactic bypassing agent regimen)

Emicizumab dose

The recommended starting dose is 3 mg/kg QW for the first 4 weeks, followed by either 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W, administered as an SC injection.

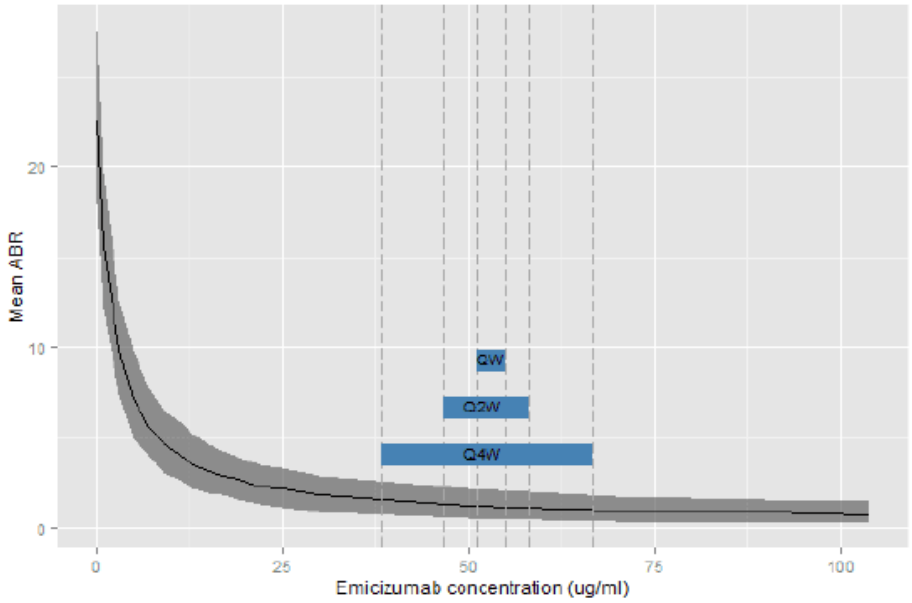
The rationale for the selected Phase III dose regimens was based upon available clinical data from Study ACE001JP and its ongoing extension Phase I/II Study ACE002JP in haemophilia A patients with and without inhibitors. These studies investigated maintenance dose of 0.3, 1, or 3 mg/kg/week and demonstrated a substantial reduction in bleeding events with prophylactic emicizumab treatment, especially at doses ≥ 1 mg/kg weekly, where a median ABR of 0 was achieved. A quantitative characterisation of the exposure-response relationship of emicizumab in these studies enabled identification of a target efficacious concentration [Yoneyama *et al.* 2017]. On the basis of population PK modelling, effective plasma concentrations were predicted to be achieved by loading doses of 3 mg/kg QW for 4 weeks followed by the maintenance dose of 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W. With a lower dosing frequency associated with a larger peak–trough fluctuation, a maintenance dose of 6 mg/kg Q4W was predicted to result in a lower trough concentration than initially targeted. However, based on simulations, this was not predicted to impact the efficacy of emicizumab in preventing bleeding event, as indicated by simulated ABR distribution [Yoneyama *et al.* 2017].

Results from Phase III clinical studies confirmed the adequacy of the selected dosing regimens. Overall, all three dosing regimens, using an equivalent cumulative dose, provided meaningful efficacy with mean ABR of 2.7 (95% CI: 1.64, 4.35) (adolescent / adult patients with inhibitors), 1.5 (95% CI: 0.89, 2.47) (adolescent / adult patients without inhibitors) and 0.3 (95% CI: 0.13, 0.52) (paediatric patients with inhibitors) with QW dosing; 1.3 (95% CI: 0.75, 2.25) (adolescent / adult patients without inhibitors) with Q2W dosing; and 2.1 (95% CI: 1.11, 4.12) (adult / adolescent patients with or without inhibitors) with Q4W dosing. A median ABR of 0 was achieved and over 55% of patients achieved 0 bleed with all dose regimens.

Graphical investigations of exposure-response relationship revealed that a similar PK exposure was observed across the ABR response categories (ABR = 0, ≥ 1- ≤ 4, or > 4). Although, a trend toward lower median emicizumab exposure was observed in patients with an ABR > 4, there was a large overlap of the PK exposure distributions by ABR category. Emicizumab exposure obtained with the three maintenance dose regimens (1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W) resulted in highly effective control of bleeding in a large majority of patients. On an individual level, however, higher exposure in patients who have suboptimal control of bleeding may be beneficial.

Conclusions from the graphical investigations were further supported by a model-based analysis of the exposure - response, which indicated a relatively flat relationship between bleed rate (ABR) and emicizumab at concentrations above 30 µg/mL (Figure below).

Figure 19: Simulated exposure-response relationship of emicizumab in haemophilia A patients



ABR=annualized bleed rate; QW=weekly; Q2W=every 2 weeks; Q4W=every 4 weeks.
Envelopes around the simulated means indicate 2.5th and 97.5th percent bounds of the prediction intervals. Stippled drop lines indicate population PK derived mean trough and maximum concentrations at maintenance doses of 1.5 mg/kg QW, 3 mg/kg Q2W and 6 mg/kg Q4W.
Notes: Patients received emicizumab 3 mg/kg QW for 4 doses followed by maintenance doses of 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W.

A close to maximal effect on bleed rates is predicted for plasma emicizumab concentrations above this threshold, a concentration expected to provide FVIII activity associated with mild to moderate disease activity. Of note, trough concentrations (i.e., the lowest concentration during a dosing interval) above this value were achieved with all three dosing regimens use in the Phase III studies (Table below).

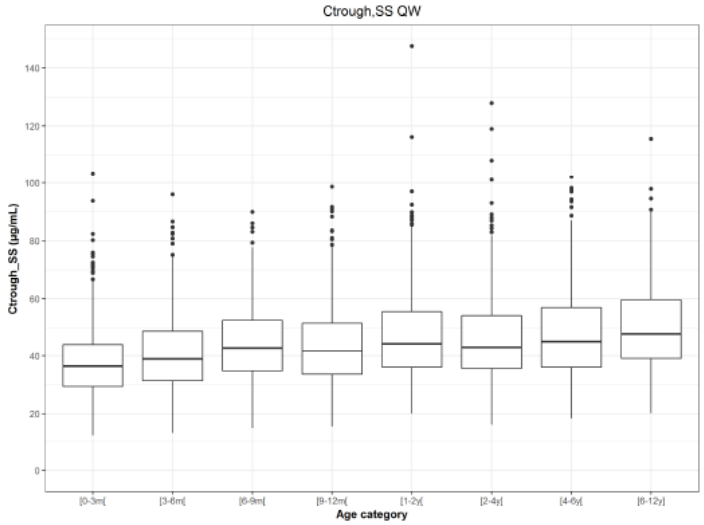
Table 14: Secondary PK parameters derived at steady-state for emicizumab 1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W dosing schedule using the primary individual PK parameters obtained by the final population PK model:

Secondary PK Parameters	1.5 mg/kg QW		3 mg/kg Q2W		6 mg/kg Q4W	
	Mean (SD)	Median [5^{th} – 95^{th}] percentiles	Mean (SD)	Median [5^{th} – 95^{th}] percentiles	Mean (SD)	Median [5^{th} – 95^{th}] percentiles
Dose Regimen Independent Parameters						
$C_{av,ss}$ (µg/mL)	53.5 (15.7)	52.3 [30.2 - 81.1]	53.5 (15.7)	52.3 [30.2 - 81.1]	53.5 (15.7)	52.3 [30.2 - 81.1]
$T_{1/2}$ (day)	26.8 (9.16)	25.1 [13.9– 41.4]	26.8 (9.16)	25.1 [13.9– 41.4]	26.8 (9.16)	25.1 [13.9– 41.4]
$T_{1/2,abs}$ (day)	1.61 (0.96)	1.27 [0.897-3.80]	1.61 (0.96)	1.27 [0.90-3.80]	1.61 (0.96)	1.27 [0.90-3.80]
Dose Regimen Dependent Parameters						
$C_{max,SS}$ (µg/mL)	54.9 (15.9)	53.9 [30.9-82.4]	58.1 (16.5)	57.0 [33.6 - 85.9]	66.8 (17.7)	65.9 [40.4-97.7]
$C_{trough,SS}$ (µg/mL)	51.1 (15.3)	49.9 [28.4 - 78.7]	46.7 (14.9)	45.6 [24.9 - 75.0]	38.3 (14.3)	36.5 [17.7 - 64.7]
$C_{max,SS}/C_{trough,SS}$	1.08 (0.03)	1.07 [1.03 - 1.15]	1.26 (0.12)	1.24 [1.12 - 1.49]	1.85 (0.46)	1.74 [1.36- 2.85]
$AUC_{ss,\tau}$ (µg/mL*day)	375 (108)	366 [211 - 568]	749 (219)	733 [423 -1135]	1499 (439)	1465 [845 - 221]

$AUC_{ss,\tau}$ = area under the concentration time curve at steady-state over the dosing interval (τ = 1, 2, or 4 weeks); $C_{max,SS}$ = maximum concentration at steady-state; $C_{trough,SS}$ = steady-state trough concentration; SD = standard deviation $T_{1/2}$ = half-life.

No clinical data in paediatric patients below the age of 1 year are available to date. Simulations of their exposure indicated that, while decrease in exposure is predicted, especially for the youngest patients (0 to 3 months old), median trough concentrations remained greater than 30 µg/mL for both QW and Q2W dosing regimens (Figures below).

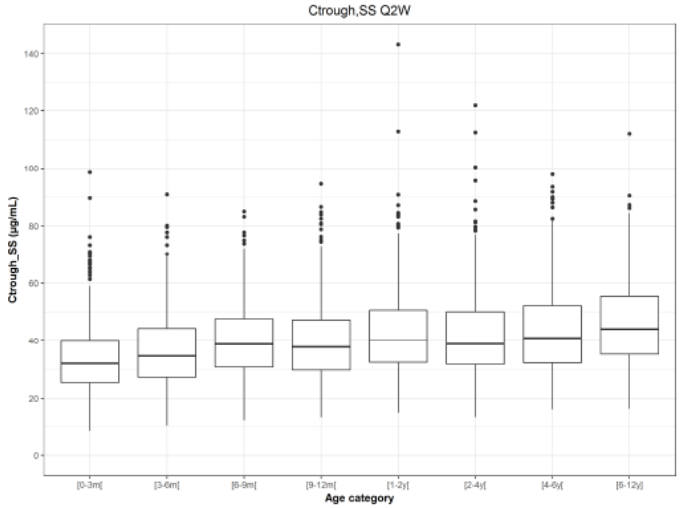
Figure 20: Ctrough,s,s by age category from birth to 12 years for patients receiving 1.5 mg/kg QW emicizumab SC doses:



$C_{trough,ss}$ = predicted plasma emicizumab trough concentration at steady-state; QW = weekly; SC = subcutaneous.

Note: Simulated exposures are represented with boxplots; estimated exposures from patients included in the updated PK database are represented with red dots

Figure 21: Ctrough,s,s by age category from birth to 12 years for patients receiving 3 mg/kg Q2W emicizumab SC doses:

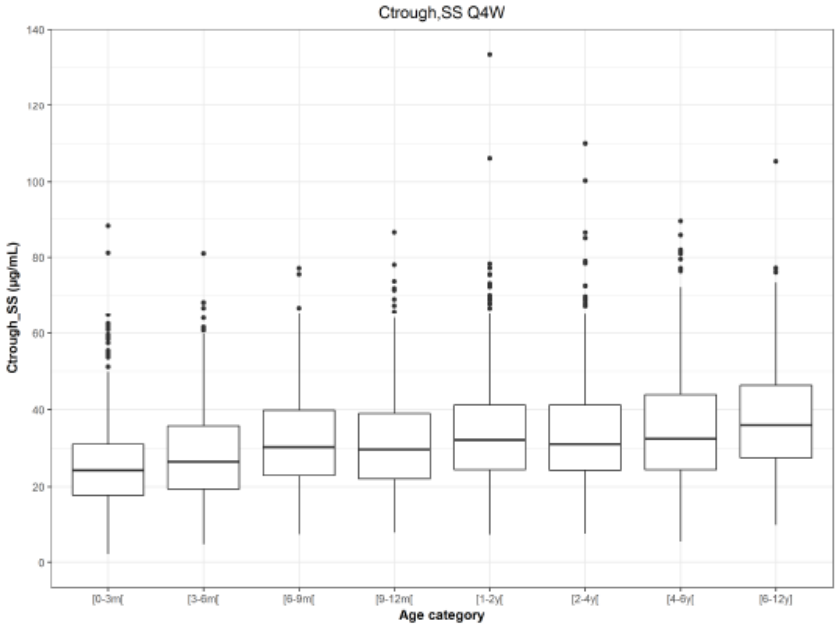


$C_{trough,ss}$ = predicted plasma emicizumab trough concentration at steady-state;; Q2W = every 2 weeks; SC = subcutaneous.

Note: Simulated exposures are represented with boxplots; estimated exposures from patients included in the updated PK database are represented with red dots

Median trough concentrations slightly below 30 µg/mL are predicted with Q4W dosing regimen in patients below 6 months of age (Figure 29), which could in theory lead to slightly lower efficacy at trough. Importantly, even at the expected trough concentration, emicizumab is expected to provide a FVIII-like activity of approximately 8- 10 IU/dL (based on an approximate conversion factor of 1 µg/mL of emicizumab to 0.3 IU/dL of equivalent factor VIII haemostatic activity derived from nonclinical data [Shima, et al. 2016]). Therefore, meaningful efficacy with all three dosing regimens is also expected in paediatric patients aged less than 1 year.

Figure 22: Ctrough,s,s by age category from birth to 12 years for patients receiving 6mg/kg Q4W emicizumab SC doses:



$C_{trough,ss}$ = predicted plasma emicizumab trough concentration at steady-state; Q4W = every 4 weeks; SC = subcutaneous.
Note: Simulated exposures are represented with boxplots; estimated exposures from patients included in the updated PK database are represented with red dots

Exposure-safety analyses also supported the recommended dosing regimens. There were no patterns of dose response for AEs. ISRs, which were the most commonly reported AE, did not appear to be related to emicizumab plasma concentration. Median PK profiles in patients who developed ISR were not different from those of patient who did not developed ISR. Likewise, there were no evidence of a relationship between emicizumab exposure and the occurrence of TMA or thromboembolic serious adverse events (SAEs). Lastly, the exposure achieved with the recommending dosing regimen (3 mg/kg QW for 4 weeks followed by either 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W) remained well below the safe and well tolerated exposure achieved at the maximum dose of 3 mg/kg weekly investigated in the Phase I/II studies.

Study HAVEN-3 (BH30071): A randomized, multicentre, open-label, Phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in haemophilia A patients without inhibitors

Methods

Study participants

Inclusion criteria

- Diagnosis of severe congenital haemophilia A (intrinsic FVIII level < 1%)
  - Aged 12 years or older at the time of informed consent
  - Body weight ≥ 40 kg at the time of screening
- A negative test for inhibitor (i.e. < 0.6 BU) within 8 weeks of enrolment
- No documented inhibitor (i.e. < 0.6 BU), FVIII half-life < 6 hours, or FVIII recovery < 66% in the last 5 years
- Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks
- For patients on no prophylaxis (episodic treatment) pre-study, ≥ 5 bleeds in the last 24 weeks prior to study entry
- Laboratory:
  - Platelet count >100,000 cells/µL, Haemoglobin > 8 g/dL
  - Bilirubin ≤ 1.5 ULN, AST & ALT ≤ 3 ULN
  - Creatinine ≤ 2.5 ULN, creatinine clearance ≥ 30 mL/min

Patients who completed successful immune tolerance induction (ITI) at least 5 years before screening were eligible, provided they had had no evidence of inhibitor recurrence (permanent or temporary) as may be indicated by detection of an inhibitor, FVIII half-life < 6 hours, or FVIII recovery < 66% since completing ITI.

Patients who were on FVIII prophylaxis for at least the last 24 weeks, could be enrolled regardless of the number of bleeds during this period. Eligibility was based on investigator's attestation of adequate prophylaxis regimen.

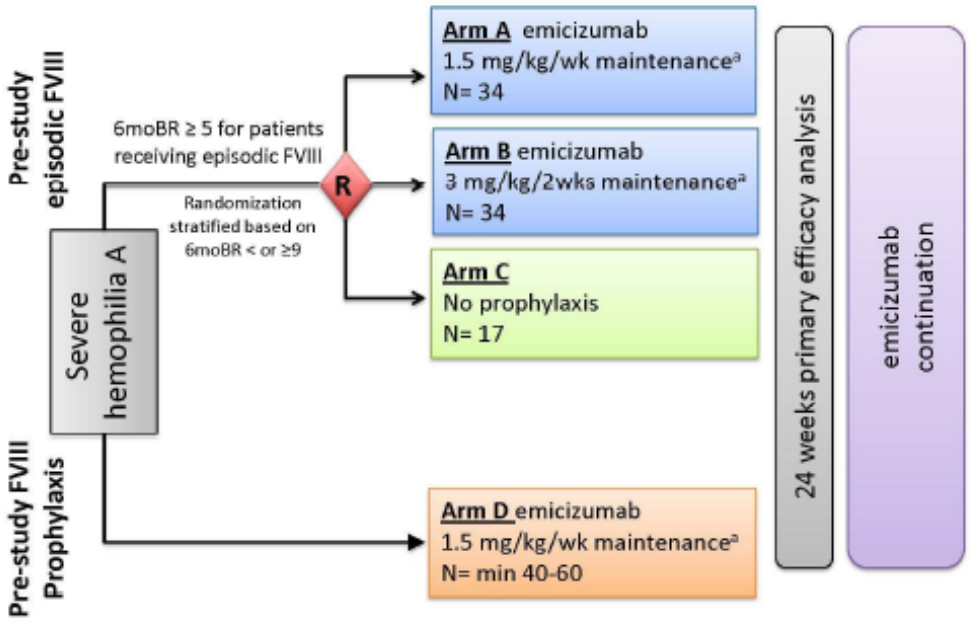
At least 40 patients who were on FVIII prophylaxis pre-enrolment had been enrolled for a minimum of 24 weeks in Study BH29768 (non-interventional)

Exclusion criteria

- Bleeding disorder other than haemophilia A
- Treated for thromboembolic disease within last 12 months
- Planned surgery
- Use of systemic immunomodulator

Treatments

Figure 23: Overview of study design



2wks = 2 weeks; 6moBR = 6 months bleed rate; FVIII = factor VIII; R = randomization; wk = week.
[a] For all patients, emicizumab was administered at a loading dose of 3 mg/kg QW for the first 4 weeks of treatment prior to starting maintenance.

Patients in Arms A, B, or C who experienced ≥ 2 qualifying bleeds within 24 weeks, had the opportunity to up-titrate their emicizumab maintenance dose to 3 mg/kg QW (also referred to as dose escalation in the protocol) starting on Week 25 (Arms A and B) or Week 49 (Arm C), if they received approval from the Medical Monitor.

Patients in Arm D who experienced ≥ 2 qualifying bleeds on prophylactic emicizumab at the maintenance dose had the opportunity to up-titrate their emicizumab dose to 3 mg/kg QW immediately after the second qualifying bleed, with approval from the Medical Monitor.

Qualifying bleeds were defined as spontaneous, verified by investigator (e.g., by imaging or physical examination) and occurring while on prophylactic emicizumab at steady-state on the maintenance dose (after the Week 5 visit).

Dose selection

The maximum clinical dose of 3 mg/kg QW was associated with a 10.3-fold and 11.2-fold safety margin for Cmax and AUCt, respectively, based on corresponding exposures at the no-adverse-effect-level (NOAEL) in nonclinical toxicology studies.

Dosing was also guided based on experience of study ACE002JP and PK population modelling.

Previous Medications for Haemophilia A

All patients reported receiving treatment with FVIII in the 24 weeks prior to enrolment:

- as episodic treatment: all patients in Arms A, B, and C

- as prophylactic treatment: all patients in Arm D. Additionally, 3 patients in Arm A, 5 patients in Arm B and 2 patients in Arm C reported, in addition to prior episodic treatment, prior prophylactic treatment with Factor VIII.

The most prevalent reason given for not receiving prophylactic treatment prior to the study for patients in Arms A, B, and C was reported as subject request (42.4%).

Concomitant Haemophilia A treatments

Patients administered haemophilia A medication to treat breakthrough bleeds as they occurred, as treatment for procedure/surgery, or as one-time prophylaxis; the bleeds and the treatments were recorded on the BMQ using the electronic hand-held device.

47.2% of subjects in Arm A and 48.6% Arm B, compared with all patients on no prophylaxis in Arm $C_{control}$ (100%), used FVIII treatment during the study, see table below; short acting FVIII was mostly used.

Table 15: Summary of non-emicizumab haemophilia medication (ITT population)

APPROVED Non-emicizumab Hemophilia Medication, Randomized Patients (ITT)
Protocol: BH30071 Snapshot: k30071a Snapshot Date: 14NOV2017 Cutoff Date: 15SEP2017
Arm C: no prophylaxis; Before up-titration

	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)
TOTAL			
Total number of patients with at least one treatment	18 (100%)	17 (47.2%)	17 (48.6%)
Total number of treatments	468	69	86
Purpose of the medication			
Preventative dose before activity	8 (44.4%)	1 (2.8%)	2 (5.7%)
Preventative dose for procedure/surgery	1 (5.6%)	1 (2.8%)	2 (5.7%)
Treatment for bleed	18 (100%)	17 (47.2%)	16 (45.7%)
FACTOR VIII (LONG-ACTING) [E.G. ELOCTA]			
Total number of patients with at least one treatment	4 (22.2%)	2 (5.6%)	2 (5.7%)
Total number of treatments	65	4	17
Purpose of the medication			
Preventative dose before activity	1 (5.6%)	0	0
Preventative dose for procedure/surgery	1 (5.6%)	0	0
Treatment for bleed	4 (22.2%)	2 (5.6%)	2 (5.7%)
FACTOR VIII (SHORT-ACTING) [E.G. ADVATE]			
Total number of patients with at least one treatment	15 (83.3%)	15 (41.7%)	16 (45.7%)
Total number of treatments	403	65	69
Purpose of the medication			
Preventative dose before activity	7 (38.9%)	1 (2.8%)	2 (5.7%)
Preventative dose for procedure/surgery	0	1 (2.8%)	2 (5.7%)
Treatment for bleed	15 (83.3%)	15 (41.7%)	15 (42.9%)

Arm C: includes no prophylaxis period only.

The proportion of patients using FVIII in Arm D was 84.1% because patients in Arm D continued their regular FVIII prophylaxis until the second emicizumab loading dose to avoid bleeds before adequate emicizumab level was reached.

Table 16: Summary of non-emicizumab haemophilia medication (all emicizumab patients)

	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)	C: 3 mg/kg emicizumab Q2W (N=16)	D: 1.5 mg/kg emicizumab QW (N=63)	Total (N=150)
TOTAL					
Total number of patients with at least one treatment	17 (47.2%)	17 (48.6%)	2 (12.5%)	53 (84.1%)	89 (59.3%)
Total number of treatments	69	86	4	405	564
Purpose of the medication					
Preventative dose before activity	1 (2.8%)	2 (5.7%)	0	47 (74.6%)	50 (33.3%)
Preventative dose for procedure/surgery	1 (2.8%)	2 (5.7%)	0	6 (9.5%)	9 (6.0%)
Treatment for bleed	17 (47.2%)	16 (45.7%)	2 (12.5%)	30 (47.6%)	65 (43.3%)
FACTOR VIII (LONG-ACTING) [E.G. ELOCTA]					
Total number of patients with at least one treatment	2 (5.6%)	2 (5.7%)	0	8 (12.7%)	12 (8.0%)
Total number of treatments	4	17	0	113	134
Purpose of the medication					
Preventative dose before activity	0	0	0	7 (11.1%)	7 (4.7%)
Preventative dose for procedure/surgery	0	0	0	2 (3.2%)	2 (1.3%)
Treatment for bleed	2 (5.6%)	2 (5.7%)	0	5 (7.9%)	9 (6.0%)
FACTOR VIII (SHORT-ACTING) [E.G. ADVATE]					
Total number of patients with at least one treatment	15 (41.7%)	16 (45.7%)	2 (12.5%)	45 (71.4%)	78 (52.0%)
Total number of treatments	65	69	4	291	429
Purpose of the medication					
Preventative dose before activity	1 (2.8%)	2 (5.7%)	0	40 (63.5%)	43 (28.7%)
Preventative dose for procedure/surgery	1 (2.8%)	2 (5.7%)	0	4 (6.3%)	7 (4.7%)
Treatment for bleed	15 (41.7%)	15 (42.9%)	2 (12.5%)	25 (39.7%)	57 (38.0%)
FRESH FROZEN PLASMA/ WHOLE BLOOD					
Total number of patients with at least one treatment	0	0	0	1 (1.6%)	1 (0.7%)
Total number of treatments	0	0	0	1	1
Purpose of the medication					
Preventative dose before activity	0	0	0	0	0
Preventative dose for procedure/surgery	0	0	0	0	0
Treatment for bleed	0	0	0	1 (1.6%)	1 (0.7%)

Arm C: includes emicizumab prophylaxis period only.

Comparator

Historical comparison was used, as described:

Non-Interventional Study NIS BH29768

This study enrolled patients with haemophilia A, particularly those with severe disease or inhibitors against Factor VIII, who suffer from bleeding episodes, which are treated with replacement or with bypassing agents. It was conducted in 12 countries at 33 sites. Patients who participated in NIS BH29768 Cohort C and who met the eligibility criteria for this study could enrol according to their prior haemophilia treatment regimen.

The primary objective was to document the number and type of bleeds in haemophilia A patients with or without FVIII inhibitors under routine clinical practice and to estimate the number of bleeds over time.

The study has three cohorts (Cohort A – patients age ≥ 12 years; B – age 0-11 years both with inhibitors; C -patients age ≥12 years without inhibitors).

The inclusion/ exclusion criteria were similar to those for the pivotal studies.

The study prospectively documented the number and types of bleeds and treatments with episodic or prophylactic FVIII agents in a comparable manner to Study BH30071, and collected information on HRQoL, health status, and safety in patients with haemophilia A, including a cohort of adult and adolescent patients without FVIII inhibitors (Cohort C).

The study design specified that at least 40 patients treated with FVIII prophylaxis and followed for a minimum of 24 weeks in the NIS were to be enrolled in Arm D of Study BH30071.

In order to avoid introducing bias to the subsequent comparative analyses the inclusion criteria and methods of data collection and follow-up in this study were as similar as possible to those used in the emicizumab interventional studies. Patients were not randomized, and were treated according to their

regular standard of care. Therefore, the treatment patterns and outcomes observed reflect real world experience.

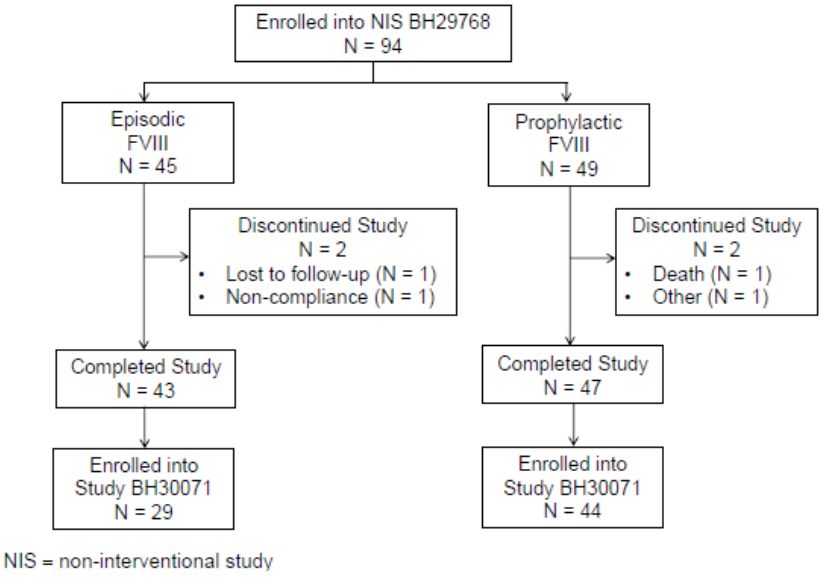
Data from NIS BH29768 served as historical control comparator in the analysis of several secondary endpoints in this study.

In Cohort C (patients ≥ 12 years old with haemophilia A and without inhibitors to FVIII), all 94 patients enrolled were included in the analysis population: 45 patients in the episodic group and 49 patients in the prophylactic group.

Patients were enrolled in the following countries: Australia, China, Costa Rica, Germany, Spain, Italy, Japan, Republic of Korea, United States of America, and South Africa.

In Cohort C, 43 patients (95.6%) in the episodic group and 47 patients (95.9%) in the prophylactic group completed the study (Figure below).

Figure 24: Patient disposition, Cohort C



Two patients (4.4%) in the episodic group and 2 patients (4.1%) in the prophylactic group discontinued the study prematurely. The reasons for withdrawal (1 patient each) were death, loss to follow-up, non-compliance, and “other” (“other” was confirmed as another case of non-compliance).

A total of 29 patients (64.4%) in the episodic group and 44 patients (89.8%) in the prophylactic group subsequently enrolled in Study BH30071.

Both the median observation time and median efficacy period were 27.7 weeks (range: 15.4 - 47.7) in the episodic group and 30.4 weeks (range: 12.4 - 45.1) in the prophylactic group.

The majority of patients (approximately two-thirds of patients in the episodic group and all but 1 patient in the prophylactic group) had an observation time and an efficacy period longer than 24 weeks, and no patient had an efficacy period shorter than 12 weeks. For the majority of patients, the study duration was driven by the time at which the patient enrolled in the interventional Study BH30071.

Demographics are summarised in the following table:

Table 17: Demographics characteristics, cohort C

	Episodic FVIII (N=45)	Prophylactic FVIII (N=49)	All Patients (N=94)
Sex			
n	45	49	94
Male	45 (100.0%)	49 (100.0%)	94 (100.0%)
Age (years)			
n	45	49	94
Mean	31.5	36.1	33.9
SD	12.7	16.1	14.7
SEM	2	2	2
Median	33.0	35.0	34.0
Min - Max	12 - 76	13 - 68	12 - 76
Age Category 1 (years)			
n	45	49	94
< 18	8 (17.8%)	6 (12.2%)	14 (14.9%)
>= 18	37 (82.2%)	43 (87.8%)	80 (85.1%)
Age Category 2 (years)			
n	45	49	94
< 65	44 (97.8%)	47 (95.9%)	91 (96.8%)
>= 65	1 (2.2%)	2 (4.1%)	3 (3.2%)
Race			
n	45	49	94
Asian	13 (28.9%)	9 (18.4%)	22 (23.4%)
Black or African American	6 (13.3%)	1 (2.0%)	7 (7.4%)
White	16 (35.6%)	37 (75.5%)	53 (56.4%)
Multiple	1 (2.2%)	1 (2.0%)	2 (2.1%)
Unknown	9 (20.0%)	1 (2.0%)	10 (10.6%)
Ethnicity			
n	45	49	94
Hispanic or Latino	9 (20.0%)	2 (4.1%)	11 (11.7%)
Not Hispanic or Latino	36 (80.0%)	47 (95.9%)	83 (88.3%)
Height (cm)			
n	40	36	76
Mean	171.80	176.14	173.85
SD	10.15	8.33	9.52
SEM	1.6	1.4	1.1
Median	172.00	176.00	174.70
Min - Max	145.0 - 193.0	158.3 - 203.0	145.0 - 203.0
Weight (kg)			
n	45	47	92
Mean	72.46	76.98	74.77
SD	18.55	14.35	16.60
SEM	2.8	2.1	1.7
Median	70.00	73.00	70.80
Min - Max	32.0 - 129.9	58.0 - 128.8	32.0 - 129.9
BSA (m2)			
n	40	36	76
Mean	1.85	1.93	1.89
SD	0.26	0.20	0.24
SEM	0.0	0.0	0.0
Median	1.85	1.91	1.86
Min - Max	1.2 - 2.5	1.6 - 2.4	1.2 - 2.5
BMI (kg/m2)			
n	40	36	76
Mean	24.57	24.93	24.74
SD	5.49	3.83	4.75
SEM	0.9	0.6	0.5
Median	23.48	23.93	23.64
Min - Max	15.2 - 38.0	19.2 - 39.8	15.2 - 39.8

BSA: Body Surface Area; BMI: Body Mass Index
n represent the number of patients contributing to the summary statistics
Percentages are based on n

Table 18: Type of haemophilia medication, cohort C

	Episodic FVIII (N=45)	Prophylactic FVIII (N=49)	All Patients (N=94)
Total number of patients with at least one treatment	45 (100.0%)	49 (100.0%)	94 (100.0%)
Total number of treatments	1455	4430	5885
Purpose of the medication			
Treatment for bleed	45 (100.0%)	31 (63.3%)	76 (80.9%)
Usual prophylaxis dose	3 (6.7%)	49 (100.0%)	52 (55.3%)
Preventative dose before activity	21 (46.7%)	22 (44.9%)	43 (45.7%)
Preventative dose for procedure/surgery	7 (15.6%)	9 (18.4%)	16 (17.0%)
Factor VIII (Long-acting)			
Total number of patients with at least one treatment	5 (11.1%)	9 (18.4%)	14 (14.9%)
Total number of treatments	122	545	667
Purpose of the medication			
Treatment for bleed	5 (11.1%)	7 (14.3%)	12 (12.8%)
Usual prophylaxis dose	1 (2.2%)	9 (18.4%)	10 (10.6%)
Preventative dose before activity	1 (2.2%)	5 (10.2%)	6 (6.4%)
Preventative dose for procedure/surgery	1 (2.2%)	1 (2.0%)	2 (2.1%)
Factor VIII (Short-acting)			
Total number of patients with at least one treatment	42 (93.3%)	41 (83.7%)	83 (88.3%)
Total number of treatments	1324	3885	5209
Purpose of the medication			
Treatment for bleed	42 (93.3%)	25 (51.0%)	67 (71.3%)
Usual prophylaxis dose	2 (4.4%)	40 (81.6%)	42 (44.7%)
Preventative dose before activity	20 (44.4%)	18 (36.7%)	38 (40.4%)
Preventative dose for procedure/surgery	6 (13.3%)	8 (16.3%)	14 (14.9%)
Cryoprecipitate [Factor-rich thawed plasma]			
Total number of patients with at least one treatment	1 (2.2%)	0	1 (1.1%)
Total number of treatments	5	0	5
Purpose of the medication			
Usual prophylaxis dose	1 (2.2%)	0	1 (1.1%)
Fresh Frozen Plasma/Whole Blood			
Total number of patients with at least one treatment	1 (2.2%)	0	1 (1.1%)
Total number of treatments	1	0	1
Purpose of the medication			
Treatment for bleed	1 (2.2%)	0	1 (1.1%)
Prothrombin Complex Concentrate			
Total number of patients with at least one treatment	1 (2.2%)	0	1 (1.1%)
Total number of treatments	3	0	3
Purpose of the medication			
Treatment for bleed	1 (2.2%)	0	1 (1.1%)

The median number of short-acting FVIII doses was 24.5 (range: 1-109) in the episodic group and 94.0 (range: 19-246) in the prophylactic group (table below)

Table 19: Treatment with FVIII (short-acting), cohort C

	Episodic FVIII (N=45)	Prophylactic FVIII (N=49)	All Patients (N=94)
Patients exposed			
n	42	41	83
Number of doses			
Mean (SD)	31.5 (24.4)	94.8 (39.2)	62.8 (45.4)
Median	24.5	94.0	58.0
Min - Max	1 - 109	19 - 246	1 - 246
Total cumulative dose - UNIT			
Mean (SD)	61068.9 (56625.6)	208432.6 (99600.1)	133863.0 (109255.5)
Median	40750.0	182000.0	123000.0
Min - Max	2000 - 209516	38000 - 487000	2000 - 487000

The medican number of long-acting FVIII doses was 17.0 (range: 2-70) in the episodic group and 60.0 (range: 28-85) in the prophylactic group (table below).

Table 20: Treatment with FVIII (long-acting, cohort C:

	Episodic FVIII (N=45)	Prophylactic FVIII (N=49)	All Patients (N=94)
Patients exposed			
n	5	9	14
Number of doses			
Mean (SD)	24.2 (26.6)	60.6 (18.6)	47.6 (27.5)
Median	17.0	60.0	50.5
Min - Max	2 - 70	28 - 85	2 - 85
Total cumulative dose - UNIT			
Mean (SD)	35300.0 (36619.0)	187212.7 (72189.7)	132958.1 (96568.9)
Median	22000.0	195000.0	111250.0
Min - Max	3000 - 98000	98000 - 300000	3000 - 300000

A total of 46 patients were included in the analysis of patient adherence to FVIII prophylaxis: 19 patients from Europe, 12 patients from the Americas, and 15 patients from Asia Pacific. These 46 patients were prescribed FVIII prophylaxis as concomitant medication with frequency category different than “other” at the start of the study and it lasted for at least 3 months. Of note, compliance during this NIS was a requirement to enter the prophylactic group of Study BH30071, which may have positively affected compliance rates.

The median proportion of weeks when patients were adherent to their FVIII prescription frequency was 86% (range: 20% - 100%). In total, 66.7% of patients had > 80% of weeks when they were compliant with their FVIII prescription frequency (i.e. received all prescribed doses). There were no noticeable differences in adherence between the geographical regions.

Past medical history was most notably hepatitis C (13.3% and 30.6%, respectively) and chronic hepatitis C (4.4% and 6.1%, respectively) for the episodic and prophylactic groups. HIV infection was reported in 4 patients (8.9%) in the episodic group and 8 patients (16.3%) in the prophylactic group.

The most common other treatments were non-steroidal anti-inflammatory drugs (20.0% and 28.6% of patients, respectively), analgesics (33.3% and 14.3%, respectively), and antiviral agents not elsewhere classified (11.1% and 14.3%, respectively).

Medical history related to haemophilia A (total number of bleeds in the previous 6 months) was reported in 43 of the 45 patients in the episodic group and in 32 of the 49 patients in the prophylactic group.

The mean number of bleeds during the 6 months prior to study entry was 10.6 in the episodic group and 2.6 in the prophylactic group. The corresponding median number of bleeds were 8.0 (range: 5 - 32) and 1.0 (range: 0 - 13), respectively.

Objectives

Primary objective:

- to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in patients with haemophilia A without FVIII inhibitors by the number of bleeds over time (i.e. bleed rate)

Secondary efficacy objectives for this study were:

- To evaluate the efficacy of prophylactic emicizumab (in each individual emicizumab arm) by the change in the number of bleeds over time compared with the patient's historical bleed rate.
- To evaluate the efficacy of prophylactic emicizumab administered at 1.5 mg/kg QW or 3 mg/kg Q2W SC compared with no prophylaxis for patients previously treated with episodic FVIII by:
  - ❖ All bleeds over time
  - ❖ Spontaneous bleeds over time
  - ❖ Joint bleeds over time
  - ❖ Target joint bleeds over time
  - ❖ HRQoL of patients according to Haem-A-QoL (aged ≥ 18) or Haemo-QoL-Short Form (aged 12-17) scores after 24 weeks
  - ❖ Health status of patients according to EuroQol 5-Dimension 5-Level Questionnaire (EQ-5D-5L) scores after 24 weeks
- To evaluate the efficacy of prophylactic emicizumab administered at 1.5 mg/kg QW SC for patients previously treated with prophylactic FVIII by:
  - ❖ Maintenance of an adequate control of bleeding by evaluation of the bleed rate

The PK objective for this study was to characterise the exposure (trough plasma concentration) to emicizumab in patients treated on weekly or every 2 weeks dosing schedule.

Outcomes / endpoints

Primary endpoint:

Bleed rate was defined as the number of bleeds over the efficacy period. A bleed was counted in the primary analysis if it was treated with coagulation factors and fulfilled the adapted International Society on Thrombosis and Haemostasis (ISTH) criteria.

The number of bleeds was also annualised for each patient using the following formula:

ABR = (Number of bleeds / Total number of days during the efficacy period) x 365.25.

Endpoints were assessed using a negative binomial regression model.

A bleed was considered to be a "treated bleed" if it was directly followed (i.e. there was not an intervening bleed) by a haemophilia medication reported to be a "treatment for bleed", irrespective of the time between the treatment and the preceding bleed.

A bleed and the first treatment thereafter were considered to be pairs (i.e. one treatment belongs to one bleed only), with the following exception: if multiple bleeds occurred on the same calendar day, the subsequent treatment was considered to apply for each of these multiple bleeds (which were, however, counted as separate 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 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.

Bleeds due to surgery/procedure were not included in the primary analysis. Only treatments that were recorded as “treatment for bleed” were included in the determination of a treated bleed.

Secondary endpoints:

Secondary endpoints followed a hierarchical framework. The level was 0.05. Following the two statistical comparisons for the primary endpoint (Arm A versus Arm Ccontrol and Arm B versus Arm Ccontrol), the secondary endpoints were included in the hierarchy in the order presented:

Table 21: Overview of efficacy endpoints

Endpoint	Arms Compared	Analysis Population	Statistical Model
Type I error-controlled			
Treated bleeds	A vs. $C_{control}$; B vs. $C_{control}$	ITT	NBR*
All bleeds	A vs. $C_{control}$; B vs. $C_{control}$	ITT	NBR*
Treated joint bleeds	A vs. $C_{control}$; B vs. $C_{control}$	ITT	NBR*
Treated spontaneous bleeds	A vs. $C_{control}$; B vs. $C_{control}$	ITT	NBR*
All bleedscompared with the patient’s historical bleed rate	intra-patient comparison, Arm D	NISP	NBR
Treated bleeds compared with the patient’s historical bleed rate	intra-patient comparison, Arm D	NISP	NBR
Haem-A-QoL Physical Health at 24 Weeks	A vs. $C_{control}$; B vs. $C_{control}$	ITT	ANCOVA*
Not type I error-controlled			
Treated target joint bleeds	A vs. $C_{control}$; B vs. $C_{control}$	ITT	NBR*
Haem-A-QoL Total Score	A vs. $C_{control}$; B vs. $C_{control}$	ITT	ANCOVA*
EQ-5D-5L VAS and Index Utility Score	A vs. $C_{control}$; B vs. $C_{control}$	ITT	ANCOVA*
Treated bleeds compared with the patient’s historical bleed rate	intra-patient comparison, Arms (A+B)	NISE	NBR
All bleeds compared with the patient’s historical bleed rate	intra-patient comparison, Arms (A+B)	NISE	NBR
Adequate control of bleeding	Arm D	NISP	upper limit of one sided 97.5% CI of mean ABR is ≤6

ANCOVA = analysis of variance; ITT = intent-to-treat; NBR = negative binomial regression model; NIS = non-interventional study

* 3-level categorical effect for treatment

Electronic Patient-Reported Outcomes

Patient-reported data were collected electronically using two devices: 1) a personal handheld mobile device for capturing bleed data and haemophilia-related medication used during the study (including emicizumab), and 2) a tablet at study sites for completing HRQoL, health status, missed days of school/work, and satisfaction/preference questionnaires.

The data were transmitted automatically after entry to a centralised secure database at the vendor.

The personal electronic handheld device and the on-site tablet were designed such that it was not possible to leave questions unanswered or to enter partial data.

Health-Related Quality-of-Life Data

The Haem-A-QoL and the Haemo-QoL-SF were used to measure HRQoL in adults (aged > 18) and adolescents (aged 12-17), respectively.

Scales are scored from 0 to 100 and lower scores are reflective of better HRQoL.

Health Status Data

Health status was measured via the EQ-5D-5L scale

Patient Satisfaction and Preference

The EmiPref recorded the patient's preference for treatment with IV FVIII or SC emicizumab, or no preference. The EmiPref is a fit for purpose questionnaire developed by the sponsor and consists of 3 questions: 1) Patients indicate whether they would prefer to take their former haemophilia treatment, the new study drug treatment, or have no preference, 2) Patients who expressed a preference were subsequently asked about the reasons for their choice and rank the top three, and 3) An open text field for any additional information about study drug experience. This questionnaire was completed by patients in Arms A, B, and D at Week 17.

Sensitivity and sub-group analyses were conducted.

The results presented in this report are based on a Clinical Cut-off date (CCOD) of 15 September 2017 for the primary efficacy analysis, which took place after all randomized patients (i.e., those assigned to Arms A, B, and C) and 59 patients (a minimum of 40 was required) from Arm D completed 24 weeks of study treatment or had withdrawn from the study.

Randomisation

Patients were stratified at randomization according to the number of bleeds they had over the last 24 weeks prior to study entry (< 9 or ≥ 9 [equivalent to ABR = 18]), to ensure a balance of patients with lower versus higher number of bleeds across the three randomized arms (Arms A, B, and C).

The primary efficacy analysis occurred after 24 weeks of emicizumab treatment because this was considered to be a sufficient period of time to reliably assess the effect of emicizumab prophylaxis on bleed rate reduction.

Patients previously treated with episodic FVIII were required to have at least 5 bleeds in the last 24 weeks prior to study entry to be eligible for enrolment. This requirement was intended to select a group of patients who had a high, unmet medical need and to enable detection of a clinically and statistically significant difference in bleed rates in this population.

Patients who were treated with prophylactic FVIII prior to enrolment were included in a separate arm to avoid introducing significant heterogeneity in baseline bleed rates and goals of care. No criteria associated with bleeding frequency were used for the inclusion of these patients in the study.

Blinding (masking)

The study was un-blinded.

Statistical methods

The results presented are based on a CCOD of 15 September 2017 for the primary efficacy analysis, which took place after all randomized patients (i.e., those assigned to Arms A, B, and C) and 59 patients (a minimum of 40 was required) from Arm D completed 24 weeks of study treatment or had withdrawn from the study.

Study populations

The primary analysis population for efficacy is the Randomized Population (intent-to-treat [ITT]), defined as all patients who were randomized to Arms A, B, and C in their originally assigned treatment arms according to IxRS.

The All Patients Population includes all patients randomized and enrolled in their originally assigned treatment arms (Arms A, B, C, and D), according to the IxRS.

The All Emicizumab Patients Population includes patients in Arms A, B, and D and patients who switched to receive emicizumab (Arm C_{emi}).

The PK-Evaluable Population includes all patients who received at least one dose of emicizumab and had at least one post-baseline emicizumab concentration result.

The Safety Population 1 (SAF1) includes all patients in Arms A, B, and D who received at least one dose of emicizumab and patients in Arm C who started the study period (defined as having had the Week 1 visit).

A subset of the SAF1 Population (SAF1ND) excludes patients in Arm D and is used for safety analyses of randomized patients.

The Safety Population 2 (SAF2) includes all patients in Arms A, B, and D who received at least one dose of emicizumab and patients in Arm C who switched to receive emicizumab and received at least one dose of emicizumab.

The Non-Interventional Study Population includes patients who participated in NIS BH29768 Cohort C prior to enrolment in Study BH30071. The NIS Population includes two subpopulations:

- the NISE Population previously treated with episodic FVIII
- the NISP Population previously treated with prophylactic FVIII according to their assigned treatment arm in Study BH30071.

The Activity-Evaluable Population includes patients who contributed reliable activity data (i.e. at least 8 valid days of data in both 2-week observation periods corresponding to baseline [Weeks 1-2] and Week 25 [Weeks 23-24], where a valid day of activity monitoring was defined as 10 or more wear hours per day).

Analysis populations are summarised:

Table 22: Analysis populations

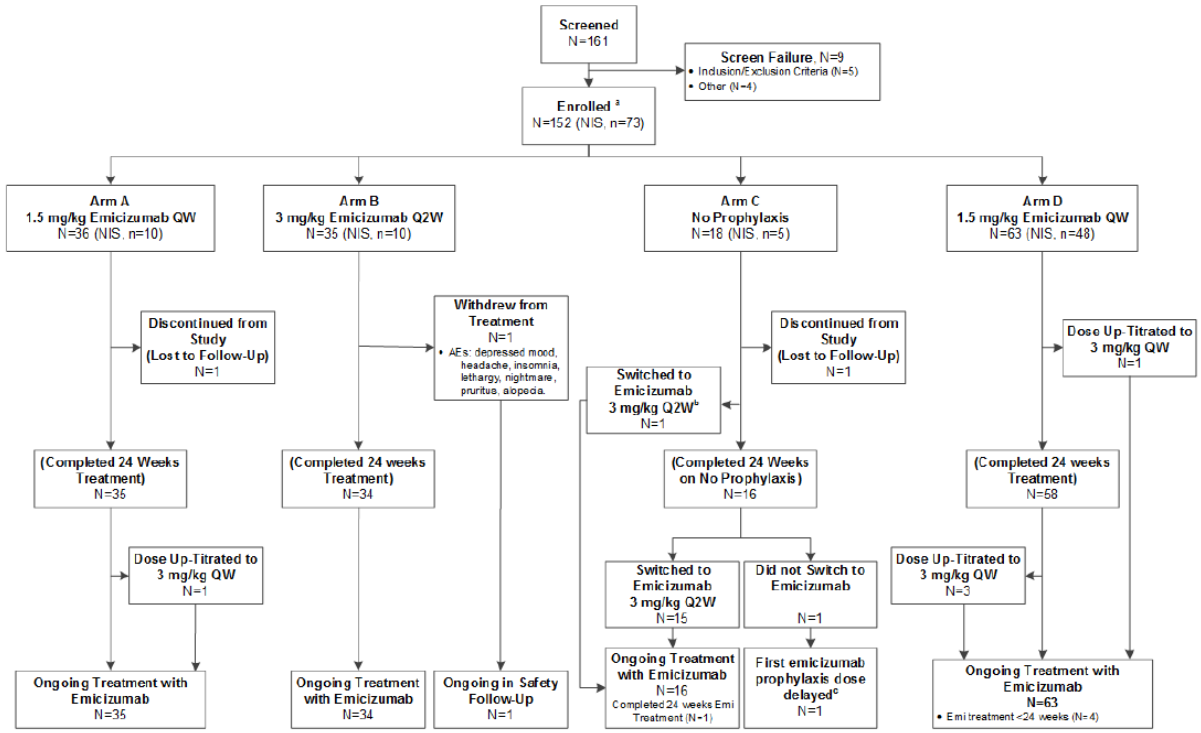
APPROVED Analysis Populations
Protocol: BH30071 Snapshot: k30071a Snapshot Date: 14NOV2017 Cutoff Date: 15SEP2017

Analysis Populations	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)	D: 1.5 mg/kg emicizumab QW (N=63)	Total (N=152)
Randomized Population (ITT)	18	36	35	0	89
Total Exclusions	0	0	0	63	63
All Patients	18	36	35	63	152
Total Exclusions	0	0	0	0	0
All Emicizumab Patients	16	36	35	63	150
Total Exclusions	2	0	0	0	2
Safety Population 1	18	36	35	63	152
Total Exclusions	0	0	0	0	0
Safety Population 2	16	36	35	63	150
Total Exclusions	2	0	0	0	2
Up-Titrated Patients	0	1	0	4	5
Total Exclusions	18	35	35	59	147
NIS Patients	5	10	10	48	73
Total Exclusions	13	26	25	15	79
Activity-Eval. Population	2	2	4	8	16
Total Exclusions	16	34	31	55	136

Results

Participant flow

Figure 25: Patient disposition



AE = adverse event; N = number of patients from Study BH30071; n = number of patients from NIS BH29768; NIS = non-interventional study; QW = once weekly; Q2W = every two weeks

[a] Patients in Arms A, B, and C were randomized in a 2:2:1 ratio; Patients in Arm D were enrolled without randomization.

[b] Patient switched to emicizumab on Day 165 (~23.5 weeks).

[c] Patient did not switch to receive emicizumab prior to the CCOD as the first emicizumab prophylaxis dose was delayed due to an intercurrent illness at Week 25

Recruitment

First Patient Enrolled: 27 September 2016

Data cut-off: 15 September 2017

Conduct of the study

Protocol Amendments

Protocol Amendment 1 was released on 12 September 2016; main points were:

- Removal of the specific FVIII prophylactic dose and frequency from the definition of FVIII prophylaxis regimen in the inclusion criterion for patients previously treated with FVIII prophylaxis (Arm D)
- Modification of the dose escalation criteria
- Addition of which bleeds (treated and/or all bleeds) the efficacy analyses were to be performed for as some patients may report bleeds that they did not treat.
- Addition of a new secondary efficacy endpoint: rate of spontaneous bleeds
- added safety updates

Protocol Amendment 2 was released on 30 November 2016; main points were:

- Update of the safety section with the most recent safety information regarding two cases of thrombotic microangiopathy
- Addition of guidance on the use of FVIII in conjunction with emicizumab.
- Addition of guidelines for dosing and monitoring bypassing agents

Protocol deviations

A total of 102 major protocol deviations occurred in 59 of 89 randomized patients.

In Arm A, 21 patients (58.3%) with 22 procedural deviations and 8 deviations related to medication, in Arm B, 27 patients (77.1%) with 53 procedural deviations and 6 deviations related to medication, and in Arm Ccontrol, 11 patients (61.1%) with 13 procedural deviations were reported (Table below).

Table 23: Major protocol deviation (ITT population):

APPROVED Major Protocol Deviations, Randomized Patients (ITT)
Protocol: BH30071 Snapshot: k30071a Snapshot Date: 14NOV2017 Cutoff Date: 15SEP2017
Arm C: no prophylaxis; Before up-titration

Category Description	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)
Total number of patients with at least one major protocol deviation	11 (61.1%)	21 (58.3%)	27 (77.1%)
Total number of major protocol deviations	13	30	59
Procedural			
Total patients	11 (61.1%)	17 (47.2%)	25 (71.4%)
Total protocol deviations	13	22	53
HRQoL, HS, pt. pref. survey/satis. Q not completed	4 (22.2%)	11 (30.6%)	19 (54.3%)
No BMQ data or emi data for > 2 consecutive weeks	6 (33.3%)	4 (11.1%)	13 (37.1%)
Missing hematology or blood chemistry per SoA	1 (5.6%)	4 (11.1%)	4 (11.4%)
BMQ/emi data not reviewed by SC >4cons wks	0	1 (2.8%)	0
Missing historical bleed rate at week 1 visit	0	1 (2.8%)	0
PD, RCR samples not collected	0	1 (2.8%)	0
Medication			
Total patients	0	8 (22.2%)	5 (14.3%)
Total protocol deviations	0	8	6
Received prohibited therapy	0	4 (11.1%)	3 (8.6%)
Study drug not received, delayed w/o med rationale	0	3 (8.3%)	1 (2.9%)
Incorrect medication or emi dose/sched. deviation	0	1 (2.8%)	1 (2.9%)

Percentages are based on N in the column headings.
Arm C: includes no prophylaxis period only.
Protocol deviation that occurred after or on randomization but before study day 1 are also reported in this output.

Withdrawal of subjects

One patient in Arm B withdrew from emicizumab treatment (3 mg/kg Q2W) after 51 days in the study due to multiple low grade AEs (depressed mood, headache, insomnia, lethargy, nightmare, pruritus and alopecia, details submitted) and was ongoing in the Safety Follow-Up period at the time of the CCOD.

One patient in Arm A (1.5 mg/kg QW) and 1 patient in Arm C (no prophylaxis) were reported by the sites as lost to follow-up after 121 and 101 days in the study, respectively. The patient in Arm C was lost to follow-up before completing 24 weeks in the study and therefore never received emicizumab.

The total observation time for all patients in the study (calculated as the time from randomization / enrolment until the CCOD or premature withdrawal from the study, including any time in the Safety Follow-up period) is presented descriptively and by week ranges in the Table below.

Table 24: Total observation Time

APPROVED Observation Time, All Patients
Protocol: BH30071 Snapshot: k30071a Snapshot Date: 14NOV2017 Cutoff Date: 15SEP2017

	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)	D: 1.5 mg/kg emicizumab QW (N=63)	Total (N=152)
Observation Time (weeks)					
n	18	36	35	63	152
Mean (SD)	32.73 (9.90)	32.92 (8.48)	33.87 (8.38)	33.51 (7.67)	33.36 (8.24)
Median	30.50	30.00	31.29	33.71	32.57
Min - Max	14.4 - 50.3	21.4 - 49.6	24.4 - 50.6	18.4 - 49.6	14.4 - 50.6
Observation Time (week categories)					
>0 w	18 (100%)	36 (100%)	35 (100%)	63 (100%)	152 (100%)
>=4 w	18 (100%)	36 (100%)	35 (100%)	63 (100%)	152 (100%)
>=12 w	18 (100%)	36 (100%)	35 (100%)	63 (100%)	152 (100%)
>=24 w	17 (94.4%)	35 (97.2%)	35 (100%)	59 (93.7%)	146 (96.1%)
>=36 w	7 (38.9%)	12 (33.3%)	14 (40.0%)	21 (33.3%)	54 (35.5%)
>=48 w	2 (11.1%)	3 (8.3%)	2 (5.7%)	1 (1.6%)	8 (5.3%)

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

Baseline data

Table 25: Summary of demographics characteristics (all patients)

	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)	D: 1.5 mg/kg emicizumab QW (N=63)	Total (N=152)
Sex					
n	18	36	35	63	152
Male	18 (100%)	36 (100%)	35 (100%)	63 (100%)	152 (100%)
Age (years)					
n	18	36	35	63	152
Mean	37.8	39.8	40.4	36.4	38.3
SD	12.9	14.0	11.4	14.4	13.5
SEM	3	2	2	2	1
Median	40.0	36.5	41.0	36.0	38.0
Min - Max	16 - 57	19 - 77	20 - 65	13 - 68	13 - 77
Age Category 1					
n	18	36	35	63	152
< 18	1 (5.6%)	0	0	7 (11.1%)	8 (5.3%)
>= 18	17 (94.4%)	36 (100%)	35 (100%)	56 (88.9%)	144 (94.7%)
Age Category 2					
n	18	36	35	63	152
< 65	18 (100%)	34 (94.4%)	34 (97.1%)	61 (96.8%)	147 (96.7%)
>= 65	0	2 (5.6%)	1 (2.9%)	2 (3.2%)	5 (3.3%)
Race					
n	18	36	35	63	152
Asian	4 (22.2%)	6 (16.7%)	10 (28.6%)	12 (19.0%)	32 (21.1%)
Black or African American	3 (16.7%)	3 (8.3%)	1 (2.9%)	1 (1.6%)	8 (5.3%)
Native Hawaiian or other Pacific Islander	0	1 (2.8%)	0	0	1 (0.7%)
White	11 (61.1%)	24 (66.7%)	20 (57.1%)	47 (74.6%)	102 (67.1%)
Unknown	0	2 (5.6%)	4 (11.4%)	3 (4.8%)	9 (5.9%)
Ethnicity					
n	18	36	35	63	152
Hispanic or Latino	0	4 (11.1%)	5 (14.3%)	7 (11.1%)	16 (10.5%)
Not Hispanic or Latino	17 (94.4%)	32 (88.9%)	30 (85.7%)	53 (84.1%)	132 (86.8%)
Not Reported	1 (5.6%)	0	0	3 (4.8%)	4 (2.6%)

Height (cm)					
n	17	34	33	63	147
Mean	171.60	174.08	174.68	175.49	174.53
SD	5.50	8.10	8.50	8.54	8.15
SEM	1.3	1.4	1.5	1.1	0.7
Median	173.00	174.50	171.60	175.00	174.40
Min - Max	160.0 - 178.0	155.0 - 193.0	160.4 - 193.0	157.0 - 205.0	155.0 - 205.0
Weight (kg)					
n	18	36	35	63	152
Mean	70.61	80.87	81.83	79.00	79.10
SD	17.27	13.58	18.93	15.42	16.30
SEM	4.1	2.3	3.2	1.9	1.3
Median	69.90	80.00	76.40	77.00	76.65
Min - Max	43.0 - 114.6	53.1 - 107.3	56.3 - 121.4	52.8 - 139.0	43.0 - 139.0
BSA (m2)					
n	17	34	33	63	147
Mean	1.82	1.95	1.96	1.94	1.93
SD	0.23	0.18	0.23	0.20	0.21
SEM	0.1	0.0	0.0	0.0	0.0
Median	1.79	1.95	1.93	1.93	1.93
Min - Max	1.4 - 2.3	1.6 - 2.4	1.6 - 2.4	1.5 - 2.6	1.4 - 2.6
BMI (kg/m2)					
n	17	34	33	63	147
Mean	23.75	26.57	26.69	25.56	25.84
SD	4.92	3.66	5.96	4.00	4.59
SEM	1.2	0.6	1.0	0.5	0.4
Median	24.15	26.44	24.96	25.06	25.01
Min - Max	16.8 - 36.2	20.0 - 33.7	19.0 - 38.4	19.2 - 40.6	16.8 - 40.6

Table 26: Haemophilia A history (all patients)

	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)	D: 1.5 mg/kg emicizumab QW (N=63)	Total (N=152)
Highest historical inhibitor titer					
n	1	1	1	0	3
Mean (SD)	0.55 (NE)	270.00 (NE)	1.80 (NE)	NE (NE)	90.78 (155.21)
Median	0.55	270.00	1.80	NE	1.80
Min - Max	0.6 - 0.6	270.0 - 270.0	1.8 - 1.8	NE - NE	0.6 - 270.0
n	18	36	35	63	152
<5 BU	1 (5.6%)	0	1 (2.9%)	0	2 (1.3%)
>=5 BU	0	1 (2.8%)	0	0	1 (0.7%)
Missing	17 (94.4%)	35 (97.2%)	34 (97.1%)	63 (100%)	149 (98.0%)
Prior episodic treatment in the last 24 weeks*					
n	18	36	35	5	94
Factor VIII	16 (88.9%)	32 (88.9%)	32 (91.4%)	4 (80.0%)	84 (89.4%)
Factor VIII long acting	3 (16.7%)	4 (11.1%)	3 (8.6%)	1 (20.0%)	11 (11.7%)
Other	0	0	1 (2.9%)	0	1 (1.1%)
Prior prophylactic treatment in the last 24 weeks*					
n	2	3	5	63	73
Factor VIII	2 (100%)	1 (33.3%)	5 (100%)	53 (84.1%)	61 (83.6%)
Factor VIII long acting	0	2 (66.7%)	0	10 (15.9%)	12 (16.4%)
Other	0	0	0	0	0
Reason for only being on an episodic treatment regimen*					
n	18	34	33	0	85
Availability	6 (33.3%)	7 (20.6%)	6 (18.2%)	0	19 (22.4%)
Price / Reimbursement	0	0	1 (3.0%)	0	1 (1.2%)
Tolerability / Side Effects	2 (11.1%)	1 (2.9%)	2 (6.1%)	0	5 (5.9%)
Efficacy	1 (5.6%)	4 (11.8%)	2 (6.1%)	0	7 (8.2%)
Frequency of Infusion / Half-Life	3 (16.7%)	4 (11.8%)	3 (9.1%)	0	10 (11.8%)
Subject Request	9 (50.0%)	12 (35.3%)	15 (45.5%)	0	36 (42.4%)
Venous Access	1 (5.6%)	7 (20.6%)	5 (15.2%)	0	13 (15.3%)
Other	3 (16.7%)	7 (20.6%)	8 (24.2%)	0	18 (21.2%)

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

The proportion of randomized patients who had ≥ 9 bleeds in the 24 weeks prior to the study entry in Arm A, Arm B, and Arm C was 75.0%, 85.7%, and 77.8%, respectively, and the proportion was 15.9% in patients enrolled in Arm D. The median number of bleeds in the 24 weeks prior to enrolment was between 11.5 and 16.5 in the randomized patients, and 2.0 in Arm D, as shown in table below:

Table 27: Summary of bleeding events in the last 24 weeks prior to study entry (all patients)

	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)	D: 1.5 mg/kg emicizumab QW (N=63)	Total (N=152)
Number of bleeds in the past 24 weeks					
n	18	36	35	63	152
Mean (SD)	21.6 (16.4)	18.0 (15.8)	15.1 (6.5)	6.4 (17.7)	13.0 (16.1)
Median	16.5	11.5	13.0	2.0	9.0
Min - Max	5 - 63	5 - 84	5 - 29	0 - 128	0 - 128
<9	4 (22.2%)	9 (25.0%)	5 (14.3%)	53 (84.1%)	71 (46.7%)
>=9	14 (77.8%)	27 (75.0%)	30 (85.7%)	10 (15.9%)	81 (53.3%)
Number of target joints prior to study entry					
n	18	36	35	63	152
Mean (SD)	2.2 (1.4)	2.1 (1.4)	2.2 (1.7)	1.0 (1.6)	1.7 (1.6)
Median	2.0	2.0	2.0	0.0	1.0
Min - Max	0 - 6	0 - 6	0 - 6	0 - 6	0 - 6
No target joint	3 (16.7%)	2 (5.6%)	8 (22.9%)	37 (58.7%)	50 (32.9%)
Any target joint(s)	15 (83.3%)	34 (94.4%)	27 (77.1%)	26 (41.3%)	102 (67.1%)
1 joint	1 (6.7%)	14 (41.2%)	5 (18.5%)	8 (30.8%)	28 (27.5%)
>1 joints	14 (93.3%)	20 (58.8%)	22 (81.5%)	18 (69.2%)	74 (72.5%)
Number of patients with missing target joints location	0	0	0	1	1

Previous and concurrent diseases other than Haemophilia A

The majority of the enrolled patients (90.8%) reported at least one baseline medical condition other than haemophilia. The disorders were fairly well balanced between treatment groups.

As expected, the most frequently reported disorders were haemophilic arthropathy and hypertension reported by 73.0% and 24.3% of patients across all treatment arms, respectively.

A large proportion of patients reported hepatitis C (17.8%) and HIV infection (15.1%). Other medical disorders were reported infrequently and were typical for the patient population with haemophilia A.

There were no clear differences across treatment groups in previous or concomitant non-haemophilia A medications that would impact the outcomes of the study. Treatments other than for Haemophilia A were analgesics

8.3% patients in Arm A (4 surgeries or procedures in 3 patients), 22.9% patients in Arm B (16 surgeries or procedures in 8 patients), and 11.1% of patients in Arm $C_{control}$ (2 surgeries or procedures in 2 patients) reported surgeries and procedures during the randomized period [procedures are described].

Outcomes and estimation

A total of 146 of 152 patients (96.1%) completed at least 24 weeks on the study at the CCOD; 35 of 36 in Arm A (97.2%), 35 of 35 in Arm B (100%); 17 of 18 in Arm C (94.4%), and 59 of 63 in Arm D (93.7%).

Patients in Arm C control who completed at least 24 weeks study participation were offered the option to switch to emicizumab at 3 mg/kg QW for 4 weeks followed by 3 mg/kg Q2W. The majority of patients in Arm C control who completed 24 weeks on no prophylaxis (15 of 16 patients) switched to receive emicizumab (Arm Cemi). One patient switched to emicizumab prior to completing 24 weeks on no prophylaxis (on Day 165 [~23.5 weeks]), and 1 patient, although having completed 24 weeks on no prophylaxis, did not switch to receive emicizumab prior to the CCOD as the first emicizumab prophylaxis dose was delayed due to an intercurrent illness at Week 25.

At the time of the CCOD, 148 patients were continuing treatment with emicizumab: 35 patients in Arm A, 34 patients in Arm B, 16 patients in Arm Cemi, and 63 patients in Arm D. One patient in Arm B was withdrawn from emicizumab treatment and was ongoing in the Safety Follow-Up, 1 patient in Arm A and 1 patient in Arm C were lost to follow-up, and, as described above, 1 patient in Arm C had not switched to emicizumab at the time of the CCOD.

One patient in Arm A (2.8%) had his dose up-titrated to 3 mg/kg QW from 1.5 mg/kg QW starting on Week 25 following ≥ 2 qualifying bleeds within 24 weeks. Four patients in Arm D (6.3%) had their dose up-titrated to 3 mg/kg QW; one patient prior to and 3 patients after completing 24 weeks of treatment on 1.5 mg/kg emicizumab QW. Per protocol, patients in Arm D were allowed to up-titrate prior to completing 24 weeks of treatment.

Emicizumab prophylaxis with the maintenance dose of 1.5 mg/kg QW resulted in a 96% reduction in rate of treated bleeds compared with no prophylaxis (ABR A/C ratio = 0.04; $p < 0.0001$); similarly, emicizumab prophylaxis with the maintenance dose of 3 mg/kg Q2W led to a 97% reduction in rate of treated bleeds, compared with no prophylaxis (ABR B/C ratio = 0.03; $p < 0.0001$), as summarised in tables below:

Table 28: Overview of efficacy (NB regression model, ITT population)

	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)
Number of Patients	18	36	35
Treated Bleeds			
ABR, model based	38.2	1.5	1.3
95% CI	[22.86; 63.76]	[0.89; 2.47]	[0.75; 2.25]
ABR Ratio (Active vs. Control)		0.04	0.03
95% CI for the ratio between bleeding rates		[0.020; 0.075]	[0.017; 0.066]
p-Value (Stratified Wald test)		<.0001	<.0001
p-Value (Non-Stratified Wald test)		<.0001	<.0001
All Bleeds			
ABR, model based	47.6	2.5	2.6
95% CI	[28.45; 79.59]	[1.63; 3.90]	[1.63; 4.29]
ABR Ratio (Active vs. Control)		0.05	0.06
95% CI for the ratio between bleeding rates		[0.028; 0.099]	[0.030; 0.103]
p-Value (Stratified Wald test)		<.0001	<.0001
p-Value (Non-Stratified Wald test)		<.0001	<.0001
Treated Joint Bleeds			
ABR, model based	26.5	1.1	0.9
95% CI	[14.67; 47.79]	[0.59; 1.89]	[0.44; 1.67]
ABR Ratio (Active vs. Control)		0.04	0.03
95% CI for the ratio between bleeding rates		[0.019; 0.085]	[0.015; 0.070]
p-Value (Stratified Wald test)		<.0001	<.0001
p-Value (Non-Stratified Wald test)		<.0001	<.0001
Treated Spontaneous Bleeds			
ABR, model based	15.6	1.0	0.3
95% CI	[7.60; 31.91]	[0.48; 1.91]	[0.11; 0.75]
ABR Ratio (Active vs. Control)		0.06	0.02
95% CI for the ratio between bleeding rates		[0.025; 0.151]	[0.006; 0.056]
p-Value (Stratified Wald test)		<.0001	<.0001
p-Value (Non-Stratified Wald test)		<.0001	<.0001

Both p-values for the Arm A vs. Arm C and for the Arm B vs. Arm C comparison are obtained via a global model with a 3-levels categorical effect for treatment.
Arm C: includes no prophylaxis period only.

Patients who were previously on episodic FVIII were randomized to receive emicizumab prophylaxis (on Arms A or B) or no prophylaxis (Arm C). All patients continue episodic FVIII treatment in case of a bleed, using FVIII products and doses as directed by their provider. This variability in FVIII cannot impact bleed-related endpoints as FVIII was administered after the occurrence of a bleed. In other words, once a patient developed symptoms of a bleed, a bleed event was counted and a subsequent intervention such as treatment does not change the number of bleeds. The study was not designed to collect or examine the hemostatic effect of FVIII and therefore no endpoint or comparison is affected by the choice of FVIII.

The proportion of patients experiencing zero treated bleeding episodes while on emicizumab prophylaxis was 55.6% and 60.0% in Arms A and B, respectively, compared to 0% in Arm Ccontrol. The proportion of patients with 0-3 treated bleeds was 91.7% and 94.3% in Arms A and B, respectively, compared to 5.6% in Arm C control.

Table 29: Annualised bleeding rate overview (ITT population)

	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)
Number of Patients	18	36	35
ABR Treated Bleeds			
model based (95% CI)	38.2 [22.86;63.76]	1.5 [0.89; 2.47]	1.3 [0.75; 2.25]
Mean (95% CI)	44.5 [32.42;59.67]	1.8 [0.17; 6.84]	1.6 [0.14; 6.62]
Median (IQR)	40.4 [25.31;56.68]	0.0 [0.00; 2.54]	0.0 [0.00; 1.89]
Min-Max	[4.27-98.66]	[0.00-10.81]	[0.00-26.83]
ABR All Bleeds			
model based (95% CI)	47.6 [28.45;79.59]	2.5 [1.63; 3.90]	2.6 [1.63; 4.29]
Mean (95% CI)	49.4 [36.61;65.25]	2.6 [0.47; 8.21]	2.8 [0.54; 8.48]
Median (IQR)	46.9 [26.09;73.92]	0.6 [0.00; 3.85]	1.6 [0.00; 3.95]
Min-Max	[6.41-98.66]	[0.00-19.22]	[0.00-26.83]
ABR Treated Spontaneous Bleeds			
model based (95% CI)	15.6 [7.60;31.91]	1.0 [0.48; 1.91]	0.3 [0.11; 0.75]
Mean (95% CI)	16.5 [9.56;26.66]	1.1 [0.03; 5.67]	0.3 [0.00; 4.29]
Median (IQR)	10.8 [2.14;25.93]	0.0 [0.00; 1.26]	0.0 [0.00; 0.00]
Min-Max	[0.00-62.31]	[0.00-8.64]	[0.00-4.18]
ABR Treated Joint Bleeds			
model based (95% CI)	26.5 [14.67;47.79]	1.1 [0.59; 1.89]	0.9 [0.44; 1.67]
Mean (95% CI)	32.1 [21.98;45.31]	1.3 [0.06; 6.02]	1.2 [0.05; 5.86]
Median (IQR)	21.3 [14.47;41.31]	0.0 [0.00; 1.91]	0.0 [0.00; 1.26]
Min-Max	[2.14-96.56]	[0.00-6.41]	[0.00-26.83]
ABR Treated Target Joint Bleeds			
model based (95% CI)	13.0 [5.22;32.33]	0.6 [0.28; 1.42]	0.7 [0.27; 1.64]
Mean (95% CI)	20.1 [12.28;30.98]	0.9 [0.01; 5.31]	1.1 [0.04; 5.77]
Median (IQR)	12.8 [0.00;39.13]	0.0 [0.00; 1.44]	0.0 [0.00; 0.00]
Min-Max	[0.00-75.57]	[0.00-6.41]	[0.00-26.83]

The mean, median and min-max are based on the Calculated ABR.
Arm C: includes no prophylaxis period only.

Table 30: Overview of efficacy intra-patient comparison (NISP population)

APPROVED Overview of Efficacy Intra-patient Comparison Arm D, Prophylactic NIS Patients
Protocol: BH30071 Snapshot: k30071a Snapshot Date: 14NOV2017 Cutoff Date: 15SEP2017
Before up-titration

	FVIII Prophylaxis (N=48)		D: 1.5 mg/kg emicizumab QW (N=48)
Number of Patients	48		48
Treated Bleeds			
ABR, model based [95% CI]	4.8 [3.22; 7.09]		1.5 [0.98; 2.33]
ABR Ratio (Active vs. Control)		0.32	
95% CI for the ratio between bleeding rates		[0.195; 0.514]	
p-Value (Non-Stratified Wald test)		<.0001	
All Bleeds			
ABR, model based [95% CI]	8.9 [5.72; 13.87]		3.3 [2.17; 5.06]
ABR Ratio (Active vs. Control)		0.37	
95% CI for the ratio between bleeding rates		[0.220; 0.626]	
p-Value (Non-Stratified Wald test)		0.0002	

Only patients who participated in the NIS BH29768 and in study BH30071 are included.
For patients initially on episodic treatment in study BH29768, only data on or after the prophylaxis prescription date from the CRF are included.
Intra-patient comparator data from non-interventional study BH29768.

NISP = non-intervention study prophylaxis population

There was a 68% reduction in rate of treated bleeds (ABR D/DNIS Ratio = 0.32, p < 0.0001) and a 63% reduction in rate of all bleeds (ABR D/DNIS Ratio = 0.37, p < 0.0002) on emicizumab prophylaxis.

An additional pre-defined secondary endpoint analysis (not type 1 error controlled) of intra-patient comparison in pooled Arms A and B (NISE Population) demonstrated a clinically meaningful reduction in rates of treated bleeds (97%) and all bleeds (96%) for emicizumab prophylaxis compared with prior episodic FVIII treatment.

Table 31: Overview of efficacy intra-patient comparison (NISE population)

APPROVED Overview of Efficacy Intra-patient Comparison Arm A and B, Episodic NIS Patients
Protocol: BH30071 Snapshot: k30071a Snapshot Date: 14NOV2017 Cutoff Date: 15SEP2017
Before up-titration

	FVIII Episodic (N=20)		A+B:emicizumab 1.5mg/kg QW and 3mg/kg Q2W (N=20)
Number of Patients	20		20
Treated Bleeds			
ABR, model based [95% CI]	34.4 [27.45; 43.14]		1.0 [0.43; 2.54]
ABR Ratio (Active vs. Control)		0.03	
95% CI for the ratio between bleeding rates		[0.014; 0.067]	
p-Value (Non-Stratified Wald test)		<.0001	
All Bleeds			
ABR, model based [95% CI]	39.6 [31.94; 49.04]		1.6 [0.85; 2.92]
ABR Ratio (Active vs. Control)		0.04	
95% CI for the ratio between bleeding rates		[0.023; 0.068]	
p-Value (Non-Stratified Wald test)		<.0001	

Only patients who participated in the NIS BH29768 and in study BH30071 are included.
Intra-patient comparator data from non-interventional study BH29768.

Bleed and Medication Questionnaire

A patient was considered to be compliant if he completed the BMQ at least every 8 days. Overall, there was high compliance in the use of the BMQ in the ITT population (99.4%, 92.5%, and 96.4% compliant days in Arm A, Arm B, and Arm Ccontrol, respectively).

Haemophilia Quality of Life Questionnaire for Adults

A patient was compliant with the Haem-A-QoL if he completed the questionnaire at the scheduled assessments (Weeks 1, 13, and 25). Overall compliance for the randomized adult patients was high (97.2%, 90.3%, and 88.0% in Arm A, Arm B, and Arm Ccontrol, respectively; details provided in the tabulated summary per visit). High compliance did not decrease over time; at no study visit was it lower than 80%.

Similarly, compliance was high for patients in Arm D; overall compliance was > 90% for each visit.

EuroQol 5-Dimension 5-Level (EQ-5D-5L)

A patient was compliant with the EQ-5D-5L if he completed the questionnaire at the scheduled assessments (Weeks 1, 13, and 25). Overall compliance for the randomized adult and adolescent patients was high (97.2%, 90.3%, and 88.7%) in Arm A, Arm B, and Arm Ccontrol, respectively. High compliance did not decrease over time; at no study visit was it lower than 80%.

Similarly, compliance was high for patients in Arm D. Overall compliance was ≥90% for each visit.

Haemophilia Quality of Life Questionnaire for Adolescents and Children-Short Form (Haemo-QoL-SF)

Five of 8 adolescents completed the questionnaire at all scheduled assessments. The other 3 adolescents did not complete the questionnaires at one of two, or two to three of three scheduled assessments.

Emicizumab Preference Survey (EmiPref)

A patient was compliant with the EmiPref if he completed the questionnaire at the scheduled assessment (Week 17). Overall, 71.4% of patients on emicizumab prophylaxis (77.8%, 61.8%, and 73.0% for Arm A, Arm B and Arm D, respectively) provided response to the EmiPref survey. The atypical timing of this assessment (i.e. no other HRQoL measures were administered at this point) contributed to sites forgetting to administer this questionnaire and leading to a number of missed assessments.

Subcutaneous-Intravenous Hemophilia Injection Satisfaction (SQ-ISHI)

A patient was compliant with the SQ-ISHI if he completed the questionnaire at the scheduled assessments (Week 1 and Week 21 or 25). However, due to an error in the tablet programming, the questionnaire could be completed at both Week 21 and Week 25. A total of 57 of 63 (90.5%) questionnaires expected to be completed at Week 1 were completed and 50 of 62 (80.6%) questionnaires expected to be completed at Week 21 were completed. At Week 25, 52 questionnaires were completed, of which more than half were completed by patients who had already completed the questionnaire at Week 21.

Activity

Participation to the activity assessment was optional (85 patients across all arms consented). An assessment was reported as compliant if the patient wore the recording device for 10 or more hours per day and for at least 8 days during each observation period. Overall, compliance for all expected assessments was 36.8% and was similar across all treatment arms (35.1% to 38.5%). Compliance was greater at baseline (48.2%)compared to Week 25 (26.9%).

In the Haem-A-QoL Physical Health Score at Week 25, patients on 1.5 mg/kg QW (Arm A) and 3 mg/kg (Arm B) Q2W emicizumab had a lower score (reflective of better physical health) compared to patients on no prophylaxis (scale 0-100; Arm Ccontrol: 44.32, Arm A: 31.81, and Arm B: 28.35). The difference in scores between Arm A and Arm B was not statistically significant (p = 0.0891), not allowing for confirmatory hypothesis testing for the endpoint included further down in the hierarchy.

Supporting the differences in scores at Week 25, a decrease in the Physical Health score over the course of 24 weeks was observed in patients on emicizumab, whereas no changes were observed in the scores of patients on no prophylaxis. The proportion of patients with improvements exceeding a responder threshold of 10 points at Week 25 was higher in patients on emicizumab prophylaxis (Arm A: 55.9% and Arm B: 54.8%), compared with patients on no prophylaxis (Arm Ccontrol: 14.3%).

Similarly, in the Haem-A-QoL Total score at Week 25, patients on 1.5 mg/kg QW and 3 mg/kg Q2W emicizumab had a lower score (reflective of better HRQoL) compared to patients on no prophylaxis (scale 0-100; Arm Ccontrol: 29.95, Arm A: 24.04, and Arm B: 21.39). A decrease in the Total score over the course of 24 weeks was also observed in patients on emicizumab, whereas no changes were observed in the scores of patients on no prophylaxis. The proportion of patients with improvements exceeding a responder threshold of 7 points at Week 25 was higher in patients on emicizumab prophylaxis (Arm A: 52.9% and Arm B: 45.2%) compared with patients on no prophylaxis (Arm Ccontrol: 28.6%).

In the EQ-5D-5L VAS and Index Utility Scores at Week 25, patients on 1.5 mg/kg QW and 3 mg/kg Q2W emicizumab had a higher score (reflective of better health) compared to patients on no prophylaxis,

however, the differences were mostly driven by a decrease from baseline in the score of patients in Arm Ccontrol (i.e., worsening).

Results are summarised in the following table:

Table 32: Overview of Health status and quality of life (ITT population)

APPROVED Overview of Health Status and QoL, Randomized Patients (ITT)
Protocol: BH30071 Snapshot: k30071a Snapshot Date: 14NOV2017 Cutoff Date: 15SEP2017
Arm C: no prophylaxis; Before up-titration

	C: No prophylaxis (N=18)	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)
Haem-A-QoL Physical Health Subscore at Week 25			
n	13	34	29
Adjusted Mean	44.32	31.81	28.35
Difference in Adjusted Means (Control vs. Active)		12.51	15.97
p-Value		0.0891	0.0349
Haem-A-QoL Total Score at Week 25			
n	13	34	29
Adjusted Mean	29.95	24.04	21.39
Difference in Adjusted Means (Control vs. Active)		5.91	8.56
p-Value		0.1269	0.0317
EQ-5D-5L Visual Analogue Scale Score at Week 25			
n	14	34	29
Adjusted Mean	72.57	76.61	81.72
Difference in Adjusted Means (Control vs. Active)		-4.04	-9.15
p-Value		0.3402	0.0373
EQ-5D-5L Index Utility Score at Week 25			
n	14	34	29
Adjusted Mean	0.63	0.76	0.76
Difference in Adjusted Means (Control vs. Active)		-0.13	-0.13
p-Value		0.0060	0.0059

Means adjusted for covariates: baseline score, treatment group and treatment by baseline interaction term.
The Haem-A-QoL is completed by patients aged 18 years and above.

Preference for Emicizumab Prophylaxis versus FVIII Prophylaxis or Episodic Treatment According to the Preference Survey (EmiPref)

A total of 95 of 134 patients in Arms A, B and D (70.9%) completed the EmiPref survey at Week 17, of which a majority (89 patients [93.7%]) reported a preference for SC emicizumab over their former IV haemophilia treatment (Table below).

Table 33: Categorical response in emicizumab preference survey by treatment arm:

APPROVED Categorical Response in Emicizumab Preference Survey by Treatment Arm, All Patients
Protocol: BH30071 Snapshot: k30071a Snapshot Date: 14NOV2017 Cutoff Date: 15SEP2017
Before up-titration

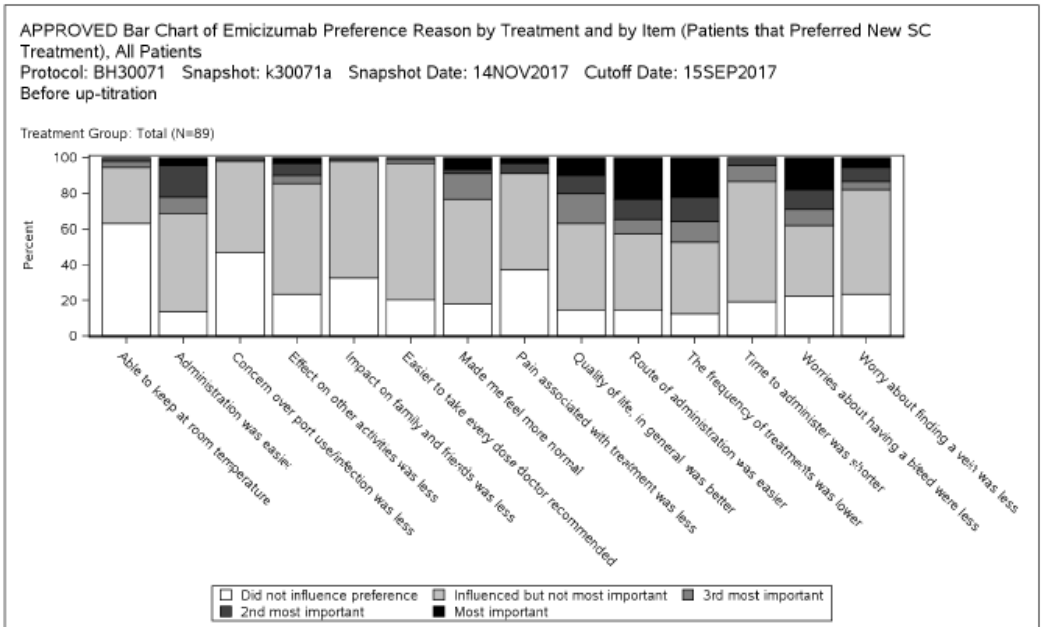
	A: 1.5 mg/kg emicizumab QW (N=36)	B: 3 mg/kg emicizumab Q2W (N=35)	D: 1.5 mg/kg emicizumab QW (N=63)	Total (N=134)
All responding patients	28	21	46	95
Prefer the new study drug treatment (SC)				
n (%)	27 (96.4%)	17 (81.0%)	45 (97.8%)	89 (93.7%)
95% CI for proportion	(81.65, 99.91)	(58.09, 94.55)	(88.47, 99.94)	(86.76, 97.65)
Prefer my old hemophilia treatment (IV)				
n (%)	0 (0.0%)	2 (9.5%)	0 (0.0%)	2 (2.1%)
95% CI for proportion	(0.00, 12.34)	(1.17, 30.38)	(0.00, 7.71)	(0.26, 7.40)
Have no preference				
n (%)	1 (3.6%)	2 (9.5%)	1 (2.2%)	4 (4.2%)
95% CI for proportion	(0.09, 18.35)	(1.17, 30.38)	(0.06, 11.53)	(1.16, 10.43)

Percentages are based on n, where n is the number of patients responding to this scale
95% CI for one sample binomial using Pearson-Clopper method

Furthermore, 97.8% of patients previously on FVIII prophylaxis (Arm D) who completed the questionnaire (45 of 46 patients) favoured emicizumab.

The two reasons most frequently ranked by patients as the most important for their preference for emicizumab treatment over the former haemophilia treatment was “the frequency of treatments was lower” and “route of administration was easier”, see table below:

Figure 26: Emicizumab preference reasons (Arms A, B and D)



Days Away from Work or School

The number of days away from work was recorded at baseline, Week 13 and Week 25 for the 4-week period preceding each data entry.

During the three 4-week assessment periods, an average of 9 patients in Arm Ccontrol (50.0%), 27 patients in Arm A (75.9%), and 22 patients in Arm B (61.9%) reported working. The same proportion of

patients reported not having missed any days of work at baseline and Week 25 in Arm Ccontrol (6 patients [33%]), whereas a small increase in the proportion of patients was seen in Arm A (baseline: 18 patients [50%]; Week 25: 24 patients [66.7%]) and Arm B (baseline: 14 patients: [40%]; Week 25: 21 patients [60.0%]).

The mean expected number of days at work was similar, with a median of 20 days across all assessment periods for the three arms. The mean proportion of days away from work was ≤ 13% for all patients.

Similarly, the number of days away from school was recorded at baseline, Week 13 and Week 25 for the 4-week period preceding each data entry. In Arm Ccontrol, 5 patients (27.8%) were enrolled at school at baseline and 2 patients (11.1 %) at Week 25. In Arm A, 8 patients (22.2%) were enrolled at school at baseline and 4 patients (11.1%) at Week 25. In Arm B, 6 patients (17.1%) were enrolled at school at baseline and 2 patients (5.7%) at Week 25. The mean proportion of days away from school was 0% in the majority of patients across all assessment periods.

Days Hospitalised

The mean number of days hospitalized within 24 weeks during the randomized period was 0.11 days for Arm Ccontrol (95% CI: 0.00, 0.35 days), 0.17 days for Arm A (95% CI: 0.00, 0.51) and 0.43 days for Arm B (95% CI: 0.00; 1.04 days), with a median of zero for the three arms (i.e., the majority of patients were not hospitalised).

Study HAVEN-3 (BH30071): A randomized, multicentre, open-label, Phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in haemophilia A patients without inhibitors.

Surgeries

A proportion of 8.3% patients in Arm A (4 surgeries or procedures in 3 patients), 22.9% patients in Arm B (16 surgeries or procedures in 8 patients), and 11.1% of patients in Arm C control (2 surgeries or procedures in 2 patients) reported surgeries and procedures during the randomized period.

One patient in Arm A (Patient ##9002) had a left and right ankle arthroplasty more than 7 and 2 years prior to study entry, respectively, that were the source of an SAE, surgery during the study, and administration of several doses of FVIII. On study Day 125, the patient reported a mild device loosening in the left ankle. On study Day 229, the AE worsened to severe intensity and the patient was hospitalized. A revision of the total arthroplasty (left ankle) for aseptic loosening of the talar component was performed on study Day 230, and the patient was administered several doses of FVIII (SHL) as preventative doses for surgery/procedure.

Surgeries and procedures during emicizumab prophylaxis included one additional event in 1 patient (6.3%) in Arm Cemi and 82 events in 16 patients (25.4%) in Arm D. Multiple repetitions of the same procedures(percutaneous drainage tube irrigation [33 repetitions], percutaneous drainage tube insertion/ removal [5 repetitions], and wound irrigation [12 repetitions]) were reported for a single patient in Arm D (Patient ##9103) as a treatment for historical peritoneo-cutaneous fistula (starting date: 22 January 2015, Day -796), and the patient was administered several doses of FVIII (SHL) as preventative doses for surgery/procedure.

One patient in Arm D (Patient ##4103) had an SAE of acute coronary syndrome, which led to hospitalization on study Day 239 and multiple subsequent procedures. The patient underwent a transthoracic echocardiogram (Day 242), a coronary angiogram (Day 243), left heart catheterization

(Day 245), and a percutaneous coronary intervention (Day 245). The patient was not administered FVIII but was administered 12 different medications for the acute coronary syndrome and related procedures.

Study BO39182 (HAVEN-4): A multicenter, open label, phase III study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab given every 4 weeks (Q4W) in patients with haemophilia A.

Methods

Study participants

Inclusion criteria

- Diagnosis of severe congenital haemophilia A or haemophilia A with FVIII inhibitors
    - Aged ≥ 12 years
    - Body weight ≥ 40 kg at screening
- Patients using rFVIIa or willing to switch to rFVIIa as primary bypassing agent for the treatment of breakthrough bleeds
- FVIII inhibitor test during screening with titre results available prior to first administration of study drug
- Laboratory:
    - Platelet count >100,000 cells/µL, Haemoglobin > 8 g/dL
    - Bilirubin ≤ 1.5 ULN, AST & ALT ≤ 3 ULN
    - Creatinine ≤ 2.5 ULN, creatinine clearance ≥ 30 mL/min

Patients without FVIII inhibitors (< 0.6 BU/mL; < 1.0 BU/mL only for laboratories with an historical sensitivity cut-off for inhibitor detection of 1.0 BU/mL) who completed successful ITI must have done so ≥ 5 years before screening and must have no evidence of inhibitor recurrence (permanent or temporary) indicated by detection of an inhibitor > 0.6 BU/mL (> 1.0 BU/mL only for laboratories with an historical sensitivity cut-off for inhibitor detection of 1.0 BU/mL) since ITI.

For patients to be enrolled into PK run-in cohort:

current episodic treatment (FVIII or bypassing agents) at the time of entry into this study and documentation of details of episodic treatment for at least 24 weeks prior to entry into this study

For patients to be enrolled into the expansion cohort:

Documentation of details of prophylactic or episodic treatment (FVIII or bypassing agents) and the number of bleeding episodes for at least 24 weeks prior to entry into this study

For patients on an episodic regimen, ≥ 5 bleeds in the prior 24 weeks, regardless of inhibitor status

Exclusion criteria

- bleeding disorder other than haemophilia A
- Ongoing or planned ITI therapy
- Patients who are at high risk for thrombotic microangiopathy

- 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
- As described: concomitant disease, condition, significant abnormality on screening evaluations or laboratory tests, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the investigator/co-investigator, pose an additional unacceptable risk in administering study drug to the patient

Treatments

Study BO39182 was designed to investigate emicizumab prophylaxis (6 mg/kg) administered in a Q4W dosing regimen in patients with haemophilia A with or without inhibitors against FVIII.

The study consists of two parts: a PK run-in part followed by an expansion part.

PK Run-In Part

The PK run-in analysis was conducted after the 7 patients had completed 6 weeks in the study. Clinical data up to 10 April 2017; analysis conducted by the Sponsor on 12 May 2017

All enrolled patients were male with severe Haemophilia A. Five patients were White, and 2 patients were Asian. The median age of patients enrolled in the PK run-in was 37.0 years (range: 14-50 years). Overall, 6 patients were adults (≥ 18 years) and 1 patient was aged 14 years. There were 3 patients (42.9%) with FVIII inhibitors, and 4 patients (57.1%) without inhibitors.

All 7 patients had been on episodic treatment for haemophilia A in the last 24 weeks prior to enrolment. The median number of bleeding events in the last 24 weeks prior to study entry was 6.0 (range: 0-30). Six of 7 patients had at least one target joint. Bleeds were located in a total of five different joints; most commonly in the ankle, knee, and elbow.

At the CCOD for this Interim CSR (18 October 2017), the median efficacy period in the PK run-in was 35.43 weeks (range: 33.4-37.4 weeks) and the median observation period was 35.41 weeks (range: 33.4-37.4 weeks).

Expansion Part

The expansion part was conducted to further investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics in a separate cohort planned to consist of approximately 40 patients. A loading dose of 3 mg/kg emicizumab was administered QW for 4 weeks followed by maintenance dose of 6 mg/kg Q4W.

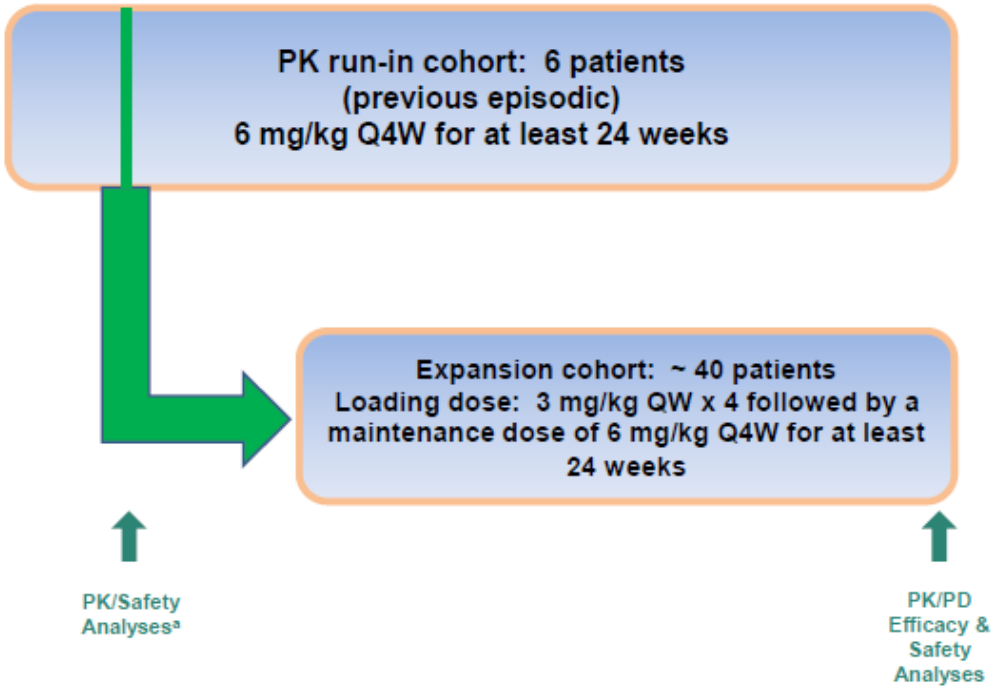
In weeks 1-25 (QW loading dose for 4 weeks and Q4W maintenance dose for 20 weeks) all administrations occurred with planned clinic visits; unassisted self-administration of the drug at the investigational site was supported.

In contrast to the PK run-in cohort, PK sampling was performed to investigate emicizumab trough concentrations (Ctrough) only.

The first patient was enrolled into the expansion part on 24 May 2017, and the last patient entered the study on 30 June 2017. An interim analysis is submitted, up to a CCOD of 18 October 2017.

Study design is summarised in the following diagram:

Figure 27: Study schema



PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; QW = every week.
[a] Analysis planned when 6th patient enrolled in the PK run-in cohort had been in the study for 6 weeks.

Rationale

The Q4W regimen option was investigated in this study in order to address current challenges concerning the limited adherence to prophylaxis in patients with haemophilia A (range from 44%-87%, references submitted).

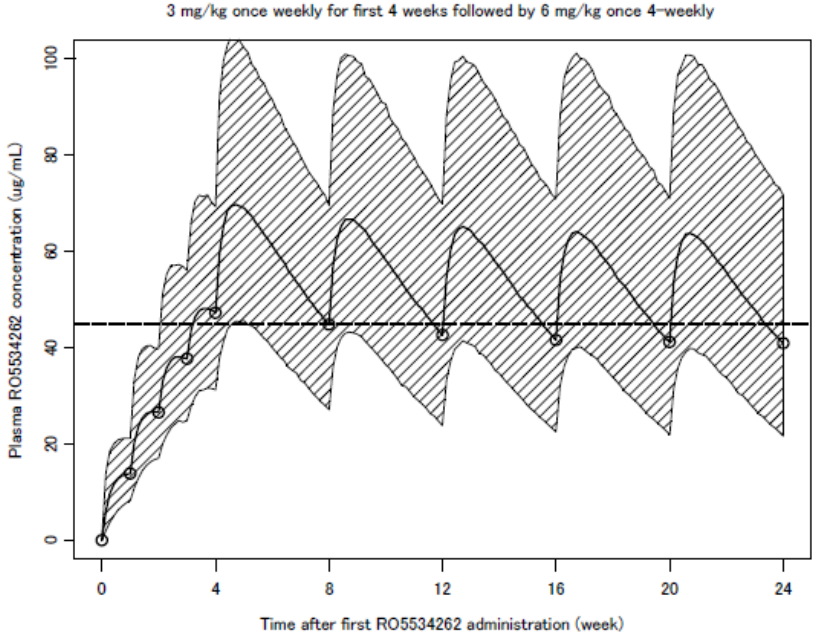
An SC Q4W maintenance regimen was investigated in this study in addition to the QW regimen and every 2 week (Q2W) regimen (which were investigated in other Phase III studies) to provide an option for patients to receive emicizumab Q4W, while maintaining the same cumulative dose.

The dosing regimens for this study were proposed based on modelling and simulation of the PK and efficacy data from patients participating in Part C of Phase I/II Study ACE001JP and its extension Study ACE002JP.

The dose of 6 mg/kg Q4W investigated in this study is equivalent in terms of cumulative dose to the dose levels of 1.5 mg QW or 3 mg/kg Q2W that have been evaluated in the other emicizumab Phase III studies (BH29884, BH29992, and BH30071). Assuming linear PK up to 6 mg/kg, model-based simulations were used to explore whether a Q4W dosing regimen could provide adequate efficacy.

The simulations suggest that a once-weekly loading dose of 3 mg/kg for the first 4 weeks, followed by a Q4W maintenance dose of 6 mg/kg would provide a maximum concentration at steady-state (Cmax) and area under the concentration-time curve within the dosing interval (AUCt) of 78.1 ± 20.9 µg/mL and 1570 ± 447 day*µg/mL, respectively.

Figure 28: Simulated plasma emicizumab concentration over time (Q4W dosing)



Q4W = every 4 weeks; RO5534262 = emicizumab.
Notes: dots and solid line = simulated median plotted at each trough sampling timepoint.
Shaded area = simulated 5- to 95-percentile range.
Broken line = target exposure level of 45 µg/mL.

The mode of action of emicizumab is identical in patients with haemophilia A irrespective of the presence of FVIII inhibitors, and data from the Phase I/II studies did not show a difference in pharmacokinetics, safety, or efficacy between patients with or without inhibitors against FVIII. Therefore, this study included patients with haemophilia A, regardless of their FVIII inhibitor status.

Patients previously treated with episodic FVIII or episodic bypassing agents were required to have ≥5 bleeds in the last 24 weeks prior to study entry to be eligible for enrolment into the expansion part. This requirement was intended to select a group of patients with haemophilia A who have a high, unmet medical need and to enable evaluation of adequate control of bleeding in this population.

Patients who had been on previous prophylactic treatment could enrol (in the expansion part only) without any requirement for a certain bleed number, because their bleeds should have been well controlled through receiving their current standard of care.

In order to exclude patients who might have a higher chance to show an immune response to foreign protein regimens (e.g. FVIII), patients without FVIII inhibitors who completed successful immune tolerance induction (ITI) ≥5 years before screening had to have no evidence of inhibitor recurrence (permanent or temporary), indicated by detection of an inhibitor, FVIII half-life < 6 hours, or FVIII recovery < 66% since ITI.

Dose modification was allowed only after completing 24 weeks on emicizumab treatment. All patients with suboptimal control of bleeding (≥ 2 qualifying bleeds within 24 weeks on emicizumab treatment) have the opportunity to increase their emicizumab maintenance dose to 3 mg/kg QW starting at Week 25 at the earliest, if they receive approval from the Medical Monitor.

There was also the option to return to a lower dose regimen.

As a measure of compliance, used and unused IMP vials were returned by study patients to the study site and appropriately accounted for.

During the study, patients could administer FVIII or bypassing agents or other haemophilia A medication to treat breakthrough bleeds, as a preventative dose before procedure / surgery or as preventative dose before activity. Data are summarised in the table below:

Table 34: Non-emicizumab haemophilia medication (expansion cohort)

APPROVED Non-emicizumab Hemophilia Medication, All Treated Patients, Expansion Cohort
Protocol: BO39182 Snapshot: j39182a Snapshot Date: 30NOV2017 Cutoff Date: 18OCT2017

	6 mg/kg emicizumab Q4W (N=41)
TOTAL	
Total number of patients with at least one treatment	24 (58.5%)
Total number of treatments	67
Purpose of the medication	
Preventative dose before activity	16 (39.0%)
Treatment for bleed	13 (31.7%)
FACTOR VIII (LONG-ACTING) [E.G. ELOCTA]	
Total number of patients with at least one treatment	4 (9.8%)
Total number of treatments	6
Purpose of the medication	
Preventative dose before activity	4 (9.8%)
FACTOR VIII (SHORT-ACTING) [E.G. ADVATE]	
Total number of patients with at least one treatment	19 (46.3%)
Total number of treatments	56
Purpose of the medication	
Preventative dose before activity	12 (29.3%)
Treatment for bleed	12 (29.3%)
RECOMBINANT FACTOR VIIA [E.G. NOVOSEVEN]	
Total number of patients with at least one treatment	1 (2.4%)
Total number of treatments	5
Purpose of the medication	
Treatment for bleed	1 (2.4%)

Patients in Expansion cohort have started with a loading dose of 3mg/kg QW for 4 weeks

The most commonly used non-emicizumab haemophilia medication while on study was short-acting FVIII (n = 19, 46.3%). Patients who received FVIII treatment (n = 18 of 19, 94.7%), used a peak dose of < 50 units/kg per treatment administration. The median number of doses administered was 2.0 (range: 1-11), and the median total cumulative dose was 69.2 units/kg (range: 13-252).

Short-acting FVIII was administered episodically as a treatment for bleeds. Most bleeds (n = 13 of 29 bleeds, 44.8%) were each treated with a cumulative dose < 25 units/kg, 9 bleeds (31.0%) were each treated with a cumulative dose of 25 to 50 units/kg, 6 bleeds (20.7%) were treated with a cumulative dose of 51 to 100 units/kg, and 1 bleed (3.4%) was treated with a cumulative dose of 101 to 150 units/kg. The median cumulative dose per bleed was 25.32 units/kg (range: 13.0-107.1), and the duration of treatment was 1 day for the majority (23 bleeds, 79.3%).

Table 35: Treatment with FVIII per treated bleed (expansion cohort)

APPROVED Treatment with Factor VIII per Treated Bleed, All Treated Patients, Expansion Cohort
Protocol: BO39182 Snapshot: j39182a Snapshot Date: 30NOV2017 Cutoff Date: 18OCT2017

	6 mg/kg emicizumab Q4W (N=41)			
	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)	35.90 (24.84)		NE (NE)	35.90 (24.84)
Median	25.32		NE	25.32
Min - Max	13.0 - 107.1		NE - NE	13.0 - 107.1
Cumulative Dose of Long-Acting FVIII administered per bleed [UNIT/kg]				
n		0	0	0
Cumulative Dose of Short-Acting FVIII administered per bleed [UNIT/kg]				
n	29		0	29
<25	13 (44.8%)		0	13 (44.8%)
25-50	9 (31.0%)		0	9 (31.0%)
51-100	6 (20.7%)		0	6 (20.7%)
101-150	1 (3.4%)		0	1 (3.4%)
>150	0		0	0
Cumulative Dose of Long-Acting FVIII administered per bleed [UNIT/kg]				
n		0	0	0
<25		0	0	0
25-50		0	0	0
51-100		0	0	0
101-150		0	0	0
>150		0	0	0
Duration of Short-Acting FVIII per bleed (days)				
n	29		0	29
1	23 (79.3%)		0	23 (79.3%)
2	2 (6.9%)		0	2 (6.9%)
3	2 (6.9%)		0	2 (6.9%)
4	1 (3.4%)		0	1 (3.4%)
>4	1 (3.4%)		0	1 (3.4%)
Duration of Long-Acting FVIII per bleed (days)				
n		0	0	0
1		0	0	0
2		0	0	0
3		0	0	0
4		0	0	0
>4		0	0	0

n is the number of cumulative doses administered to treat a bleed.
Patients in Expansion cohort have started with a loading dose of 3mg/kg QW for 4 weeks

Objectives

Study BO39182 (also known as HAVEN 4) is an ongoing multi-centre, open-label, non-randomized study designed to investigate the efficacy, safety, pharmacokinetics, pharmacodynamics, HRQoL, and patient preference of emicizumab prophylaxis (6 mg/kg) administered in a Q4W dosing regimen in patients with haemophilia A with or without inhibitors against FVIII.

The objectives of the PK run-in include the following:

- To investigate the pharmacokinetics of emicizumab after single and multiple (Q4W) SC administration of 6 mg/kg
- To assess the safety and tolerability of emicizumab after Q4W SC administration of 6 mg/kg

The efficacy objectives of the expansion part include the following:

- To evaluate the efficacy of prophylactic emicizumab on [described] aspects of bleeding

Sample size

The analysis populations for the PK run-in and expansion parts were not pooled. Each part is analysed separately.

The efficacy period for each patient started on the day of the first emicizumab dose and ended at the CCOD for this primary analysis, when the last enrolled patient reached 24 weeks of treatment.

The median duration of the efficacy period for the 41 patients included in the efficacy analysis was 25.57 weeks (range: 24.1-29.4 weeks), as shown below:

Table 36: Efficacy period duration (expansion cohort)

APPROVED Efficacy Period, All Treated Patients, Expansion Cohort
Protocol: BO39182 Snapshot: j39182b Snapshot Date: 14FEB2018 Cutoff Date: 15DEC2017

	6 mg/kg emicizumab Q4W (N=41)
Efficacy Period (weeks)	
n	41
Mean (SD)	25.98 (1.47)
Median	25.57
Min - Max	24.1 - 29.4
Efficacy Period (week categories)	
>0 w	41 (100%)
>=4 w	41 (100%)
>=12 w	41 (100%)
>=24 w	41 (100%)

n represents the number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
Patients in Expansion cohort have started with a loading dose of 3mg/kg QW for 4 weeks

Program: /opt/BIOSTAT/prod/cdt30064/t_ds_eff.sas
Output: /opt/BIOSTAT/prod/ct30064s/j39182b/reports/t_ds_eff_P1_TRT_EXP.out
15FEB2018 9:59 Page 1 of 1

At the CCOD all patients had received all 4 loading doses (i.e. one dose per week during the first 4 weeks) and at least six maintenance dose injections (Q4W).

Although permitted after an efficacy period of > 24 weeks per protocol, there were no dose up-titrations.

Randomisation

This was a single arm study.

Blinding (masking)

This was an open label study.

Statistical methods

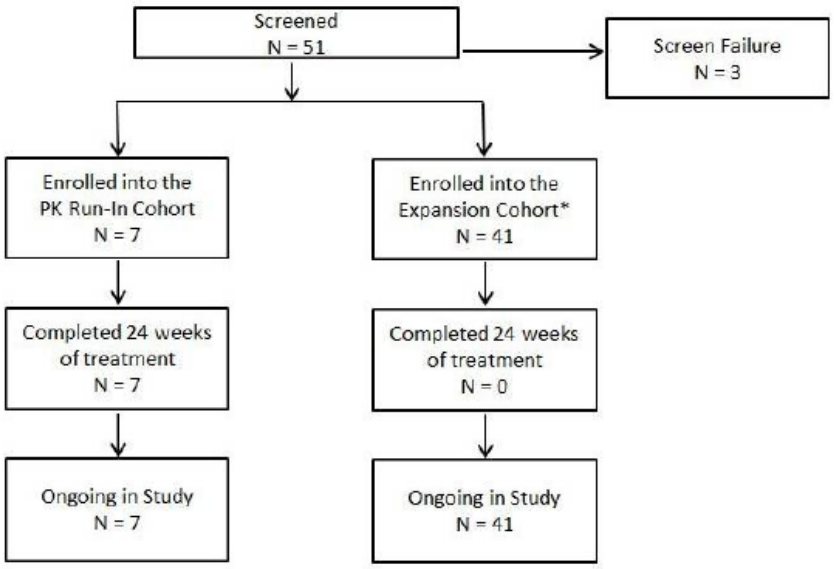
According to the protocol, optional interim analyses at various time points were permitted to support regulatory submissions. At the time of writing of this Interim CSR, the expansion part had completed enrolment but the *primary analysis had not yet been reached*. The primary analysis is planned to be conducted after the last enrolled patient completes the 24-week treatment period, is lost to follow-up, or has withdrawn, whichever occurs first.

Results

Participant flow

The overall patient disposition in Study BO39182 is shown below:

Figure 29: Patient disposition for study BO39182 (PK run-in expansion parts)



N = number of patients

* Note: Enrollment into the expansion part did not begin until completion of the pre-specified safety and PK analysis in the PK run-in part. Results of those analyses are presented in Section 4.

The reasons for screen failures were: expected failure to comply with visits (treatment plans), concomitant disease that interferes with conduct of the study, and patient decision.

At the CCOD, all 41 patients in the expansion part had started study treatment; however, none had completed more than 24 weeks of treatment.

Recruitment

Expansion Phase:

First Patient Entered: 24-May-2017

Last Patient Entered: 30-Jun-2017

Data cut-off: 15-Dec-2017

Conduct of the study

Protocol Amendments

The original study Protocol BO39182 (Version 1) was approved on 24 March 2016.

Protocol amendment 1 (version 2) was approved on 19 November 2016. The amendment included safety information on thromboembolic and thrombotic microangiopathy events observed in Study BH29884.

[The first patient enrolled into the study in January 2017 and so no patients were enrolled under Protocol version 1.]

Protocol Amendment 2 was released on 25 July 2017 (Version 3) and included updated information on safety findings of thrombotic microangiopathy in Study BH29884 and ways to mitigate risks.

Clarifications on aPCC and anti-fibrinolytics use, on laboratory monitoring of coagulation status after any bypassing agent use and aspects of safety were added.

Baseline data

Table 37: Summary of demographics characteristics (expansion cohort)

	6 mg/kg emicizumab Q4W (N=41)
Sex	
n	41
Male	41 (100%)
Age (years)	
n	41
Mean	38.7
SD	15.7
SEM	2
Median	39.0
Min - Max	14 - 68
Age Category 1	
n	41
< 18	3 (7.3%)
>= 18	38 (92.7%)
Age Category 2	
n	41
< 65	38 (92.7%)
>= 65	3 (7.3%)
Race	
n	41
Asian	8 (19.5%)
Black or African American	1 (2.4%)
White	31 (75.6%)
Unknown	1 (2.4%)
Ethnicity	
n	41
Hispanic or Latino	2 (4.9%)
Not Hispanic or Latino	38 (92.7%)
Unknown	1 (2.4%)
Height (cm)	
n	41
Mean	171.96
SD	7.19
SEM	1.1
Median	173.00
Min - Max	154.6 - 191.0
Weight (kg)	
n	41
Mean	72.82
SD	13.32
SEM	2.1
Median	74.70
Min - Max	45.9 - 101.8
BSA (m2)	
n	41
Mean	1.85
SD	0.18
SEM	0.0
Median	1.86
Min - Max	1.5 - 2.2
BMI (kg/m2)	
n	41
Mean	24.59
SD	4.17
SEM	0.7
Median	23.97
Min - Max	17.5 - 33.2

n represents the number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
Patients in Expansion cohort have started with a loading dose of 3mg/kg QW for 4 weeks

All patients (N = 41) were male. Most (n = 31, 75.6%) were White. The median age of enrolled patients was 39.0 years (range: 14 – 68 years). Most (n = 38, 92.7%) were adults (aged ≥ 18 years), and 3

patients (7.3%) were aged <18 years. There were 3 patients (7.3%) ≥65 years of age enrolled in the study.

A summary of haemophilia history is provided:

Table 38: Haemophilia A history (expansion cohort):

APPROVED Hemophilia History, All Treated Patients, Expansion Cohort
Protocol: BO39182 Snapshot: j39182a Snapshot Date: 30NOV2017 Cutoff Date: 18OCT2017

	6 mg/kg emicizumab Q4W (N=41)
Hemophilia severity at baseline	
n	41
Mild	1 (2.4%)
Moderate	0
Severe	40 (97.6%)
Patient Inhibitor Status at study entry	
n	41
Inhibitor	5 (12.2%)
Non-Inhibitor	36 (87.8%)
Time from Factor VIII inhibitor diagnosis date (months)	
n	11
Mean (SD)	234.67 (128.58)
Median	259.78
Min - Max	12.0 - 404.8
<24 months	2 (18.2%)
24-<48 months	0
48-<72 months	0
>=72 months	9 (81.8%)
Highest historical inhibitor titer	
n	11
Mean (SD)	1090.99 (2700.93)
Median	52.00
Min - Max	0.9 - 9000.0
n	41
<5 BU	2 (4.9%)
>=5 BU	9 (22.0%)
Unknown	15 (36.6%)
Missing	15 (36.6%)
Previously treated with ITI	
n	41
Yes	4 (9.8%)
No	37 (90.2%)
Time from most recent ITI date (years)	
n	4
Mean (SD)	5.856 (6.925)
Median	4.453
Min - Max	0.05 - 14.47

* Multiple answers are possible.
ITI = Immune Tolerance Induction.
n represents the number of patients contributing to summary statistics.
Percentages are based on n.
Patients in Expansion cohort have started with a loading dose of 3mg/kg QW for 4 weeks

Table 39: Haemophilia A history (expansion cohort continued):

APPROVED Hemophilia History, All Treated Patients, Expansion Cohort
Protocol: BO39182 Snapshot: j39182a Snapshot Date: 30NOV2017 Cutoff Date: 18OCT2017

	6 mg/kg emicizumab Q4W (N=41)
n	4
<2 years	2 (50.0%)
2-5 years	0
>5 years	2 (50.0%)
Unknown	0
Prophylactic/Episodic Status	
n	41
Prophylactic	30 (73.2%)
Episodic	11 (26.8%)
Prior episodic treatment in the last 24 weeks*	
n	19
Prothrombin complex concentrate	2 (10.5%)
Recombinant factor VIIA	1 (5.3%)
Factor VIII long acting	3 (15.8%)
Factor VIII short acting	14 (73.7%)
Cryoprecipitate	0
Fresh Frozen Plasma/Whole Blood	0
Other	0
Prior prophylactic treatment in the last 24 weeks*	
n	30
Prothrombin complex concentrate	2 (6.7%)
Recombinant factor VIIA	1 (3.3%)
Factor VIII long acting	5 (16.7%)
Factor VIII short acting	23 (76.7%)
Cryoprecipitate	0
Fresh Frozen Plasma/Whole Blood	0
Other	0

* Multiple answers are possible.
ITI = Immune Tolerance Induction.
n represents the number of patients contributing to summary statistics.
Percentages are based on n.
Patients in Expansion cohort have started with a loading dose of 3mg/kg QW for 4 weeks

40 patients (97.6%) had haemophilia classified by the investigator as severe. 11 patients (28.9%) on study had a history of FVIII inhibitor diagnosis. 6/11 patients did not test positive for FVIII inhibitors at study entry. Out of these 6 patients, 2 had undergone ITI. The mean time from FVIII inhibitor diagnosis was 234.7 months, with 9 of 11 patients diagnosed ≥ 72 months prior to study entry.

30 patients (73.2%) were categorized as being on prior prophylactic treatment, mainly short acting FVIII (23 patients, 76.7%).

Episodic treatment in the 24 weeks prior to the study start was recorded for 19 patients (11 patients who were on episodic treatment and 8 patients who were on prophylactic treatment), mostly short acting FVIII (14 patients, 73.7%).

Table 40: Summary of bleeding events in the last 24 weeks prior to study entry (expansion cohort):

APPROVED Bleeding Events in the Last 24 weeks Prior to Study Entry, All Treated Patients, Expansion Cohort
Protocol: BO39182 Snapshot: j39182a Snapshot Date: 30NOV2017 Cutoff Date: 18OCT2017

	6 mg/kg emicizumab Q4W (N=41)
Number of bleeds in the past 24 weeks	
n	41
Mean (SD)	9.0 (15.2)
Median	5.0
Min - Max	0 - 90
<9	28 (68.3%)
>=9	13 (31.7%)
Number of target joints prior to study entry	
n	41
Mean (SD)	1.4 (1.5)
Median	1.0
Min - Max	0 - 5
No target joint	16 (39.0%)
Any target joint(s)	25 (61.0%)
1 joint	8 (32.0%)
>1 joints	17 (68.0%)
Location of target joint(s) at study entry*	
n	25
Left shoulder	0
Left elbow	9 (36.0%)
Left wrist	0
Left fingers/thumb	0
Left hip	2 (8.0%)
Left knee	11 (44.0%)
Left ankle	5 (20.0%)
Left sole/heel	0
Left toes	0
Right shoulder	2 (8.0%)
Right elbow	9 (36.0%)
Right wrist	0
Right fingers/thumb	0
Right hip	2 (8.0%)
Right knee	3 (12.0%)
Right ankle	14 (56.0%)
Right sole/heel	0
Right toes	0

* 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).
Patients in Expansion cohort have started with a loading dose of 3mg/kg QW for 4 weeks

The median number of bleeds in the last 24 weeks prior to study entry was 5.0 (range: 0-90). 25 patients (61.0%) had at least one target joint. A total of 9 different target joint locations were reported; ankle, knee, and elbow were the most common target joint locations.

Outcomes and estimation

The efficacy period for each patient started on the day of the first emicizumab dose and ended at the CCOD for this primary analysis, when the last enrolled patient reached 24 weeks of treatment.

The median duration of the efficacy period for the 41 patients included in the efficacy analysis was 25.57 weeks (range: 24.1-29.4 weeks), as shown in the table below:

Table 41: Efficacy period duration (expansion cohort):

APPROVED Efficacy Period, All Treated Patients, Expansion Cohort
Protocol: BO39182 Snapshot: j39182b Snapshot Date: 14FEB2018 Cutoff Date: 15DEC2017

	6 mg/kg emicizumab Q4W (N=41)
Efficacy Period (weeks)	
n	41
Mean (SD)	25.98 (1.47)
Median	25.57
Min - Max	24.1 - 29.4
Efficacy Period (week categories)	
>0 w	41 (100%)
>=4 w	41 (100%)
>=12 w	41 (100%)
>=24 w	41 (100%)

n represents the number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
Patients in Expansion cohort have started with a loading dose of 3mg/kg QW for 4 weeks

At the CCOD all patients had received all 4 loading doses (i.e. one dose per week during the first 4 weeks) and at least six maintenance dose injections (Q4W).

Although permitted after an efficacy period of > 24 weeks per protocol, there were no dose up-titrations.

An overview of the ABR for all bleed-related efficacy endpoints is shown below:

Table 42: Overview of efficacy –Bleed related endpoints (expansion cohort):

APPROVED ABR Overview, All Treated Patients, Expansion Cohort
Protocol: BO39182 Snapshot: j39182b Snapshot Date: 14FEB2018 Cutoff Date: 15DEC2017

	6 mg/kg emicizumab Q4W (N=41)
Number of Patients	41
Treated Bleeds	
Patients with zero bleeds	23 (56.1%)
ABR, model based (95% CI)	2.4 [1.38; 4.28]
Mean ABR, Calculated (95% CI)	2.4 [0.38; 7.86]
Median ABR, Calculated (IQR)	0.0 [0.00; 2.08]
Min-Max, Calculated ABR	[0.00-32.07]
All Bleeds	
Patients with zero bleeds	12 (29.3%)
ABR, model based (95% CI)	4.5 [3.10; 6.60]
Mean ABR, Calculated (95% CI)	4.5 [1.35;10.96]
Median ABR, Calculated (IQR)	2.1 [0.00; 5.89]
Min-Max, Calculated ABR	[0.00-37.42]
Treated Spontaneous Bleeds	
Patients with zero bleeds	34 (82.9%)
ABR, model based (95% CI)	0.6 [0.27; 1.53]
Mean ABR, Calculated (95% CI)	0.6 [0.00; 4.93]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-8.21]
Treated Joint Bleeds	
Patients with zero bleeds	29 (70.7%)
ABR, model based (95% CI)	1.7 [0.82; 3.68]
Mean ABR, Calculated (95% CI)	1.7 [0.16; 6.79]
Median ABR, Calculated (IQR)	0.0 [0.00; 1.85]
Min-Max, Calculated ABR	[0.00-28.51]
Treated Target Joint Bleeds	
Patients with zero bleeds	35 (85.4%)
ABR, model based (95% CI)	1.0 [0.31; 3.26]
Mean ABR, Calculated (95% CI)	1.0 [0.02; 5.55]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-28.51]

Patients in Expansion cohort have started with a loading dose of 3mg/kg QW for 4 weeks

The NB model-based ABR for treated bleeds was 2.4 (95% CI: 1.38, 4.28), and the median ABR was 0.0 (IQR: 0.00, 2.08).

The majority of patients (n = 23, 56.1%) did not experience any treated bleeds while receiving emicizumab prophylaxis. In total, 90.2% (n = 37) of patients experienced 0 to 3 treated bleeds.

The model-based ABR for treated spontaneous bleeds was 0.6 (95% CI: 0.27, 1.53), and the median ABR was 0.0 (IQR: 0.00, 0.00). Most patients (n = 34, 82.9%) did not experience any treated spontaneous bleeds while receiving emicizumab prophylaxis, and 97.6% of patients experienced 0 to 3 treated spontaneous bleeds.

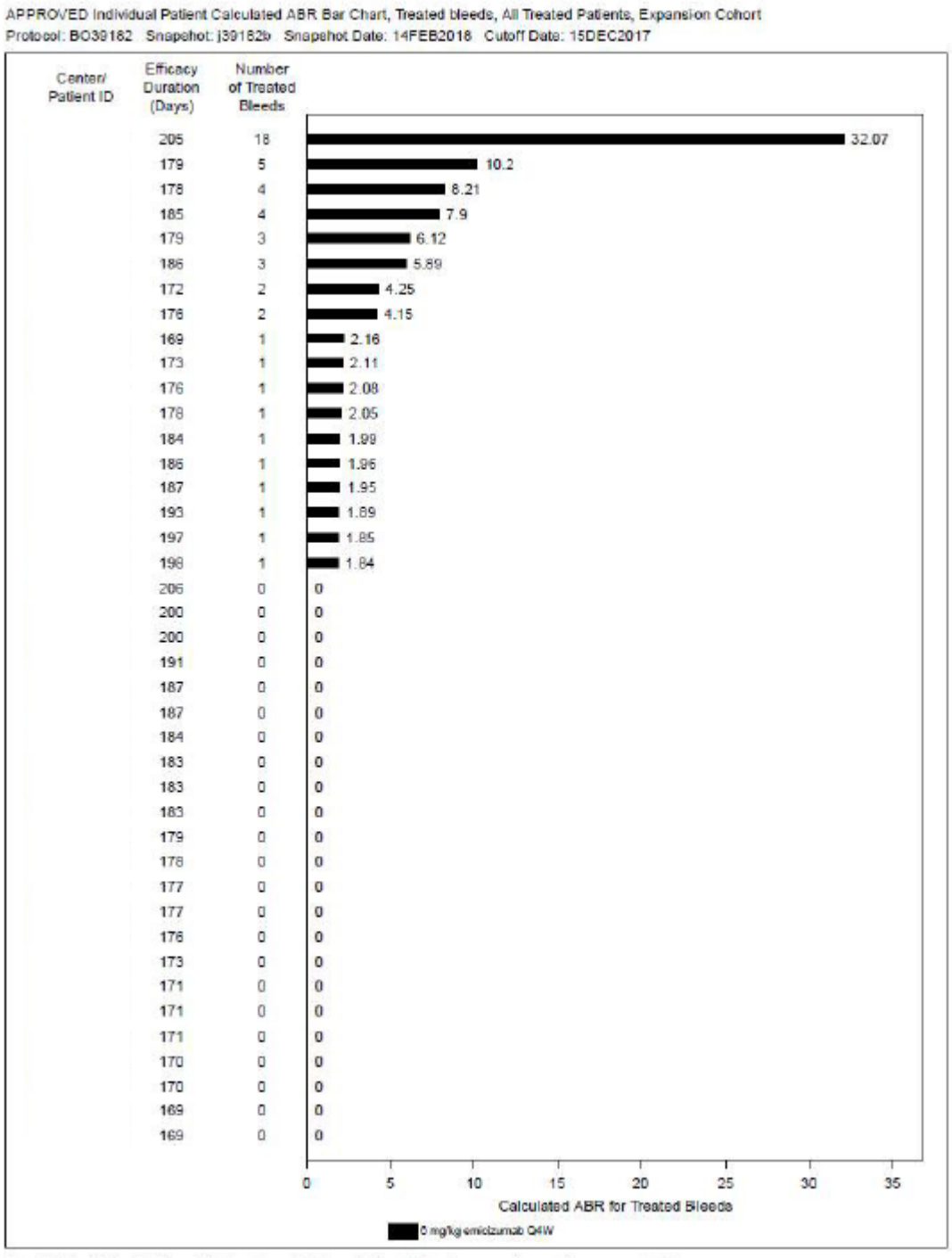
The model-based ABR was 1.7 (95% CI: 0.82, 3.68) for treated joint bleeds and 1.0 (95% CI: 0.31, 3.26) for treated target joint bleeds. The median ABR was 0.0 (IQR: 0.00, 1.85) for treated joint bleeds and 0.0 (IQR: 0.00, 0.00) for treated target joint bleeds

The model-based ABR for bleeds of type 'all bleeds' was 4.5 (95% CI: 3.10, 6.60), and the median ABR was 2.1 (IQR: 0.00, 5.89). Twelve (29.3%) patients experienced zero all bleeds. The majority of patients (n = 33, 80.5%) experienced 0 to 3 all bleeds.

Six patients had more than 2 treated bleeds. The majority of these bleeds were traumatic (27 out of 37 bleeds, 73%). One patient had 18 treated bleeds (ABR = 32.07), all of which were traumatic. For this patient, 16 out of the 18 treated bleeds were in target joints. No obvious risk factors have been identified for this patient.

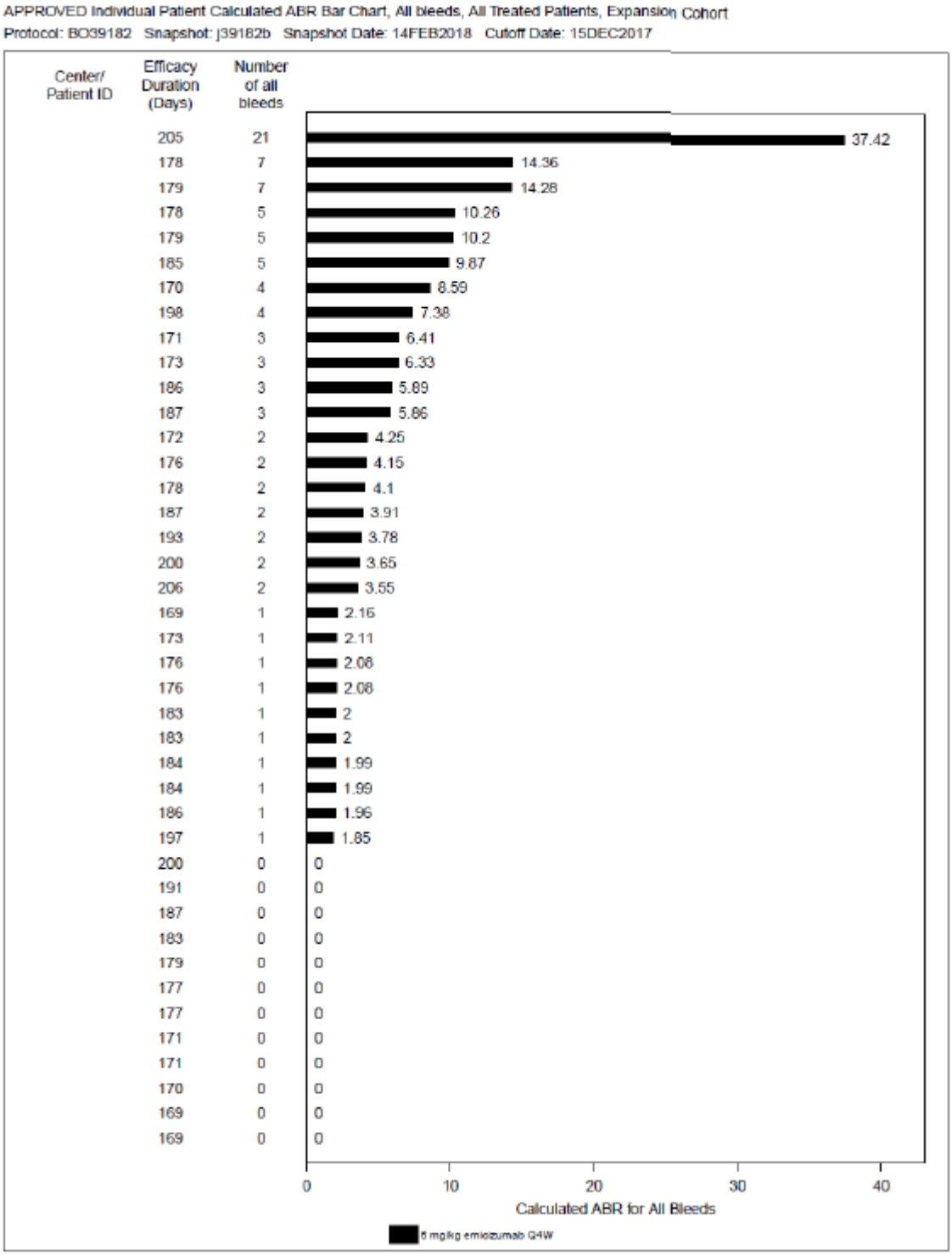
Twelve (29.3% [95% CI: 16.1, 45.5]) patients experienced 0 all bleeds (i.e. ABR = 0) while receiving emicizumab prophylaxis. The majority of patients (n = 33, 80.5%) experienced 0 to 3 bleeds, and the ABR was ≤ 10 in 87.8% (95% CI: 73.8, 95.9) of patients.

Figure 30: Calculated ABR in individual patients, treated bleeds (expansion cohort)



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

Figure 31: Calculated ABR in individual patients, all Bleeds (expansion cohort)



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

Haem-A-QoL (Patients aged 18 years or older)

At the time of the CCOD for this primary analysis, all of the 38 adult patients had completed the Haem-A-QoL questionnaires at baseline and at Week 13 visit. At Week 25 visit, 37 adult patients had completed the Haem-A-QoL questionnaires.

The mean (SD) Haem-A-QoL Total Score at baseline was 39.41 (17.91) and 26.32 (16.62) at Week 25, representing a numerical mean improvement from baseline of -13.62 (95% CI: -18.36, -8.88), an amount that was greater than the 7-point responder threshold, where lower scores are reflective of better HRQoL.

Taking into account the responder threshold of a 7-point change, 25 of 37 (67.6%) patients recorded an improvement larger than the responder threshold at Week 25.

Haemo-QoL-SF (Adolescents, 12-17 Years of Age)

At the time of the CCOD, all 3 adolescent patients (12−17 years of age) had completed the Haemo-QoL-SF questionnaire at the Week 25 visit. Given thesmall number of adolescent patients, the results from the HRQoL assessments should be interpreted with caution.

Low scores on Physical Health (denoting high levels of quality of life) were observed at baseline for each of the 3 adolescent patients who completed the Haemo-QoL-SF (18.8, 18.8, and 6.3). For the 2 patients reporting 18.8 at baseline, scores improved to 12.5 and 0.0 at Week 25. For the patient with a baseline score of 6.3, a reduction in Physical Health was observed at Week 25.

EQ-5D-5L Visual Analog Scale Results at Week 25

The mean (SD) EQ-5D-5L VAS Score at baseline was 74.39 (19.36) and 79.53 (15.27) at Week 25 representing a numerical improvement from baseline (5.53, 95% CI: 1.15, 9.90) as higher scores are reflective of better health state.

Fourteen of 40 patients (35.0%) reported an improvement in the EQ-5D-5L VAS Score between baseline and Week 25, which was larger than the responder threshold (7 points), indicating a clinically meaningful improvement. Improvements in VAS scores were observed for most patients.

EQ-5D-5L Index Utility Score at Week 25

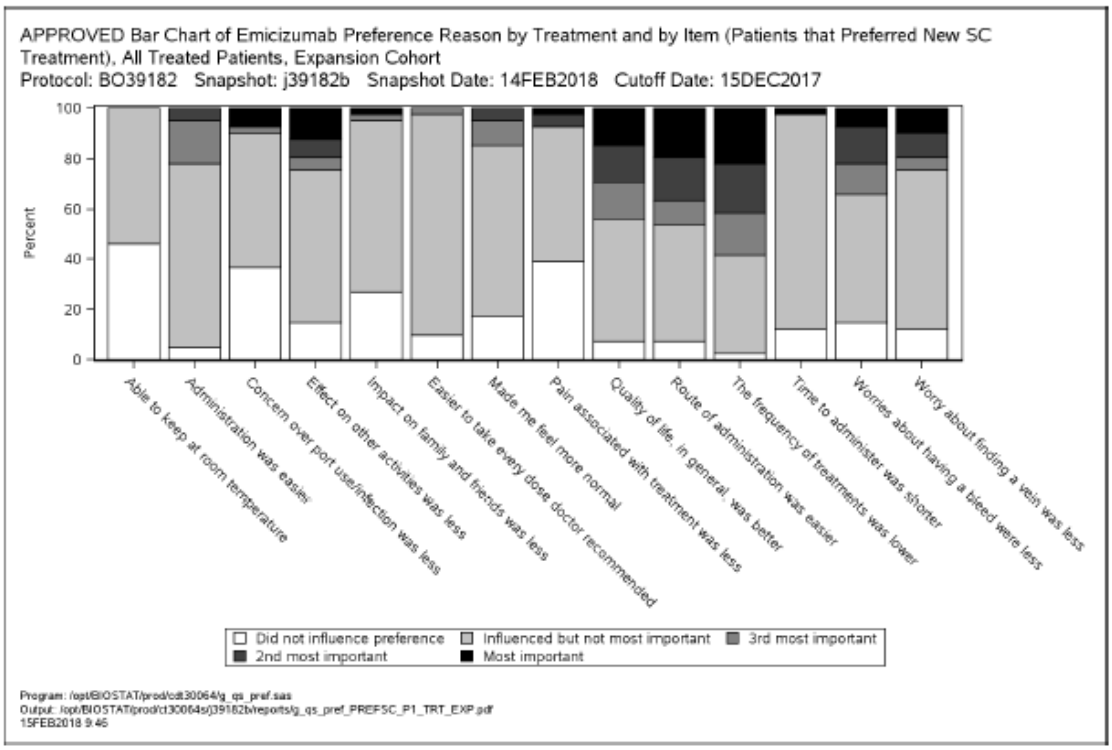
The mean (SD) EQ-5D-5L Index Utility Score at baseline was 0.69 (0.24) and 0.75 (0.22) at Week 25 representing a numerical improvement from baseline (0.06, 95%CI: 0.03, 0.10), as higher scores are reflective of better health status. Improvements in the Index Utility Scores were observed for most patients.

Nineteen of 40 patients (47.5%) reported an improvement in the EQ-5D-5L Index Utility Score between baseline and Week 25, which was larger than the responder threshold (0.07 points).

Emicizumab Preference Survey

The EmiPref survey was administered once during the study at Week 17. All 41 patients in the expansion cohort provided categorical responses. All patients (100%) preferred the Q4W emicizumab SC treatment.

Figure 32: Bar chart of emicizumab preference reason by treatment and by item (all treated patients)



The reasons selected most frequently as most important for preference to the new SC treatment were "the frequency of treatments was lower" (22.0%), followed by "the route of administration was easier" (19.5%), and "quality of life, in general, was better" (14.6%).

Number Of Days Away From School and / or Work

The number of days away from work was analyzed up to the Week 25 visit. Twenty eight (68.3%) patients were working at the time of enrolment. Twenty-seven patients (65.9%) were still working in the four weeks leading to Week 25; during which 61.0% of working patients reported not missing work (compared with 53.7% working patients who reported no missed working days at baseline).

The mean (SD) expected number of days at work was generally similar between baseline (15.46 [6.30]) and Week 25 (16.78 [6.02]). The mean number of days away from work at baseline was 0.75 compared with 0.15 at Week 25. The mean proportion of days away from work at baseline was 0.05 (95% CI: 0.01, 0.10), compared with 0.01 (95% CI: 0.00, 0.02) at Week 25.

Ten patients (24.4%) were enrolled in school at Week 25 (same as at baseline), and one patient missed a day of school while on study (compared with 6 patients [mean of 1.8 days away from school] at baseline).

The mean (SD) expected number of days at school at baseline was 13.70 (8.49) compared with 14.10 (7.74) at Week 25. The mean proportion of days away (with respect to expected school days) at baseline was 0.12 (95% CI: 0.01, 0.24), compared with 0.03 (95% CI: 0.00, 0.10) at Week 25.

Number Of Days Hospitalized

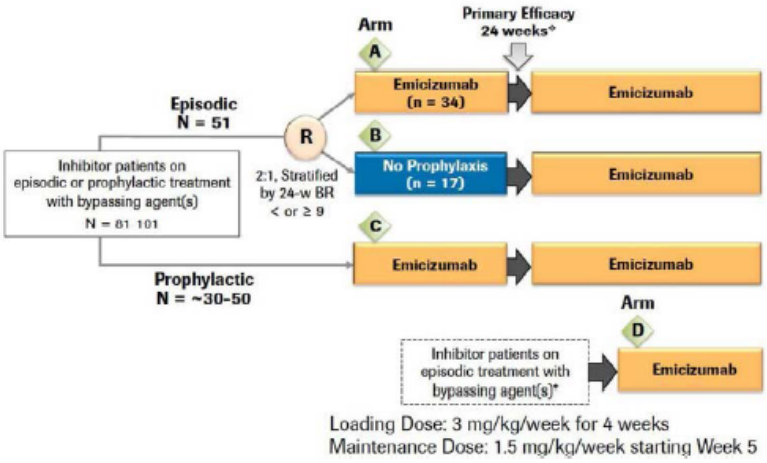
At the time of the clinical cut-off, no patients had been hospitalized.

Study BH29884 (HAVEN 1): A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients with inhibitors

Methods

This is a randomised, multicentre, open label, Phase III clinical study enrolling patients aged 12 years or older with haemophilia A who have inhibitors against FVIII,

Figure 33: Overview of study design – study BH29884



R = randomized; 24-w BR = 24-week bleed rate prior to study entry.
Source: Primary CSR

Study participants

Key inclusion criteria were diagnosis of congenital haemophilia A in patients age 12 and above of any severity and documented history of high-titre inhibitor (i.e. ≥5 BU); documentation of treatment with episodic or prophylactic bypassing agents for at least the last 24 weeks; ≥ 6 bleeds in the last 24 weeks prior to screening (if on an episodic bypassing agent regimen) or ≥2 bleeds in the last 24 weeks prior to screening (if on a prophylactic bypassing agent regimen).

Key exclusion criteria were ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with FVIII except for patients who had received a treatment regimen of FVIII prophylaxis with concurrent bypassing agent prophylaxis, as well as planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study.

The exclusion criteria were amended (amendment 2) to exclude patients who are at high risk of thrombotic microangiopathy (TMA) as part of the safety changes.

Treatments

The study evaluates prophylactic treatment with emicizumab at a dose of 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC thereafter. Emicizumab was administered as a SC injection in the lower abdomen, upper arm, or thigh at patient's discretion.

Dose-up titration was allowed after at least 24 weeks on emicizumab prophylaxis. Patients could increase their dose from 1.5 mg/kg QW to 3 mg/kg QW, if they met certain criteria (two spontaneous and clinically

significant bleeds after loading dose period of which one verified by physician) and received approval from the Medical Monitor.

Comparator

Historical comparison was used: Non-Interventional Study NIS BH29768 as described (see above).

Objectives

Primary objective:

The primary efficacy objective of this study was to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in patients with haemophilia A with inhibitors (Arms A and B) after 24 weeks of emicizumab treatment.

Secondary objectives:

The secondary efficacy objectives for this study was compare prophylactic emicizumab treatment with no prophylaxis (Arms A and B) and to compare the bleed rate of prophylactic emicizumab treatment with bleed rate prior to study entry (intra-patient comparison; Arms A and C).

Exploratory objectives:

The exploratory efficacy objective for this study is to evaluate the impact of prophylactic emicizumab compared with no prophylaxis on school/work attendance and hospitalisation.

Outcomes / endpoints

Primary endpoint:

- Annualized bleed rate, defined as the number of treated bleeds over the efficacy period

Secondary endpoints:

- All bleeds, treated joint bleeds, treated target joint bleeds, treated spontaneous bleeds, and Haem-A-QoL, Haemo-QoL-SF and EQ- 5D-5L
- The number of days away from school/work and days hospitalized

Sample size

The total sample size for this study was based on both clinical rather than statistical considerations, considering the limited number of patients with haemophilia A with inhibitors available for participation in clinical studies and to collect sufficient data to assess the safety and efficacy of emicizumab. A sample size calculation was conducted to assess the adequacy of the randomised comparison.

Sample size calculations were performed for a range of values of λt and λc. A sample size of 45 patients, assuming a randomisation ratio of 2:1 (30 patients in Arm A and 15 patients in Arm B control), would achieve a power of more than 95% for λt and λc ranging from 1 to 4 and 18 to 30, respectively assuming patients were followed for 24 weeks.

The primary analysis included all randomised patients, regardless of their length of follow-up.

Randomisation

Patients were assigned to one of 4 treatment arms.

- Patients treated previously with an episodic regimen were randomized 2:1 to receive emicizumab prophylaxis (Arm A) or no prophylaxis (Arm B control), and stratified according to the number of bleeds they had experienced over the last 24 weeks prior to study entry (< 9 or ≥ 9 bleeds).
- Patients treated previously with a prophylactic regimen of bypassing agents were enrolled in Arm C to receive emicizumab prophylaxis.
- Patients who participated in non-interventional study (NIS) BH29768 and who were previously treated with bypassing agents but were unable to enrol in Arms A, B or C were enrolled into Arm D.

Blinding (masking)

This was an open label study.

Statistical methods

Analysis Populations

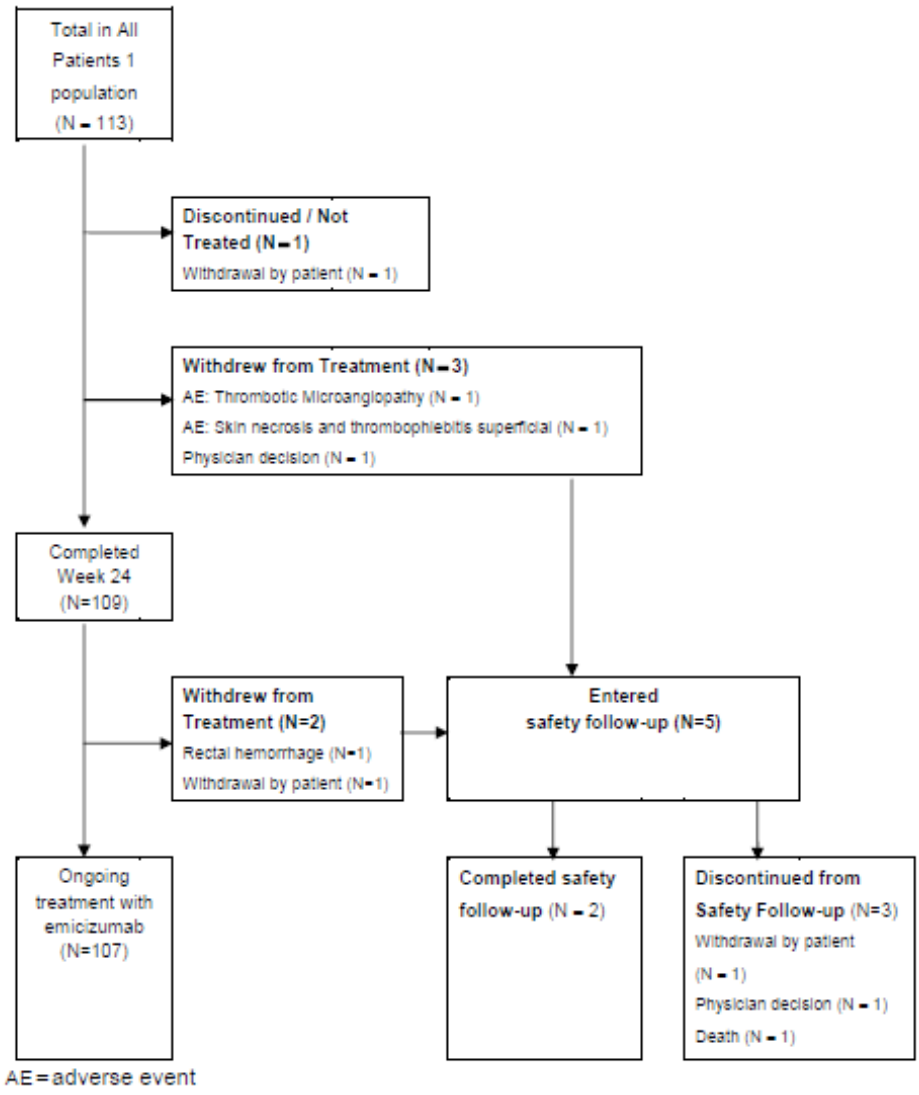
- All Patients (All Patients 1 = all patients randomized or enrolled)
- All Emicizumab Patients (All Patients 2 = includes Arms A, C, and D and Arm B patients who switched to receive emicizumab (Arm Bemi).)
- the Safety Population 2 all patients who received at least one dose of emicizumab, and for Arm B it includes only the patients who received at least one dose of emicizumab after completing the first 24 weeks with no emicizumab (Arm Bemi).

Results

Participant flow

Disposition is summarised in the following figure:

Figure 34: Patient disposition



AE = adverse event

Recruitment

First patient enrolled 18 Nov 2015

Last Patient Entered: 17 Mar 2017

Last Patient Randomized: 11 May 2016

Data cut-off: 08 Sep 2017

Patients were enrolled at 14 countries (44 investigational sites): Australia (2), Costa Rica (1), France (4), Germany (3), Great Britain (3), Italy (2), Japan (7), New Zealand (1), Poland (4), South Africa (1), South Korea (1), Spain (3), Taiwan (1), USA (11).

Conduct of the study

There were two amendments to the original protocol. Amendment 1 (21th of April 2016) introduced changes to the planned number of patients enrolled to Arm C and added Arm D. These are not considered to have impact on the outcome analyses. Amendment 2 (released on 30th of November 2016), after the data cut-off date, formalised the changes to administration of bypassing agents that were originally implemented via the DILs (from 7th and 17th of October 2016) following 4 patients who experienced SAEs (2 patients with thromboembolic events and 2 patients with thrombotic microangiopathy), considered to be related to the concomitant use of aPCC. Furthermore, a new efficacy objective to evaluate the clinical effect of emicizumab prophylaxis on the number of spontaneous bleeds over time (spontaneous bleed rate) was added. This was despite it being included as an endpoint in the SAP.

Protocol deviations

The total number of major protocol deviations were slightly lower in the control arm (ITT population: Arm B 16.7% vs 20% Arm A), due to the open label design. Procedural major protocol deviations were equally balanced between the two groups (Arm A 14.3% vs Arm B 16.7%); two patients in the Arm A had medication deviations.

Table 43: Major protocol deviation (ITT population) - study BH29884

Category Description	B: no prophylaxis (N=18)	A:1.5mg/kg emicizumab QW (N=35)
Total number of patients with at least one major protocol deviation	3 (16.7%)	7 (20.0%)
Total number of major protocol deviations	3	9
Procedural		
Total patients	3 (16.7%)	5 (14.3%)
Total protocol deviations	3	6
Missing entire scheduled hematology/chemistry labs	1 (5.6%)	3 (8.6%)
Absent bleed/med data for > 2 consecutive weeks	2 (11.1%)	0
Missing baseline EQ-5D-5L, HRQoL questionnaires	0	2 (5.7%)
>= 2 absent periodic EQ-5D-5L, HRQoL questionnaires	0	1 (2.9%)
Medication		
Total patients	0	2 (5.7%)
Total protocol deviations	0	3
Dose/sched. deviations: study drug or hemoph. med.	0	2 (5.7%)
Study drug not received, delayed w/o med rationale	0	1 (2.9%)

Percentages are based on N in the column headings.
Arm B: includes no prophylaxis period only.
Includes data before up-titration only, for patients whose dose was up-titrated.
Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks

Table 44: Major Protocol Deviations (All Emicizumab Patients) –study BH29884

Category Description	A:1.5mg/kg emicizumab QW (N=35)	B:1.5mg/kg emicizumab QW (N=13)	C:1.5mg/kg emicizumab QW (N=49)	D:1.5mg/kg emicizumab QW (N=7)	Total (N=104)
Total number of patients with at least one major protocol deviation	7 (20.0%)	2 (15.4%)	10 (20.4%)	2 (28.6%)	21 (20.2%)
Total number of major protocol deviations	9	2	19	4	34
Procedural					
Total patients	5 (14.3%)	0	8 (16.3%)	2 (28.6%)	15 (14.4%)
Total protocol deviations	6	0	15	4	25
Missing entire scheduled hematology/chemistry labs	3 (8.6%)	0	2 (4.1%)	2 (28.6%)	7 (6.7%)
>= 2 absent periodic EQ-5D-5L, HRQoL questionnaires	1 (2.9%)	0	3 (6.1%)	0	4 (3.8%)
Absent bleed/med data for > 2 consecutive weeks	0	0	4 (8.2%)	0	4 (3.8%)
Missing baseline EQ-5D-5L, HRQoL questionnaires	2 (5.7%)	0	1 (2.0%)	1 (14.3%)	4 (3.8%)
(Arm C) Enrollment w/o prior Med Monitor approval	0	0	1 (2.0%)	0	1 (1.0%)
Medication					
Total patients	2 (5.7%)	2 (15.4%)	2 (4.1%)	0	6 (5.8%)
Total protocol deviations	3	2	4	0	9
Dose/sched. deviations: study drug or hemoph. med.	2 (5.7%)	0	1 (2.0%)	0	3 (2.9%)
Study drug not received, delayed w/o med rationale	1 (2.9%)	2 (15.4%)	0	0	3 (2.9%)
Received incorrect study drug or hemophilia med.	0	0	1 (2.0%)	0	1 (1.0%)
Received prohibited therapy	0	0	1 (2.0%)	0	1 (1.0%)

Percentages are based on N in the column headings.
Arm B: includes emicizumab prophylaxis period only.
Arm A, B and D patients on no previous prophylaxis; Arm C patients on previous prophylaxis with bypassing agent
Includes data before up-titration only, for patients whose dose was up-titrated.
Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks

Baseline data

Population: Haemophilia A patients aged ≥ 12 years with documented historical high-titre inhibitors (≥ 5 BUs) against FVIII who were treated with episodic or prophylactic bypassing agents prior to study entry, with ≥ 6 bleeds in the last 24 weeks prior to screening (if on an episodic bypassing agent regimen) or ≥ 2 bleeds in the last 24 weeks prior to screening (if on a prophylactic bypassing agent regimen).

Demographic characteristics are presented for the All Patients population (n=113):

Table 45: Summary of patient demographics (all patients 1)

t_dmt01_il02_ip23as1_ip13as1_ALL1 APPROVED Demographic Characteristics, All patients 1
Protocol: BH29884 Snapshot: k29884m Snapshot Date: 23OCT2017 Cutoff Date: 08SEP2017

Arm B: both periods; Before and after up-titration

	B: no prophylaxis (N=18)	A:1.5mg/kg emicizumab QW (N=35)	C:1.5mg/kg emicizumab QW (N=49)	D:1.5mg/kg emicizumab QW (N=11)	Total (N=113)
Sex					
n	18	35	49	11	113
Male	18 (100.0%)	35 (100.0%)	49 (100.0%)	11 (100.0%)	113 (100.0%)
Age (years)					
n	18	35	49	11	113
Mean	37.2	35.8	25.6	39.0	31.9
SD	13.7	13.9	16.8	16.1	16.2
SEM	3	2	2	5	2
Median	35.5	38.0	17.0	39.0	29.0
Min - Max	13 - 65	12 - 68	12 - 75	19 - 68	12 - 75
Age Category 1					
n	18	35	49	11	113
< 18	2 (11.1%)	4 (11.4%)	26 (53.1%)	0	32 (28.3%)
>= 18	16 (88.9%)	31 (88.6%)	23 (46.9%)	11 (100.0%)	81 (71.7%)
Age Category 2					
n	18	35	49	11	113
< 65	17 (94.4%)	34 (97.1%)	47 (95.9%)	10 (90.9%)	108 (95.6%)
>= 65	1 (5.6%)	1 (2.9%)	2 (4.1%)	1 (9.1%)	5 (4.4%)

Race					
n	18	35	49	11	113
American Indian or Alaska Native	0	0	1 (2.0%)	0	1 (0.9%)
Asian	3 (16.7%)	10 (28.6%)	8 (16.3%)	0	21 (18.6%)
Black or African American	4 (22.2%)	4 (11.4%)	3 (6.1%)	0	11 (9.7%)
Native Hawaiian or Other Pacific Islander	1 (5.6%)	0	0	0	1 (0.9%)
White	10 (55.6%)	21 (60.0%)	33 (67.3%)	11 (100.0%)	75 (66.4%)
Unknown	0	0	4 (8.2%)	0	4 (3.5%)
Ethnicity					
n	18	35	49	11	113
Hispanic or Latino	1 (5.6%)	4 (11.4%)	12 (24.5%)	1 (9.1%)	18 (15.9%)
Not Hispanic or Latino	17 (94.4%)	31 (88.6%)	37 (75.5%)	10 (90.9%)	95 (84.1%)
Height (cm)					
n	17	34	48	10	109
Mean	175.05	171.16	167.61	173.47	170.42
SD	7.83	9.23	10.15	6.75	9.57
SEM	1.9	1.6	1.5	2.1	0.9
Median	175.50	169.50	169.55	173.50	171.00
Min - Max	163.0 - 185.5	151.5 - 194.0	147.4 - 189.0	165.0 - 188.0	147.4 - 194.0
Weight (kg)					
n	18	35	49	11	113
Mean	81.64	75.86	67.56	69.61	72.57
SD	23.61	18.31	17.92	16.82	19.44
SEM	5.6	3.1	2.6	5.1	1.8
Median	79.45	72.00	65.50	70.00	71.40
Min - Max	55.9 - 156.3	51.1 - 131.2	40.1 - 108.2	51.0 - 109.0	40.1 - 156.3
BSA (m2)					
n	17	34	48	10	109
Mean	1.96	1.88	1.76	1.84	1.83
SD	0.25	0.23	0.26	0.19	0.25
SEM	0.1	0.0	0.0	0.1	0.0
Median	1.96	1.85	1.79	1.85	1.84
Min - Max	1.7 - 2.6	1.5 - 2.4	1.3 - 2.2	1.6 - 2.2	1.3 - 2.6
BMI (kg/m2)					
n	17	34	48	10	109
Mean	26.86	26.09	23.81	23.72	24.99
SD	7.99	5.66	4.99	5.97	5.89
SEM	1.9	1.0	0.7	1.9	0.6
Median	25.97	24.35	23.54	23.03	23.99
Min - Max	16.2 - 52.4	19.2 - 47.2	15.1 - 36.2	17.6 - 38.8	15.1 - 52.4

n represents the number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
Arm A and B patients on no previous prophylaxis randomized to emicizumab or no prophylaxis; Arm C patients on previous prophylaxis with bypassing agent; Arm D patients on no previous prophylaxis
Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks

Numbers analysed

113 patients in total enrolled (Arm A: 35, Arm B: 18, Arm C: 49, Arm D: 11 patients)

An additional 4 patients had been enrolled to Arm D of the study between the Primary CSR and the cut-off for this Update CSR; these patients' demographics were consistent with the previously described population.

Outcomes and estimation

The overall median efficacy period was 60.29 (range: 0.1 - 94.3) weeks.

Table 46: Efficacy period duration (all patients 2)

t_udst01_il03_ip22asl_ip11asl_ALL2 APPROVED Efficacy Period, All patients 2
Protocol: BH29884 Snapshot: k29884m Snapshot Date: 23OCT2017 Cutoff Date: 08SEP2017

Arm B: prophylaxis; Before up-titration

	A:1.5mg/kg emicizumab QW (N=35)	B:1.5mg/kg emicizumab QW (N=18)	C:1.5mg/kg emicizumab QW (N=49)	D:1.5mg/kg emicizumab QW (N=11)	Total (N=113)
Efficacy Period (weeks)					
n	35	18	49	11	113
Mean (SD)	65.31 (25.49)	45.79 (15.81)	65.38 (15.27)	40.84 (14.81)	59.85 (21.09)
Median	74.71	52.36	62.29	49.43	60.29
Min - Max	0.1 - 94.3	4.7 - 62.3	24.0 - 90.7	24.0 - 60.3	0.1 - 94.3
Efficacy Period (week categories)					
>0 w	35 (100.0%)	18 (100.0%)	49 (100.0%)	11 (100.0%)	113 (100.0%)
>=4 w	34 (97.1%)	18 (100.0%)	49 (100.0%)	11 (100.0%)	112 (99.1%)
>=12 w	32 (91.4%)	17 (94.4%)	49 (100.0%)	11 (100.0%)	109 (96.5%)
>=24 w	31 (88.6%)	17 (94.4%)	49 (100.0%)	11 (100.0%)	108 (95.6%)
>=36 w	28 (80.0%)	13 (72.2%)	46 (93.9%)	6 (54.5%)	93 (82.3%)
>=48 w	28 (80.0%)	13 (72.2%)	46 (93.9%)	6 (54.5%)	93 (82.3%)
>=74 w	20 (57.1%)	0	18 (36.7%)	0	38 (33.6%)

n represents the number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
Arm A, B and D patients on no previous prophylaxis; Arm C patients on previous prophylaxis with bypassing agent
Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks

The majority (82.3%) of patients had ≥ 48 weeks follow-up at cut-off.

Bleed Rates in All Emicizumab-Treated Patients

Model-based ABR (95% CI) for treated bleeds across all treatment arms in the all emicizumab-treated patients was 2.7 (1.64, 4.35), mean (95% CI) calculated ABR was 2.8 (0.53, 8.45). These results are consistent with those reported in the Primary CSR (4.6 and 4.7 respectively).

Median calculated ABR was zero for all endpoints (i.e., treated bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds), consistent with the Primary CSR.

Results are summarised in the following table:

Table 47: Annualised bleed rate overview (all patients 2)

	A:1.5mg/kg emicizumab QW (N=35)	B:1.5mg/kg emicizumab QW (N=18)	C:1.5mg/kg emicizumab QW (N=49)	D:1.5mg/kg emicizumab QW (N=11)	Total (N=113)
Number of Patients	35	18	49	11	113
Treated Bleed					
ABR, model based (95% CI)	2.2 [1.21; 4.01]	0.7 [0.27; 1.85]	3.4 [1.59; 7.36]	2.2 [0.38;12.93]	2.7 [1.64; 4.35]
Mean ABR, Calculated (95% CI)	3.0 [0.63; 8.80]	0.6 [0.00; 4.91]	3.5 [0.86; 9.57]	2.2 [0.32; 7.60]	2.8 [0.53; 8.45]
Median ABR, Calculated (IQR)	0.0 [0.00; 2.22]	0.0 [0.00; 0.96]	0.0 [0.00; 1.46]	0.0 [0.00; 1.01]	0.0 [0.00; 1.46]
Min-Max, Calculated ABR	[0.00-33.72]	[0.00-4.41]	[0.00-95.66]	[0.00-13.04]	[0.00-95.66]
All Bleed					
ABR, model based (95% CI)	4.1 [2.59; 6.58]	2.0 [1.18; 3.43]	4.7 [2.54; 8.71]	2.8 [1.04; 7.67]	4.1 [2.91; 5.79]
Mean ABR, Calculated (95% CI)	5.1 [1.71;11.87]	1.9 [0.20; 6.99]	4.9 [1.55;11.49]	2.9 [0.56; 8.56]	4.3 [1.23;10.64]
Median ABR, Calculated (IQR)	2.0 [0.00; 7.07]	1.0 [0.00; 3.04]	0.7 [0.00; 3.02]	0.9 [0.00; 4.05]	1.0 [0.00; 4.05]
Min-Max, Calculated ABR	[0.00-33.72]	[0.00-6.47]	[0.00-110.88]	[0.00-13.04]	[0.00-110.88]
Treated Spontaneous Bleed					
ABR, model based (95% CI)	0.9 [0.48; 1.55]	0.3 [0.10; 0.67]	2.2 [0.97; 5.16]	1.4 [0.16;11.78]	1.5 [0.89; 2.51]
Mean ABR, Calculated (95% CI)	1.3 [0.07; 6.15]	0.2 [0.00; 4.12]	2.4 [0.36; 7.78]	1.4 [0.08; 6.19]	1.6 [0.13; 6.58]
Median ABR, Calculated (IQR)	0.0 [0.00; 1.37]	0.0 [0.00; 0.00]	0.0 [0.00; 0.67]	0.0 [0.00; 0.00]	0.0 [0.00; 0.73]
Min-Max, Calculated ABR	[0.00-11.24]	[0.00-1.05]	[0.00-65.22]	[0.00-8.45]	[0.00-65.22]
Treated Joint Bleed					
ABR, model based (95% CI)	0.6 [0.20; 1.81]	0.2 [0.08; 0.75]	0.4 [0.16; 1.10]	0.9 [0.12; 6.48]	0.5 [0.28; 1.03]
Mean ABR, Calculated (95% CI)	0.9 [0.02; 5.44]	0.2 [0.00; 4.11]	0.5 [0.00; 4.62]	0.9 [0.01; 5.34]	0.6 [0.00; 4.87]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]	0.0 [0.00; 0.00]	0.0 [0.00; 0.00]	0.0 [0.00; 0.00]	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-14.25]	[0.00-1.76]	[0.00-8.70]	[0.00-7.39]	[0.00-14.25]
Treated Target Joint Bleed					
ABR, model based (95% CI)	0.1 [0.02; 0.39]	0.1 [0.03; 0.51]	0.3 [0.11; 0.98]	0.6 [0.10; 3.46]	0.3 [0.14; 0.67]
Mean ABR, Calculated (95% CI)	0.4 [0.00; 4.46]	0.1 [0.00; 3.90]	0.4 [0.00; 4.42]	0.6 [0.00; 4.83]	0.4 [0.00; 4.39]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]	0.0 [0.00; 0.00]	0.0 [0.00; 0.00]	0.0 [0.00; 0.00]	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-7.13]	[0.00-0.96]	[0.00-8.70]	[0.00-4.22]	[0.00-8.70]

Arm A: model based ABR according to the NB model including the comparator arm and stratification factor, corresponding to the primary and secondary endpoints.
Arm B: includes emicizumab prophylaxis period only.
Arm A, B and D patients on no previous prophylaxis; Arm C patients on previous prophylaxis with bypassing agent
Includes data before up-titration only, for patients whose dose was up-titrated.
Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks

Categorised Numbers of Bleeds

The following descriptive analyses of number of bleeds and ABR in the All Patients 2 population indicated that the majority of the patients experienced 0 - 3 bleeds for the following:

- Treated Bleeds Categorized Analysis and ABR: 85.0% of all patients receiving emicizumab treatment experienced 0-3 treated bleeds
- All Bleeds Categorized Analysis and ABR: 69.0% of all patients receiving emicizumab treatment experienced 0-3 all bleeds
- Treated Joint Bleeds Categorized Analysis and ABR: 96.5% of all patients receiving emicizumab treatment experienced 0-3 treated joint bleeds
- Treated Target Joint Bleeds Categorized Analysis and ABR: 96.5% of all patients receiving emicizumab treatment experienced 0-3 treated target joint bleeds
- Categorized Analysis of Treated Spontaneous Bleeds and ABR: 95.6% of all patients receiving emicizumab treatment experienced 0-3 treated spontaneous bleeds

58.1% of all bleeds reported in all emicizumab-treated patients during the study occurred in joints

About half of the bleeds (48.1%) were of spontaneous nature and half (48.6%) were of traumatic cause; the remainder were due to procedure/surgery.

Results of Health Status / Quality of Life / Days Away from Work or School / Days Hospitalized are consistent with the previous study report.

Overall, 5 patients had their dose up-titrated from 1.5 to 3 mg/kg/week.

Two patients were described in the Primary CSR.

- One patient had ≥2 spontaneous and clinically significant bleeds in the last 24 weeks on emicizumab, both of which occurred after the end of loading dose period. These bleeds were physician-verified based upon physical examination and discussion with the patient at the time of the bleeds; the patient was up-titrated after 27 weeks (Study Day 183). This patient had an ABR Treated Bleeds of 6.02 before up-titration and 0 after up-titration.
- One patient had ≥2 spontaneous and clinically significant non-limb-threatening joint bleeds after the loading dose period. These bleeds were verified based upon physician's assessment of the patient's condition; patient was up-titrated at Week 25 (Study Day 169). This patient had an ABR of 6.52 before up-titration and 0 after up-titration.

Three patients were up-titrated between the analysis presented in the Primary CSR and the cut-off for this Update CSR:

- One patient had ≥2 spontaneous and clinically significant bleeds in the last 24 weeks on emicizumab- both of which occurred after the end of loading dose period and presented an increased frequency of bleeds. These bleeds were physician-verified based upon physical examination and discussion with the patient at the time of the bleeds as well as diagnostic imaging and clinical examination; the patient was up-titrated after 25 weeks (Study Day 170). This patient had an ABR Treated Bleeds of 25.93 before up-titration and 0 after up-titration.
- One patient had ≥2 spontaneous and clinically significant bleeds in the last 24 weeks on emicizumab- both of which occurred after the end of loading dose period. The patient demonstrated significant haemophilic arthropathy and thickened synovium consistent with recurrent bleed events and increasing risk of additional bleeds. These bleeds were physician-verified based upon diagnostic imaging and discussion with the patient at the time of the bleeds; the patient was up-titrated after 25 weeks (Study Day 169). This patient had an ABR Treated Bleeds of 95.66 before up-titration and 25.75 after up-titration.
- One patient had ≥2 spontaneous and clinically significant bleeds in the last 24 weeks on emicizumab- both of which occurred after the end of loading dose period. The patient experienced non-limb threatening joint bleeds. These bleeds were physician-verified based upon clinical examination and discussion with the patient at the time of the bleeds; the patient was up-titrated after 25 weeks (Study Day 169). This patient had an ABR Treated Bleeds of 13.04 before up-titration and 5.92 after up-titration.

The mean model-based ABR (2.7 bleeds), and calculated ABR (2.8 bleeds) were consistent with the primary analysis (4.6 and 4.7 bleeds respectively):

Table 48: Summary of treated bleeds (annualised bleed rate) by clinical cut-off dates (all patients 2)

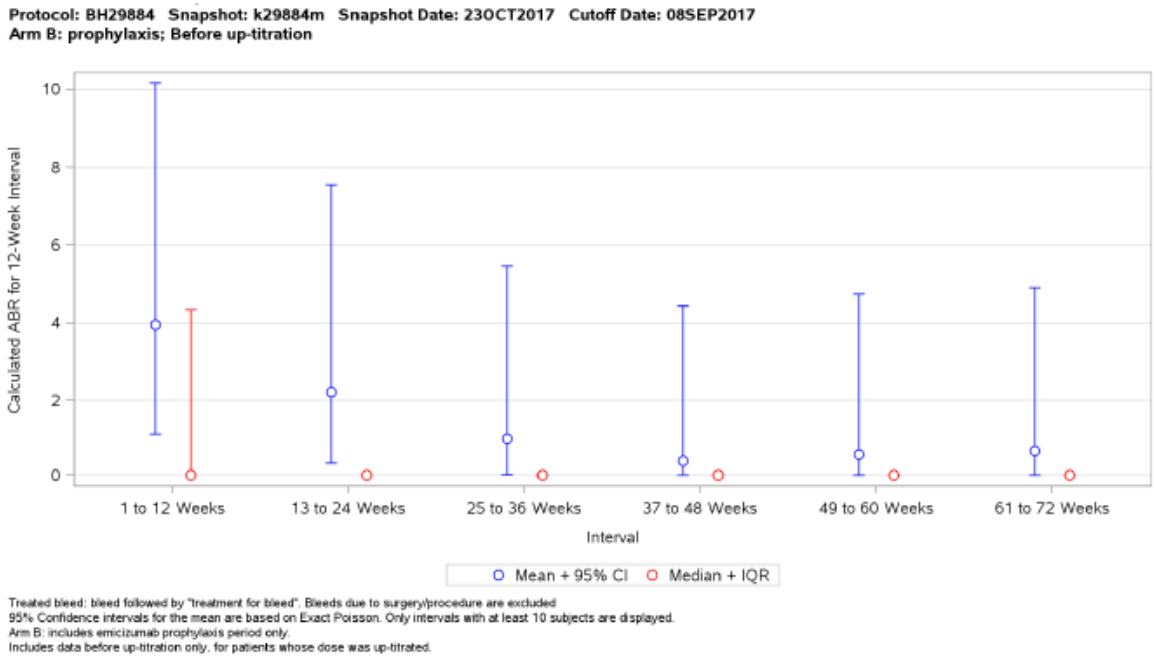
	Primary CSR CCOD 25 October 2016	Update CSR CCOD 08 September 2017
Number of Patients	104	113
Treated Bleed		
ABR, model based (95% CI)	4.6 (2.74, 7.57)	2.7 (1.64, 4.35)
Mean ABR, calculated (95% CI)	4.7 (1.47, 11.27)	2.8 (0.53, 8.45)
Median ABR, calculated (95% CI)	0.0 (0.00, 3.55)	0.0 (0.00, 1.46)
Min – Max, calculated ABR	0.00 – 98.72	0.00 – 95.66

ABR = annualized bleed rate; CCOD = clinical cutoff date; CI = confidence interval; CSR = clinical study report

Median calculated ABR was 0 for all endpoints (i.e., treated bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds) except for the 'all bleeds' endpoint.

Mean calculated ABRs for treated bleeds estimated over the last 12 weeks fell by Week 12 (i.e. first interval), and improvement was sustained beyond Week 48; whereas the median remained at zero. Assessment of the mean and median ABRs is provided by 12-week interval to describe the effect of emicizumab over time:

Figure 35: Mean and median calculated annualised bleed rate per 12-week interval, treated bleeds (all patients 2)



Mean calculated ABRs for treated bleeds estimated by interval decreased over time and the improvement was sustained up to Week 72; whereas the median remained consistently at zero.

These data demonstrate the long term efficacy of emicizumab and the decrease in ABR over time may explain the decrease seen on calculated ABR over the entire efficacy period when compared with the Primary CSR.

The percentage of patients with no treated bleeds over the last 12 weeks reached approximately 80% overall by Week 48, and remained consistent beyond Week 48, further underscoring long term efficacy of emicizumab over time.

Study BH29884 (HAVEN 1): A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients with inhibitors

Surgeries

The majority of all bleeds reported in all emicizumab-treated patients during the study occurred in joints (58.1%). When analysing the cause of all bleeds for all patients on emicizumab treatment, about half of the bleeds (48.1%) were of spontaneous nature and half (48.6%) were of traumatic cause; the remainder were due to procedure / surgery.

Table 49: Surgery replacement

	A:1.5mg/kg emicizumab QW (N=35)	B:1.5mg/kg emicizumab QW (N=18)	C:1.5mg/kg emicizumab QW (N=49)	D:1.5mg/kg emicizumab QW (N=11)	Total (N=113)
Total number of patients with at least one treatment	19 (54.3%)	5 (27.8%)	28 (57.1%)	3 (27.3%)	55 (48.7%)
Total number of treatments	351	26	652	30	1059
Purpose of the medication					
Treatment for bleed	19 (54.3%)	5 (27.8%)	24 (49.0%)	3 (27.3%)	51 (45.1%)
Preventative dose before activity	3 (8.6%)	2 (11.1%)	11 (22.4%)	0	16 (14.2%)
Preventative dose for procedure/surgery	4 (11.4%)	0	8 (16.3%)	0	12 (10.6%)
Prothrombin Complex Concentrate					
Total number of patients with at least one treatment	12 (34.3%)	1 (5.6%)	15 (30.6%)	1 (9.1%)	29 (25.7%)
Total number of treatments	115	6	111	1	233
Purpose of the medication					
Treatment for bleed	12 (34.3%)	1 (5.6%)	14 (28.6%)	1 (9.1%)	28 (24.8%)
Preventative dose before activity	0	1 (5.6%)	3 (6.1%)	0	4 (3.5%)
Preventative dose for procedure/surgery	1 (2.9%)	0	1 (2.0%)	0	2 (1.8%)
Recombinant Factor VIIa					
Total number of patients with at least one treatment	15 (42.9%)	5 (27.8%)	23 (46.9%)	3 (27.3%)	46 (40.7%)
Total number of treatments	225	20	538	29	812
Purpose of the medication					
Treatment for bleed	15 (42.9%)	5 (27.8%)	19 (38.8%)	3 (27.3%)	42 (37.2%)
Preventative dose before activity	3 (8.6%)	1 (5.6%)	8 (16.3%)	0	12 (10.6%)
Preventative dose for procedure/surgery	3 (8.6%)	0	7 (14.3%)	0	10 (8.8%)
Factor VIII (Short-acting)					
Total number of patients with at least one treatment	1 (2.9%)	0	1 (2.0%)	0	2 (1.8%)
Total number of treatments	11	0	3	0	14
Purpose of the medication					
Preventative dose for procedure/surgery	1 (2.9%)	0	0	0	1 (0.9%)
Treatment for bleed	0	0	1 (2.0%)	0	1 (0.9%)

Arm B: includes emicizumab prophylaxis period only.
Arm A, B and D patients on no previous prophylaxis; Arm C patients on previous prophylaxis with bypassing agent
Includes data before up-titration only, for patients whose dose was up-titrated.
Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks

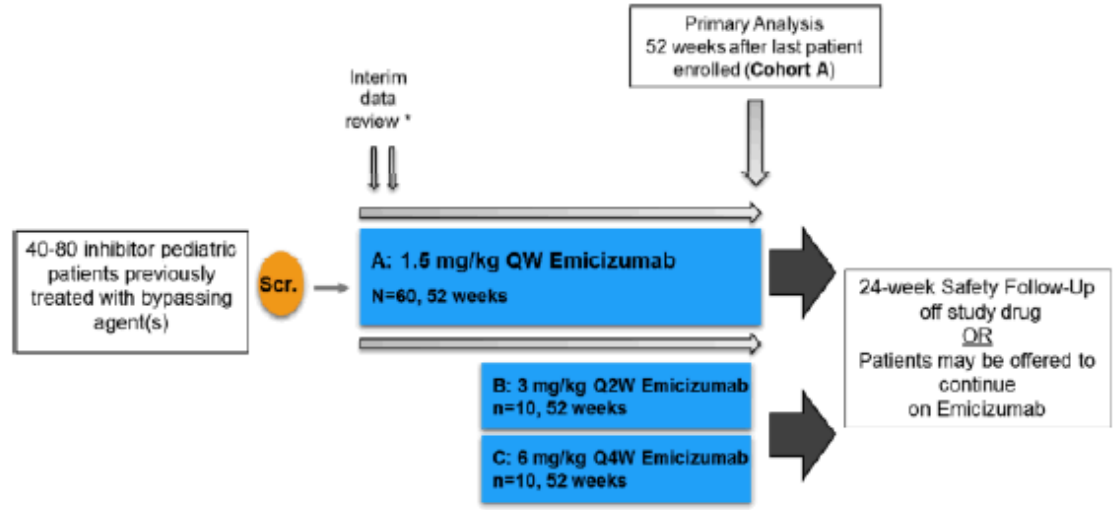
The use of concomitant non-emicizumab haemophilia A treatments was comparable with the Primary CSR.

Study BH29992 (HAVEN 2): A multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of subcutaneous administration of emicizumab in haemophilia A paediatric patients with inhibitors

Methods

A single-arm, multicentre, open-label, Phase III clinical study with the following design:

Figure 36: Study schema



JMC=Joint Monitoring Committee; Q2W=every 2 weeks; Q4W=every 4 weeks; QW=weekly; Scr=screening.

Study participants

Key inclusion/ exclusion criteria were similar to study BH29884. It is patients with a diagnosis of congenital haemophilia A with a body weight of less than 40 kg, but at least 3 kg, of any severity and documented history of high-titre inhibitor (i.e., ≥ 5 BU) and required treatment with bypassing agents. Criteria for past history of bleeding was different to study BH29884. For patients > 2 years of age, if on an episodic bypassing agent regimen this is: ABR of ≥ 6 (e.g., 3 bleeds in the last 24 weeks) or if on a prophylactic bypassing agent regimen, inadequately controlled (e.g., 2 bleeds since starting prophylaxis or 1 life-threatening bleed) or CVAD placement medically not feasible or deemed unsafe by investigator. For patients < 2 years determined by investigator to be in high unmet medical need. Adequate haematological, hepatic, and renal function.

Regarding ITI, contrary to study BH29884, patients awaiting initiation of ITI and patients in whom ITI had failed are eligible with a 72-hour washout period prior to the first emicizumab administration.

Treatments

A weekly loading dose of 3.0 mg/kg SC for the first 4 weeks (Day 1 of each week) followed by a maintenance dose of 1.5 mg/kg/week SC (Day 1 of each week) for cohort A. [subjects are not yet recruited to cohorts B and C (cohorts added as protocol amendment 3 dated 01 Sept 2017)].

Patients are to receive emicizumab for a minimum of 52 weeks.

Comparator Non- interventional study NIS BH29768

In the comparator study patients received treatment with aPCC or treatments with rFVIIa or both aPCC and rFVIIa (see above).

Objectives

The objectives of the study were to investigate (with no formal hypothesis testing) the efficacy, safety, and PK of once weekly SC administration of emicizumab in paediatric patients with haemophilia A with FVIII inhibitors who were receiving treatment with bypassing agents; with the following efficacy endpoints: to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate, with analysis for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds); to evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate (intra-patient comparison); to characterise the efficacy of up-titration on both an intra-patient and population level, also on the basis of the number of bleeds over time; to evaluate the HRQoL of children 8-17 years of age according to Haemo-QoL-Short Form (SF) (completed by patients); to evaluate proxy-reported HRQoL and aspects of caregiver burden using the Adapted Inhib-QoL Including Aspects of Caregiver Burden questionnaire for all children (completed by caregivers); to assess the number of days missed from day-care/school and days hospitalised.

Outcomes / endpoints

Table 50: *BH29992 study endpoints*

Endpoint	Definition	Primary Analysis Population
Treated bleeds	Treated bleeds that met 72HR	Treated population <12 years
All bleeds	Treated and non-treated bleeds that met 72HR	Treated population <12 years
Treated spontaneous bleeds	Treated bleeds with no known contributing factor (e.g., trauma, surgery) that met 72HR	Treated population <12 years
Treated joint bleeds	Treated bleeds where type = "joint" that met 72HR	Treated population <12 years
Treated target joint bleeds	Joint bleeds (as above) in a target joint at baseline (defined as ≥3 bleeds into the same joint over the last 24 weeks prior to study entry)	Treated population <12 years
Intra-patient comparisons	Treated bleeds (as above) All bleeds (as above) Treated spontaneous bleeds (as above) Treated joint bleeds (as above)	Intra-patient, NIS, Treated population <12 years Intra-patient, NIS, Treated population <12 years Intra-patient, NIS, Treated population <12 years
Adapted Inhib-QoL	Total score at 24 weeks*	Treated population <12 years
Haemo-QoL-SF	Total score and PHS at 24 weeks*	Treated population <12 years

Sample size

The sample size for this study was based on feasibility and clinical considerations. Hence, at least 20 children younger than 12 years of age and up to approximately 60 patients with haemophilia A with FVIII inhibitors who were receiving treatment with bypassing agents were to be enrolled in this study.

During the study, re-assessment of the initially specified sample size based on enrolment consideration was possible.

Randomisation

This was a single arm study.

Blinding (masking)

This was an open-label study.

Statistical methods

Analysis populations

The All Patients population and the Treated population were identical and comprised 63 patients treated with emicizumab, because no patients discontinued between enrolment and start of treatment. This was the main analysis population for safety analyses. The main analysis population for efficacy analyses was patients aged ≤12 years who had >12 weeks on study and comprised 59 patients (also referred to as "ABR Patients <12 years"). The other analysis populations are summarized in the Table below. No patients had their dose up-titrated.

Table 51: Overview of analysis populations

Population	n
All Patients	63
Treated Patients (Main analysis population for safety)	63
Treated Patients <12 Years (Main analysis population for HRQoL)	60
ABR Patients	62
ABR Patients <12 Years (Main analysis population for all bleed related endpoints)	59
NIS Patients	19
NIS Patients on Study BH29992 for ≥12 Weeks and <12 Years (Main intra-patient analysis population)	18
Patients ≤2 Years	10
Patients ≥12 Years and <40 kg Body Weight	3
Pharmacokinetic-Evaluable Patients	63
Individual Up-Titration Patients	0

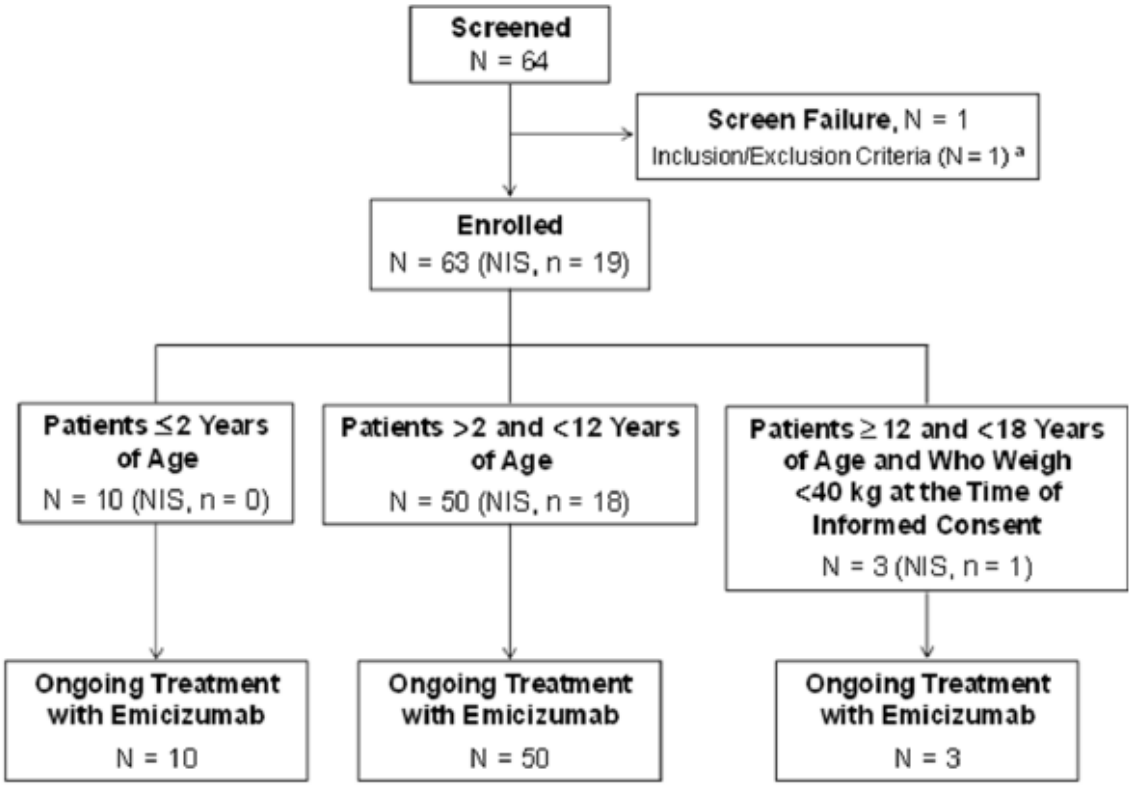
ABR=annualized bleed rate; HRQoL=health-related quality of life; NIS=non-interventional study.

19 patients had participated in the non-intervention study NIS BH29768. Eighteen (of the 19) patients had been on the study for at least 12 weeks at the time of the cut-off date and were included in the intra-patient comparison.

Results

Participant flow

Figure 37: Patient disposition CONSORT diagram



N=number of patients from Study BH29992; n=number of patients from NIS;

NIS=non-interventional study.

Note: Patients exposed to emicizumab started with loading dose 3 mg/kg/week for 4 weeks. All patient enrolled to date (Cohort A) received 1.5 mg/kg emicizumab QW.

[a] Patient did not fulfill the following inclusion criterion: Adequate hepatic function, defined as total bilirubin ≤1.5×age adapted ULN (excluding Gilberts syndrome) and AST and ALT≤3×age adapted ULN at the time of screening

Recruitment

First patient enrolled 22 Jul 2016

interim analysis cut-off date 05 Oct 2017

Patients were enrolled at 25 centres in the following countries: United States (8 sites), Japan (5), Turkey (3), France (2), Spain (2), Germany (1), Great Britain (1), Italy (1), South Africa (1), and Costa Rica (1).

Conduct of the study

Protocol amendment 3 was released on 01 Sept 2017

- Two cohorts (designated as Cohorts B and C; patients 2-11 years of age) have been added to the study to investigate additional, less frequent emicizumab dosing schedules (Q2W and Q4W), which would allow the option to select a preferred schedule, while still delivering the same cumulative dose.
- Approximately 80 patients are now planned to be included in the study, with 60 patients in Cohort A and 20 patients in the additional Cohorts B and C (10 patients each).
- The up-titration schema was modified with removal of the 2.25 mg/kg QW dosing level. This was based on an interim data review characterizing exposure at 1.5 mg/kg QW in patients 2-12 years of age to be similar to adolescent/adult patients. As such, the up-titration dose will be the same used in adolescent/adult patients (3 mg/kg QW).
- A new safety risk associated with emicizumab has been added as follows:

  Life-threatening bleeding due to unreliable standard coagulation tests and inhibitors assays in the setting of emicizumab. Coagulation laboratory tests (including, but not limited to, aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by Bethesda assay) are not reliable and are impacted by the presence of emicizumab and, therefore, are not reflecting the patients underlying haemostatic status accurately.

Protocol deviations

A total of 46 major protocol deviations occurred in 26 of 63 patients (41.3%) in the All Patients population (24 patients [38.1%] experienced 42 procedural deviations, 3 patients [4.8%] experienced 3 deviations relating to medication, and 1 patient [1.6%] experienced one deviation relating to inclusion criteria.

Numbers analysed

Table 52: Overview of analysis populations

Population	n
All Patients	63
Treated Patients (Main analysis population for safety)	63
Treated Patients <12 Years (Main analysis population for HRQoL)	60
ABR Patients	62
ABR Patients <12 Years (Main analysis population for all bleed related endpoints)	59
NIS Patients	19
NIS Patients on Study BH29992 for ≥12 Weeks and <12 Years (Main intra-patient analysis population)	18
Patients ≤2 Years	10
Patients ≥12 Years and <40 kg Body Weight	3
Pharmacokinetic-Evaluable Patients	63
Individual Up-Titration Patients	0

ABR=annualized bleed rate; HRQoL=health-related quality of life; NIS=non-interventional study.

19 patients had participated in the non-intervention study NIS BH29768. Eighteen (of the 19) patients had been on the study for at least 12 weeks at the time of the cut-off date and were included in the intra-patient comparison.

Table 53: Major protocol deviations (all patients)

t_pdt01_mde_ALL APPROVED Major Protocol Deviations, All Patients

Maintenance Dose at Enrollment
Protocol: BH29992 Snapshot: i29992r Snapshot Date: 16NOV2017 Cutoff Date: 05OCT2017

Category Protocol Deviation Term	1.5mg/kg emicizumab QW (N=63)
Total number of patients with at least one major protocol deviation	26 (41.3%)
Total number of major protocol deviations	46
Procedural	
Total patients	24 (38.1%)
Total protocol deviations	42
No EMQ data or emi data for > 2 consecutive weeks	11 (17.5%)
Any HRQoL questionnaires not completed	10 (15.9%)
Missing hematology or blood chemistry per SoA	8 (12.7%)
>2 consecutive PK missed in 1st 12wks of given emi	1 (1.6%)
Missing historical bleed rate at week 1 visit	1 (1.6%)
Medication	
Total patients	3 (4.8%)
Total protocol deviations	3
Received prohibited therapy	3 (4.8%)
Inclusion criteria	
Total patients	1 (1.6%)
Total protocol deviations	1
Adequate hematologic, renal and liver function	1 (1.6%)

Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks
Percentages are based on N in the column headings.

Baseline data

Table 54: Summary of demographic characteristics (all patients)

t_dmt01_mde_ALL APPROVED Demographic Characteristics, All Patients

Maintenance Dose at Enrollment
Protocol: BH29992 Snapshot: i29992r Snapshot Date: 16NOV2017 Cutoff Date: 05OCT2017

	1.5mg/kg emicizumab QW (N=63)
Sex	
n	63
Male	63 (100.0%)
Age (years)	
n	63
Mean	6.6
SD	3.5
SEM	0
Median	7.0
Min - Max	1 - 15
Age Category 1 (years)	
n	63
0 - <2	5 (7.9%)
2 - <6	17 (27.0%)
6 - <12	38 (60.3%)
>=12	3 (4.8%)
Age Category 2 (years)	
n	63
0 - <=2	10 (15.9%)
>2	53 (84.1%)
Age Category 3 (years)	
n	63
0 - <8	38 (60.3%)
>=8	25 (39.7%)
Race	
n	63
American Indian or Alaska Native	0
Asian	10 (15.9%)
Black or African American	11 (17.5%)
Multiple	2 (3.2%)
Native Hawaiian or other Pacific Islander	0
White	34 (54.0%)
Unknown	6 (9.5%)
Ethnicity	
n	63
Hispanic or Latino	5 (7.9%)
Not Hispanic or Latino	56 (88.9%)
Not Stated	1 (1.6%)
Unknown	1 (1.6%)

All enrolled patients were male.

A summary of haemophilia history is provided in the table below.

Table 55: Haemophilia A history (all patients)

t_uhht_01_mde_ALL APPROVED Hemophilia History, All Patients

Maintenance Dose at Enrollment
Protocol: BH29992 Snapshot: i29992r Snapshot Date: 16NOV2017 Cutoff Date: 05OCT2017

	1.5mg/kg emicizumab QW (N=63)
Number of hospitalization days in the last 24 weeks	
n	63
Mean (SD)	3.0 (10.2)
Median	0.0
Min - Max	0 - 66
n	63
0 days	47 (74.6%)
1-6 days	10 (15.9%)
>6 days	6 (9.5%)
Hemophilia severity at baseline	
n	63
Mild	2 (3.2%)
Moderate	1 (1.6%)
Severe	60 (95.2%)
Time from Factor VIII inhibitor diagnosis date [months]	
n	63
Mean (SD)	61.24 (37.85)
Median	64.33
Min - Max	0.5 - 142.4
n	63
<24 months	15 (23.8%)
24 - <48 months	11 (17.5%)
48 - <72 months	10 (15.9%)
>=72 months	27 (42.9%)
Highest historical inhibitor titer [BU]	
n	61
Mean (SD)	644.7 (1123.6)
Median	215.0
Min - Max	5 - 7200
n	63
<5 BU	0
>=5 BU	61 (96.8%)
Unknown	2 (3.2%)
Previously treated with ITI	
n	63
Yes	43 (68.3%)
No	20 (31.7%)
Time from most recent ITI date [years]	
n	40
Mean (SD)	3.78 (2.69)
Median	3.01
Min - Max	0.7 - 9.8
n	63
<2 years	14 (22.2%)
2-5 years	15 (23.8%)
>5 years	11 (17.5%)
Unknown	23 (36.5%)
Current treatment regimen	
n	63
Episodic	16 (25.4%)
Prophylactic	47 (74.6%)

Table 56: Haemophilia A history (all patients continued)

t_uhht_01_mde_ALL APPROVED Hemophilia History, All Patients

Maintenance Dose at Enrollment
Protocol: BH29992 Snapshot: i29992r Snapshot Date: 16NOV2017 Cutoff Date: 05OCT2017

	1.5mg/kg emicizumab QW (N=63)
Number of patients with prior episodic treatment in the last 24 weeks*	
n	28
Prothrombin complex concentrate	18 (64.3%)
Recombinant factor VIIa	24 (85.7%)
Factor VIII long acting	0
Factor VIII short acting	1 (3.6%)
Cryoprecipitate	0
Fresh Frozen Plasma/Whole Blood	0
Other	1 (3.6%)
Number of patients with prior prophylactic treatment in the last 24 weeks*	
n	47
Prothrombin complex concentrate	26 (55.3%)
Recombinant factor VIIa	17 (36.2%)
Factor VIII long acting	1 (2.1%)
Factor VIII short acting	9 (19.1%)
Cryoprecipitate	0
Fresh Frozen Plasma/Whole Blood	0
Other	7 (14.9%)
Reason for being only on episodic treatment*	
n	19
Availability	8 (42.1%)
Price / Reimbursement	3 (15.8%)
Tolerability / Side Effects	3 (15.8%)
Efficacy	5 (26.3%)
Frequency of Infusion / Half-Life	4 (21.1%)
Subject Request	2 (10.5%)
Venous Access	5 (26.3%)
Other	5 (26.3%)

Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks
ITI = Immune Tolerance Induction
n represents the number of patients contributing to summary statistics.
Percentages are based on n.
* Multiple answers are possible.

The majority of patients (95.2%) had severe haemophilia.

The mean time from FVIII inhibitor diagnosis was 61.24 months, with 27 patients (42.9%) diagnosed ≥72 months prior to study entry.

Patients with a documented history of high inhibitor titre were enrolled in this study. The mean highest historical inhibitor titre was 644.7 BU/mL. No patient had FVIII inhibitor titre <5 BU/mL.Overall, 43 patients (68.3%) had previously been treated with ITI. The majority (74.6%) of patients were treated with a prophylactic regimen prior to enrolment, with 16 patients (25.4%) previously on episodic treatment.

There was a median of 6 bleeds in the last 24 weeks prior to study entry (range: 0-155 bleeds).

Table 57: Summary of bleeding events in the last 24 weeks prior to study entry (all patients)

t_ubet_01_mde_ALL APPROVED Patient Bleeding Events in the Last 24 Weeks prior to Study Entry, All Patients

Maintenance Dose at Enrollment
Protocol: BH29992 Snapshot: i29992r Snapshot Date: 16NOV2017 Cutoff Date: 05OCT2017

	1.5mg/kg emicizumab QW (N=63)
Number of bleeds in the last 24 weeks	
n	63
Mean (SD)	11.1 (20.2)
Median	6.0
Min - Max	0 - 155
Number of target joints prior to study entry	
n	63
Mean (SD)	0.7 (1.1)
Median	0.0
Min - Max	0 - 5
No target joint	40 (63.5%)
Any target joint	23 (36.5%)
1 target joint	8 (34.8%)
>1 target joint	15 (65.2%)

The number of bleeds in the last 24 weeks prior to study entry was reported directly by the investigators and not collected prospectively. Overall, 23 patients (36.5%) had at least one target joint, and of those with target joints, 65.2% had >1 target joint.

Medical History Other than Haemophilia A

Overall, 37 of 63 patients (58.7%) reported at least one medical condition other than haemophilia. The most frequently reported conditions were haemophilic arthropathy (14.3%), seasonal allergy (9.5%), and iron deficiency anaemia (6.3%). All other medical conditions were each reported by <5.0% of the patients. One patient (#7013) experienced 4 events of haemorrhage intracranial prior to the study.

Previous medications were reported for 12 patients (19.0%), and analgesics was the most frequently reported class of medications, reported in 5 patients (7.9%).

Concomitant Medications other than for Haemophilia A

The majority of patients (53 patients, 84.1%) received at least one concomitant treatment after baseline. The most frequently reported class of medications was analgesics (30 patients, 47.6%) followed by vaccines, toxoids and serologic agents, antihistamines, and haemostatics (> 20% patients).

A total of 16 patients (25.4%) had vaccinations during the study. Of a total of 46 vaccinations received, 35 were SC, and 11 were intramuscular. Three AEs of vaccination site erythema were associated with the concomitant administration of SC vaccinations in 3 patients.

Numbers analysed

63 paediatric patients (60 patients < 12 years of age, including 10 patients ≤ 2 years, and 3 patients ≥ 12 years of age and < 40 kg) with congenital haemophilia A with FVIII inhibitors, who were receiving bypassing agents as a previous treatment.

Of the 63 patients, 19 patients had participated in the non-intervention study NIS BH29768.

Outcomes and estimation

The primary efficacy data is presented for the ABR Patients <12 Years population with at least 12 weeks of treatment (n=59). Results are summarised in the following table:

Table 58: Annualised bleed rate overview (treated patients aged < 12 years, ABR population)

t_ueft_ovabr_bm_mde_ABR_TRT1 APPROVED ABR Overview, ABR Population, Treated Patients Aged <12 Years

Maintenance Dose at Enrollment
Protocol: BH29992 Snapshot: i29992r Snapshot Date: 16NOV2017 Cutoff Date: 05OCT2017

	1.5mg/kg emicizumab QW (N=59)
Number of Patients	59
Treated Bleed	
ABR, model based (95% CI)	0.3 [0.13; 0.52]
Mean ABR, Calculated (95% CI)	0.3 [0.00; 4.20]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-4.54]
All Bleed	
ABR, model based (95% CI)	3.8 [2.20; 6.52]
Mean ABR, Calculated (95% CI)	3.8 [0.99; 9.95]
Median ABR, Calculated (IQR)	0.0 [0.00; 3.42]
Min-Max, Calculated ABR	[0.00-64.14]
Treated Spontaneous Bleed	
ABR, model based (95% CI)	0.0 [0.00; 0.17]
Mean ABR, Calculated (95% CI)	0.0 [0.00; 3.72]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-0.85]
Treated Joint Bleed	
ABR, model based (95% CI)	0.2 [0.07; 0.39]
Mean ABR, Calculated (95% CI)	0.2 [0.00; 4.08]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-4.54]
Treated Target Joint Bleed	
ABR, model based (95% CI)	0.1 [0.01; 0.65]
Mean ABR, Calculated (95% CI)	0.1 [0.00; 3.91]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-4.54]

Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks
ABR calculated for patients who have been on the study for at least 12 weeks on the same dose (including the loading doses).
Model based ABR according to the NB model.

Overall, 51 of the 59 patients (86.4%) had 0 treated bleeds (ABR=0) while receiving emicizumab prophylaxis. Eight patients (13.6%) had 11 treated bleeds, all but 1 were traumatic. No patient reported >2 treated bleeds.

The number of all bleeds experienced in the study was mainly driven by 4 patients (6.7%) who experienced >10 bleeds each. Of these, 1 patient experienced 36 bleeds, 1 patient experienced 17 bleeds, and 2 patients experienced 14 bleeds each.

Overall, 58 of 59 patients (98.3%) had reported 0 treated spontaneous bleeds (ABR=0). One patient (1.7%) experienced 1 treated spontaneous bleed (ABR of 0.85, efficacy period=431 days), categorized as “other” (left hip).

Overall, 53 of 59 patients (89.8%) reported 0 treated joint bleeds (ABR=0). Treated joint bleeds were reported by 6 patients with individual ABRs ranging from 0.88 to 4.54.

Similarly, 57 of 59 patients (96.6%) reported 0 treated target joint bleeds (ABR=0). Treated target joint bleeds were reported by 2 patients whose individual ABRs were 1.86 (efficacy period=196 days) and 4.54 (efficacy period=161 days).

Intra-patient comparison in study NIS BH29768

Nineteen patients enrolled in Study BH29992 had previously participated in non-intervention study NIS BH29768 and therefore had data available to serve as a historical comparator and allow for an intra-patient comparison. Of these, 18 patients were <12 years of age and had been in this study for at least 12 weeks at the time of the cut-off and were therefore included in the intra-patient comparison ("NIS Patients on BH29992 for ≥12 Weeks and <12 Years" population).

The efficacy period in NIS BH29768 for the 18 patients ranged from 61-309 days, while in Study BH29992, it ranged from 184-441 days. The median duration of efficacy period in Study BH29992 for the 18 patients was 59.0 weeks (range: 26.3-63.0).

Prior to enrolling in Study BH29992, 15 of 18 patients <12 years old were on prophylactic treatment with bypassing agents, and 3 patients were on episodic treatment with bypassing agents.

The negative binomial regression model analysis of treated bleeds in the intra-patient comparison showed a 98% reduction in bleed rate (i.e. ABR ratio of 0.02 [95% CI: 0.008; 0.043]) with emicizumab prophylaxis compared with previous prophylactic/episodic bypassing agent treatment:

Table 59: Negative binomial analysis of treated bleeds, intra-patient comparison, NIS patients, treated patients aged < 12 years

t_ueft_nb_CABRTR72_NIS_ABR_mde_TRT1_APPROVED Negative Binomial Analysis of Treated bleeds, Intra-Patient Comparison, NIS patients, ABR
Population, Treated Patients Aged <12 Years

Maintenance Dose at Enrollment
Protocol: BH29992 Snapshot: i29992r Snapshot Date: 16NOV2017 Cutoff Date: 05OCT2017

	Prophylactic/Episodic Bypassing Agents (N=18)		1.5mg/kg emicizumab QW (N=18)
Number of Patients	18		18
ABR, model based	19.8		0.4
95% CI	[15.31;25.69]		[0.15; 0.88]
ABR Ratio		0.02	
95% CI for the ratio between bleeding rates		[0.008;0.043]	
Difference in ABR		19.4	

Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks
Treated bleed: bleed followed by "treatment for bleed". Bleeds due to surgery/procedure are excluded.
Only patients who participated in the NIS BH29768 and in study BH29992 are included.

In NIS BH29768 the median ABR for treated bleeds was 16.2 (ABR range: 0 [illegible]45.85) and treated bleeds per patient ranged from 0 [illegible]30 bleeds. In contrast, for these same patients during participation in Study BH29992, the median ABR was 0 (range: 0-1.86) and most patients (14 of 18) had no treated bleeds. The number of treated bleeds per patient was no more than 2 for any patient (4 patients had treated bleeds, 2 of whom had 1 treated bleed each and the other 2 had 2 bleeds each). In these 4 patients, emicizumab prophylaxis decreased the ABR compared with NIS BH29768 by 95.9%, 94.5%, 90.3%, and 86.3%.

Table 60: Intra-patient ABR comparison of categorised number of bleeds and ABR, treated bleeds (treated patients aged < 12 years, ABR population

1_uipl_CABRTR72_NIS_mdl_ABR_TRT1 APPROVED Listing of Intra-patient ABR comparison, Treated Bleeds, NIS patients, ABR Population,
Treated Patients Aged <12 Years

Protocol: BH29992 Snapshot: i29992r Snapshot Date: 16NOV2017 Cutoff Date: 05OCT2017

Maintenance Dose at Enrollment: 1.5mg/kg emicizumab QW (N=18)

Center/ Patient ID	Duration of Efficacy Period in BH29768 (Days)	Number of Bleeds in BH29768	ABR in BH29768	Duration of Efficacy Period in BH29992 (Days)	Number of Bleeds in BH29992	ABR in BH29992	ABR % reduction
	239	30	45.85	196	1	1.86	95.94
	149	1	2.45	441	0	0.00	100.00
	118	4	12.38	431	2	1.69	86.31
	232	7	11.02	256	0	0.00	100.00
	128	5	14.27	427	0	0.00	100.00
	128	12	34.24	427	0	0.00	100.00
	79	2	9.25	409	1	0.89	90.34
	159	5	11.49	392	0	0.00	100.00
	252	10	14.49	226	0	0.00	100.00
	102	5	17.90	409	0	0.00	100.00
	280	19	24.78	184	0	0.00	100.00
	120	8	24.35	428	0	0.00	100.00
	115	10	31.76	417	2	1.75	94.48
	255	18	25.78	198	0	0.00	100.00
	309	12	14.18	185	0	0.00	100.00
	122	6	17.96	441	0	0.00	100.00
	138	12	31.76	427	0	0.00	100.00
	61	0	0.00	441	0	0.00	NA

Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks
ABR calculated for patients who have been on the study for at least 12 weeks on the same dose (including the loading doses).
Treated bleed: bleed followed by "treatment for bleed". Bleeds due to surgery/procedure are excluded.

Overall, for treated bleeds, 14 of 18 patients (77.8%) had experienced 0 bleeds in Study BH29992 (ABR=0) and 13 of 18 patients (72.2%) had a 100% reduction in ABR compared with the NIS. Fifteen patients (83.3%) had an ABR >10 in NIS BH29768 compared with 0 patients in Study BH29992.

Overall, all patients showed at least an 86% reduction in the ABR in Study BH29992 as compared to the NIS BH29768. One patient had an ABR of 0 while on prophylactic bypassing agent treatment in NIS BH29768 and on emicizumab prophylaxis in Study BH29992.

At the cut-off, 10 patients aged <2 years had been enrolled in the study and treated with emicizumab prophylaxis (Median: 23.86 weeks, range: 8.3-29.6 weeks).

Nine of these patients (90.0%) had an efficacy period of ≥12 weeks, and 5 patients (50.0%) had an efficacy period of ≥24 weeks. Only 1 patient <2 years of age had an efficacy period of <12 weeks (8.3 weeks) because enrolment in this age group was still open after the enrolment to Cohort A had been closed.

None of the 10 patients had a treated bleed or a spontaneous bleed. Two of the 10 patients reported at least one bleed (untreated), with a total of 5 traumatic non-joint, non-muscle bleeds, categorized as “other”.

In one of these patients, the 3 traumatic bleeds were located on the mouth, right shin, and forehead. In the other patient, the 2 traumatic bleeds were located on the right ear and mouth.

There were no spontaneous, joint, or muscle bleeds in this subgroup.

Patients ≥12 Years of Age (Weight <40 kg)

At the cut-off, 3 patients aged ≥12 years (weight <40 kg) had been enrolled in the study and treated with emicizumab prophylaxis. Of these 3 patients, 1 patient experienced 0 bleeds (over an efficacy period of 164 days), 1 patient experienced 1 bleed (over an efficacy period of 193 days), and 1 patient experienced 4 bleeds (over an efficacy period of 435 days) (

The patient with 4 bleeds had 2 treated bleeds, 1 of which was a traumatic bleed classified as “other” (non-joint, non-muscle) of the left cheek/face, and the other was a spontaneous muscle bleed in the lower left abdomen. The other patient had experienced 1 treated spontaneous bleed classified as “other” of the left fingers/thumb.

The compliance rate with electronic data collection was 92.3% for Adapted Inhib-QoL and 88.2% for Haemo-QoL SF.

Study BH29992 (HAVEN 2): A multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of subcutaneous administration of emicizumab in hemophilia A pediatric patients with inhibitors

Surgeries

Non- emicizumab Haemophilia medication in study BH29992

Medications for Haemophilia A: A total of 15 out of 63 patients received a haemophilia medication other than emicizumab during the study.

Table 61: Non-emicizumab haemophilia medication (treated patients)

t_ucmt02_mde_TRT APPROVED Non-emicizumab Hemophilia Medication, Treated Patients

Maintenance Dose at Enrollment
Protocol: BH29992 Snapshot: i29992r Snapshot Date: 16NOV2017 Cutoff Date: 05OCT2017

	1.5mg/kg emicizumab QW (N=63)
Total number of patients with at least one treatment	15 (23.8%)
Total number of treatments	43
Purpose of the medication	
Treatment for bleed	11 (17.5%)
Preventative dose before activity	4 (6.3%)
Preventative dose for procedure/surgery	2 (3.2%)
Prothrombin Complex Concentrate	
Total number of patients with at least one treatment	2 (3.2%)
Total number of treatments	2
Purpose of the medication	
Treatment for bleed	1 (1.6%)
Preventative dose for procedure/surgery	1 (1.6%)
Recombinant Factor VIIa	
Total number of patients with at least one treatment	14 (22.2%)
Total number of treatments	41
Purpose of the medication	
Treatment for bleed	11 (17.5%)
Preventative dose before activity	4 (6.3%)
Preventative dose for procedure/surgery	1 (1.6%)

Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks
Percentages are based on N.
Patient 3021 received one day treatment with Byclot (which contains both, Factor VII and Factor X). This dose is 4500 ug recorded under rFVIIa.

Of these, only 2 patients received aPCC (1 dose each: 32.82 units/kg for the treatment of a bleed; and 49.78 units/kg as a preventative dose for surgery/procedure). A total of 14 patients were treated with rFVIIa, mainly to treat bleeds (11 patients), rather than as preventative doses before activity (4 patients) or for surgery / procedure (1 patient). One patient (age 12 years, weight 38 kg) was treated with activated Factor VII concentrate containing factor X (FX) (Byclot), (1 dose; 113.07 µg/kg) to treat a bleed. This dose was recorded as rFVIIa, because Byclot is not currently included as a possible treatment category on the BMQ.

Summary of main studies

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 62: Summary of efficacy for study BH29884 (HAVEN-1)

Title: A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in haemophilia A patients with inhibitors		
Study identifier	BH29884 (HAVEN 1)	
Design	Open-label, four arm trial, with a randomized comparison (2:1) comparing emicizumab prophylaxis (Arm A) to no prophylaxis (Arm B) over a period of 24 weeks (ITT population); Arm C recruiting patients previously treated with prophylactic regimens of bypassing agents (allowing comparison with data from non-interventional study NIS29768); Arm D including patients unable to be enrolled in Arms A, B or C After 24 weeks, subjects in arm B were permitted to transfer to emicizumab; all other arms continued on emicizumab First patient entered: 18 Nov 2015 Last Patient Randomised: 11 May 2016 Emicizumab was administered at a weekly loading dose of 3.0 mg/kg SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC Timing for analysis: time length of exposure to emicizumab	
Treatments groups	Arm A	Emcizumab prophylaxis
	Arm B	Initially managed with no prophylaxis (episodic bypassing agents) and then transferred to emicizumab
	Arm C	Emicizumab prophylaxis
	Arm D	Emicizumab prophylaxis

Endpoints and definitions	Endpoints	treated bleeds (annualized bleed rate, defined as the number of treated bleeds over the efficacy period excl. bleeds due to surgery/ procedures) All bleeds treated joint bleeds treated target joint bleeds treated spontaneous bleeds
	Other endpoints	Haem-A-QoL Haemo-QoL-SF EQ-5D-5L
Database cut-off	08 Sept 2017	

Results

Analysis population:
All Emicizumab Patients ("All Patients 2" includes Arms A, C, and D and Arm B patients who switched to receive emicizumab (Arm Bemi).)

Time description:
The overall median efficacy period was 60.29 (range: 0.1 - 94.3) weeks.

Annualised bleed rate overview

Negative binomial model-based annualised bleed rate (95% CI) for treated bleeds across all treatment arms

82.3% of patients had ⩾ 48 weeks follow-up at study cut-off

ABR = 2.7 (1.64, 4.35)

Table 63: Summary of efficacy for study BH29992 (HAVEN-2)

Title: A multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of subcutaneous administration of emicizumab in haemophilia A paediatric patients with inhibitors	
Study identifier	BH29992 (HAVEN 2)

Design	Multi-centre, open label study, no comparator First patient entered: 22 Jul 2016 Emicizumab administered at a weekly loading dose of 3.0 mg/kg SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC subjects are not yet recruited to cohorts B (maintenance dose 3mg/kg q2w) and C (maintenance dose 6mg/kg q4w) Primary analysis will be at 52 weeks after last patient enrolled Study is on-going		
Treatments groups	Arm A		Emcizumab prophylaxis
Endpoints and definitions	Endpoints	treated bleeds [annualized bleed rate, defined as the number of treated bleeds over the efficacy period excl. bleeds due to surgery/ procedures] All bleeds treated joint bleeds treated target joint bleeds treated spontaneous bleeds	
	Other endpoints	Intra-patient comparison to results in non-interventional study Haem-A-QoL Haemo-QoL-SF EQ-5D-5L	
Database cut-off	05 Oct 2017		

Results

59 patients taking part

At the time of the cut-off date, no patient discontinued treatment or had their dose up-titrated.

For the ABR Patients <12 Years population, the median duration of the efficacy period was 29.6 weeks (range: 18.4-63.0). Most patients (79.7%) had an efficacy period ≥24 weeks.

Annualised bleed rate overview

Zero bleeds

Data on 59 paediatric subjects with at least 12 weeks exposure reported [open label, uncontrolled]

51/59 patients (86.4%) had 0 treated bleeds (annualised bleed rate =0) while receiving emicizumab prophylaxis.

58/59 patients (98.3%) had reported 0 treated spontaneous bleeds (annualised bleed rate =0)

Table 64: Summary of efficacy for study BH30071 (HAVEN-3):

Title: A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in haemophilia A patients without inhibitors			
Study identifier	BH30071 (HAVEN 3)		
Design	Open-label, multi-centre First patient entered: 27 Sept 2016 Emicizumab was administered at a weekly loading dose of 3.0 mg/kg SC for the first 4 weeks followed by a maintenance dose, described for each arm Primary efficacy analysis at 24 weeks		
Treatments groups	Arm A (previous management episodic)		Emcizumab prophylaxis at 3 mg/kg QW SC for 4 weeks, followed by 1.5 mg/kg QW SC maintenance
	Arm B (previous management episodic)		Emicizumab prophylaxis at 3 mg/kg QW SC for 4 weeks, followed by 3 mg/kg Q2W SC maintenance
	Arm C (previous management episodic)		No prophylaxis / control arm Able to switch to 3mg/kg emicizumab prophylaxis after 24 weeks
	Arm D (previous management prophylactic)		Emcizumab prophylaxis at 3 mg/kg QW SC for 4 weeks, followed by 1.5 mg/kg QW SC maintenance
Endpoints and definitions	Endpoints	treated bleeds [annualized bleed rate, defined as the number of treated bleeds over the efficacy period excl. bleeds due to surgery/ procedures] All bleeds treated joint bleeds treated target joint bleeds treated spontaneous bleeds	
	Other secondary endpoints	Intra-patient comparison to results in non-interventional study Haem-A-QoL physical Haemo-QoL-total EQ-5D-5L	
Database cut-off	11 Sept 2017		

Results

Over 94% of subjects have over 24 weeks of study time

Annualized bleed rates

Annualised bleed rate:

negative binomial model-based annualised bleed rate for all treated bleeds (excluding bleeds owing to surgery / procedures)

For 36 subjects exposed to 1.5mg/kg ecicizumab qw sc,
ABR = 1.5 (95% CI: 0.89, 2.47).

96% reduction compared with no prophylaxis (annualised bleed rate cohort A / cohort C ratio = 0.04; p < 0.0001)

For 35 subjects exposed to 3mg/kg ecicizumab q2w sc,
ABR = 1.3 (95% CI: 0.75, 2.27)

97% reduction compared with no prophylaxis (annualised bleed rate cohort B / cohort C ratio = 0.03; p < 0.0001)

For 18 subjects who did not receive prophylaxis
ABR = 38.2 (95% CI: 22.86, 63.76)

negative binomial model-based annualised bleed rate for all bleeds (excluding bleeds owing to surgery / procedures)

For 35 subjects exposed to 3mg/kg ecicizumab q2w sc
ABR = 2.6 (95% CI: 1.63, 4.29)

94% reduction compared with no prophylaxis (annualised bleed rate cohort B / cohort C ratio = 0.06; p < 0.0001)

For 18 subjects who did not receive prophylaxis
ABR = 47.6 (95% CI: 20.45, 79.59)

Table 65. Summary of efficacy for study 39182 (HAVEN-4)

Title: A multicenter, open-label, phase III study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab given every 4 weeks (Q4W) in patients with hemophilia A.			
Study identifier	BH39182 (HAVEN 4)		
Design	Single arm, open-label, multi-centre study A PK run-in phase was conducted on 7 patients for 6 weeks / these patients then went on to the 'expansion phase' An additional 41 patients were enrolled (and are on-going) in the 'expansion phase' First patient entered: 30 Jan 2016 Last Patient entered: 27 Feb 2017 Primary analysis at 24 weeks An interim report is submitted		
Treatments groups	PK arm		Emicizumab prophylaxis 6mg/kg SC q4w
	Expansion cohort		Emicizumab was administered at a weekly loading dose of 3.0 mg/kg SC for the first 4 weeks followed by a maintenance dose of 6 mg/kg/week SC q4w
Endpoints and definitions	Endpoints	treated bleeds (annualized bleed rate, defined as the number of treated bleeds over the efficacy period excl. bleeds due to surgery/ procedures) All bleeds treated joint bleeds treated target joint bleeds treated spontaneous bleeds	
	Other endpoint	Survey of patient preference	
Database cut-off	15-Dec-2017		

Results

Time period of exposure: the median duration of the efficacy period for the 41 patients included in the efficacy analysis was 25.57 weeks (range: 24.1-29.4 weeks).

At the CCOD all patients had received all 4 loading doses (i.e. one dose per week during the first 4 weeks) and at least six maintenance dose injections (Q4W).

Zero bleeds
41 patients in main study cohort [open label, uncontrolled]

56.1% patients did not experience any treated bleeds while receiving emicizumab prophylaxis.

90.2% (n = 37) of patients experienced 0 to 3 treated bleeds.

negative binomial model-based annualised bleed rate for treated bleeds

ABR = 2.4 (95% CI: 1.38, 4.28)

negative binomial model-based annualised bleed rate for all bleeds

ABR = 4.5 (95% CI: 3.10, 6.60)

Supportive studies

Supporting data were provided from the Phase I and I/II studies (ACE001JP, ACE002JP, and JP29574) and the non-interventional study (NIS) BH29768 – as described under Clinical Pharmacology and Clinical Efficacy above.

Clinical studies in special populations

Extrapolation of benefit-risk of emicizumab to patient groups not directly studied

Reference to studies BH30071, BH29992, BO39182 and BH29884 are provided.

Generalization of Efficacy and Safety to Paediatric Patients Without Inhibitors

The data for emicizumab in paediatric patients < 12 years is derived from Study BH29992, which included only patients with FVIII inhibitors. However, in regards to the use of emicizumab, patients with or without FVIII inhibitors comprise a single population, and safety and efficacy may be generalized between them. The MAH has also submitted notification of information obtained on an additional 33 paediatric subjects.

Factor VIII inhibitors do not recognize emicizumab or interfere with its binding to FIXa and FX, and therefore emicizumab restores haemostasis to a similar degree in patients with or without FVIII inhibitors. This is further substantiated by the observed similar trough plasma concentrations of emicizumab in patients with or without FVIII inhibitors at a given dosing regimen and confirmed by the comparable safety profile and efficacy observed in Study BH29884 and Study BH30071. Therefore, the efficacy, safety, and pharmacokinetics observed in paediatric patients with FVIII inhibitors in Study BH29992 are generalisable to paediatric patients without FVIII inhibitors.

Pathophysiology of Haemophilia A is not Changed by Inhibitors against Factor VIII

Factor VIII inhibitors represent an alloimmune response against exogenously infused FVIII and thus are essentially ADAs. While inhibitors have a notable impact on patient management, they do not change the underlying pathophysiology or the fundamental disease characteristics of haemophilia A, and as such do not represent evolution or progression of the disease. Indeed, the severe coagulopathy results from absence of FVIII, and the presence of inhibitors only compromises the ability to prevent or treat bleeds with FVIII replacement therapy.

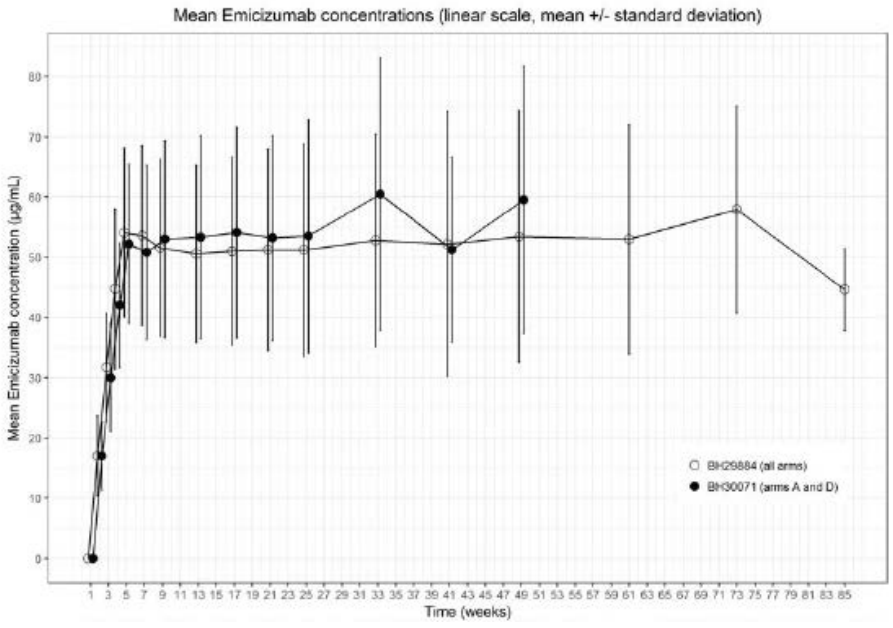
Traditionally, in trials of coagulation factors, patients without inhibitors have contributed to studies of FVIII whereas patients with inhibitors have contributed to studies of bypassing agents simply because each type of therapy is intended for each subpopulation only. This has led, together with the differences in standard of care and the unmet need, to the dichotomization of patients with or without inhibitors in the current (pre-emicizumab) haemophilia A therapy framework, which is not relevant when considering patients treated with emicizumab.

Emicizumab Mechanism of Action and PK are Unaffected by Presence of Inhibitors

The unique mechanism of action of emicizumab makes any distinction between patients with or without inhibitors irrelevant in this context. Emicizumab bridges FIXa and FX to restore the function of missing FVIIIa. Since it has no structural relationship or sequence homology to FVIII, inhibitors do not recognize emicizumab, interfere with its binding toFIXa and FX, or affect levels of FIXa or FX. Thus, emicizumab has the same impact on the underlying pathophysiology of haemophilia A (i.e., lack of FVIII function) whether or not inhibitors are present.

Importantly, similar trough plasma concentrations of emicizumab were observed at steady state in patients with and without FVIII inhibitors receiving the 1.5 mg/kg QW maintenance dose in Study BH29884 and Study BH30071, respectively. Steady state was achieved after 4 loading doses and remained stable at the maintenance dose (mean trough concentrations of approximately 52 µg/ml in both studies:

Figure 38: Mean emicizumab trough concentrations (QW dosing regimen) in studies BH29884 and BH300071



The comparable trough plasma concentrations are an experimental proof that emicizumab pharmacokinetics is unaffected by either the presence of inhibitors or by the use of different concomitant haemophilia A treatments (e.g., FVIII or bypassing agents).

These data indicate that in regard to emicizumab, patients with or without inhibitors comprise a single population, and therefore the observed efficacy benefit in Study BH29992 is generalizable to all paediatric patients with haemophilia A.

Generalization of Efficacy and Safety of Q2W Regimen to Adult Patients With Inhibitors

The MAH posits that the efficacy and safety for emicizumab can be generalized between patients with or without FVIII inhibitors. Therefore, the efficacy and safety observed with the emicizumab Q2W regimen in adults and adolescents in BH30071 is applicable to all adults and adolescents with haemophilia A, irrespective of inhibitor status.

Importantly, although the dose administered Q2W is twice the weekly dose, due to emicizumab's slow absorption, the mean maximum plasma concentration (Cmax) is only minimally higher. Modelling of emicizumab plasma-time concentration profiles shows that 95th percentiles of Cmax are 82.4 and 85.9 ug/mL for the QW and Q2W regimens, respectively (X-link SCP Section 3.2.8). Thus, the safety profile of QW emicizumab maintenance in adults with FVIII inhibitors (in Study BH29884) can be considered representative of the safety profile in adults with FVIII inhibitors should they receive Q2W emicizumab maintenance.

Extrapolation of Q2W and Q4W Regimens to Paediatric Patients

The data for emicizumab in paediatric patients < 12 years is derived from Study BH29992, which included only QW maintenance dosing. However, as emicizumab PK and efficacy is similar in adult, adolescent, and paediatric patients, the efficacy of the Q2W and Q4W maintenance dosing regimens observed in Studies BH30071 and BO39182 in adult and adolescent patients ≥ 12 years may be extrapolated to paediatric patients < 12 years.

Haemophilia A is a congenital disease with a similar pathophysiology throughout the patient's life and same treatment paradigm regardless of age. Emicizumab concentration measurements from Studies BH29992, BH29884 and BH30071 demonstrate concordance of PK in paediatric and adult patients receiving emicizumab QW. These data indicate that age does not affect exposure to emicizumab. Thus, the PK observed in adults receiving Q2W or Q4W maintenance dosing regimens can be extrapolated to paediatric patients and, with it, the robust and clinically meaningful efficacy for these additional regimens as observed in Studies BH30071 and BO39182.

Importantly, the 95th percentile of emicizumab concentrations at Cmax is estimated to be approximately 82.4, 85.9, and 97.7 µg/mL in the QW, Q2W and Q4W regimens, respectively. Thus, since the various regimens result in a comparable Cmax, the acceptable safety profile of QW emicizumab maintenance established in Study BH29992 would be predicted to be representative of the safety profile of children who would receive Q2W or Q4W emicizumab maintenance.

Background

In accordance with EMA and FDA guidelines and positions on extrapolation (EMA/199678/2016; EMA/478467/2016; EMA/129698/2012; Dunne et al. 2011), the initial emicizumab approval was supported by a PK-based extrapolation of the efficacy of emicizumab from adult/adolescent patients with inhibitors (evaluated in the randomized controlled trial BH29884) to children with inhibitors (evaluated in the single-arm descriptive paediatric trial BH29992), to support an indication of emicizumab prophylaxis in adult and paediatric patients with haemophilia A with inhibitors, using a weekly maintenance dose of 1.5 mg/kg. These studies demonstrated consistent exposure in adults, adolescents, and children, allowing for extrapolation of efficacy from adult / adolescent to paediatric patients. Study BH29992 also provided adequate safety data to characterize the safety profile of emicizumab in children.

This approach is in line with several paediatric approvals in haemophilia A that have been obtained based on a randomized study with hypothesis testing in adolescents and adults, which formally demonstrated efficacy, and a descriptive paediatric study which investigated the safety and PK (e.g., Adynovate (pegylated full-length rFVIII), Eloctate (rFVIII, Fc fusion protein) and Nuwiq (rFVIII, B-domain deleted)).

Haemophilia A has Similar Pathophysiology in Children and Adults

Haemophilia A is a congenital disease in which the lack of FVIII function since birth results in severe bleeding diathesis throughout patients' lives. Accordingly, restoring FVIII function and thereby adequate hemostasis is the ultimate goal of management, independent of age. Coagulation factors in newborns and adults are qualitatively similar in their molecular weights and degree of glycosylation (Hassan et al. 1990). The

coagulation cascade is almost mature at birth, with well-balanced hemostasis and thrombosis, and is fully mature at 6 months of age (Andrew et al. 1987, Revel-Vilk et al. 2012). Notably, FVIII activity at birth is equivalent to adult activity level and remains stable from the newborn period onwards (Kuhle et al. 2003). Consequently, dosing strategies are similar for adult and for paediatric haemophilia A patients, including infants (Mahlangu et al. 2014, Young et al. 2015). Emicizumab mimics FVIII activity and binds the same qualitatively identical factor FIX (FIX) and FX, and should therefore be efficacious in children with haemophilia A, as confirmed in HAVEN 2.

Pharmacokinetics and Exposure-Response Relationship

Study BH29992 provides key paediatric exposure data for patients from 1 to 12 years of age receiving 1.5 mg/kg QW maintenance dose. The observed PK profiles in patients aged ≤ 12 years are consistent with those observed in patients aged > 12 years in Study BH29884 and Study BH30071. Steady state was reached with plasma concentrations of 52.8 µg/mL and 53.4 µg/mL at Week 5, in Study BH29992 and in pooled Studies BH29884 and BH30071, respectively. Thereafter, mean plasma concentrations remained stable. Importantly, similar emicizumab trough concentrations were observed in the various age categories with the QW regimen (the 5 patients aged < 2 years achieved trough concentrations similar to older children within the same study and to adults in Study BH29884).

The consistent PK measurements regardless of age indicate that the emicizumab PK observed in adult/adolescents with Q2W or Q4W regimens may be extrapolated to paediatric patients. The previously submitted exposure-efficacy analysis (an updated analysis is included in the filing) establishes a link between PK and efficacy. Therefore, the Sponsor posits that the age-consistent PK observed with the QW regimen allows extrapolation of the observed efficacy in adults receiving emicizumab maintenance doses with the Q2W (Study BH30071) or Q4W (Study BO39182) regimens to children.

Figure 39: Mean plasma emicizumab concentration versus time profiles for patients ≥ 12 years (Studies BH29884 and BH30071) compared with patients < 12 years (study BH29992)

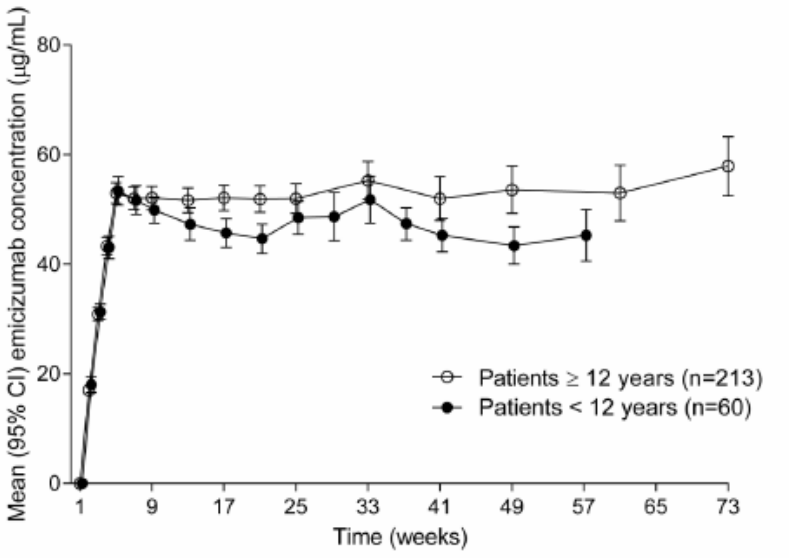


Figure 40: Mean plasma emicizumab concentration versus time profiles for patients ≥ 12 years (Studies BH29884 and BH30071) compared with patients < 12 years (study BH29992)

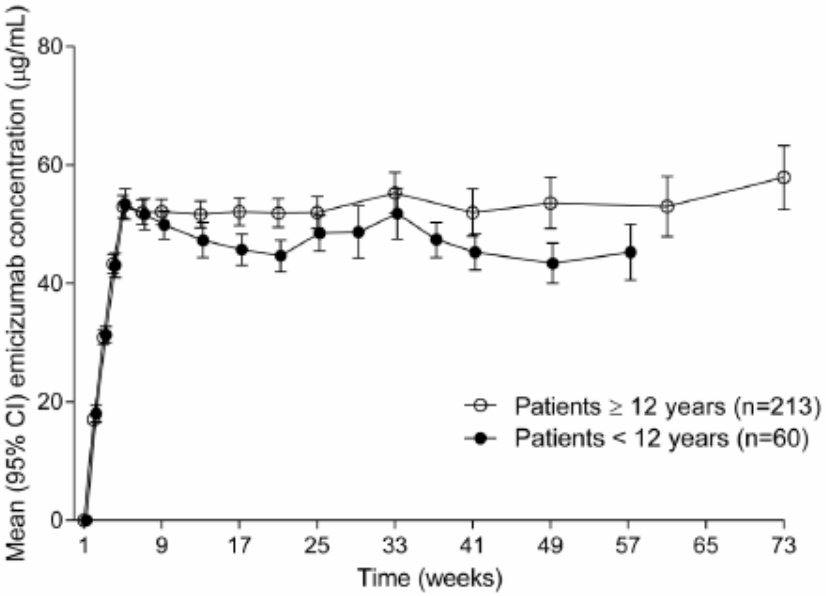


Table 66: Secondary PK paramters derived at steady-state for emicizumab 1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W dosing schedule using the primary individual PK parameters obtained by the final population PK model:

Secondary PK Parameters	1.5 mg/kg QW		3 mg/kg Q2W		6 mg/kg Q4W	
	Mean (SD)	Median [5th – 95th] percentiles	Mean (SD)	Median [5th – 95th] percentiles	Mean (SD)	Median [5th – 95th] percentiles
Dose Regimen Independent Parameters						
$C_{av,ss}$ (µg/mL)	53.5 (15.7)	52.3 [30.2 - 81.1]	53.5 (15.7)	52.3 [30.2 - 81.1]	53.5 (15.7)	52.3 [30.2 - 81.1]
$T_{1/2}$ (day)	26.8 (9.16)	25.1 [13.9– 41.4]	26.8 (9.16)	25.1 [13.9– 41.4]	26.8 (9.16)	25.1 [13.9– 41.4]
$T_{1/2,abs}$ (day)	1.61 (0.96)	1.27 [0.897-3.80]	1.61 (0.96)	1.27 [0.90-3.80]	1.61 (0.96)	1.27 [0.90-3.80]
Dose Regimen Dependent Parameters						
$C_{max,SS}$ (µg/mL)	54.9 (15.9)	53.9 [30.9-82.4]	58.1 (16.5)	57.0 [33.6 - 85.9]	66.8 (17.7)	65.9 [40.4-97.7]
$C_{trough,SS}$ (µg/mL)	51.1 (15.3)	49.9 [28.4 - 78.7]	46.7 (14.9)	45.6 [24.9 - 75.0]	38.3 (14.3)	36.5 [17.7 - 64.7]
$C_{max,SS}/C_{trough,SS}$	1.08 (0.03)	1.07 [1.03 - 1.15]	1.26 (0.12)	1.24 [1.12 - 1.49]	1.85 (0.46)	1.74 [1.36- 2.85]
$AUC_{ss,\tau}$ (µg/mL*day)	375 (108)	366 [211 - 568]	749 (219)	733 [423 -1135]	1499 (439)	1465 [845 - 221]

$AUC_{ss,\tau}$ = area under the concentration time curve at steady-state over the dosing interval (τ = 1, 2, or 4 weeks); $C_{max,SS}$ = maximum concentration at steady-state; $C_{trough,SS}$ = steady-state trough concentration; SD = standard deviation $T_{1/2}$ = half-life.

2.4.2. Discussion on clinical efficacy

This MAH applied for two additional posology recommendations for adults and children with haemophilia A with and without factor VIII inhibitors. The proposed dosing regimen includes a loading dose of 3 mg/kg once weekly followed by a maintenance dose of either 3 mg/kg every two weeks or 6 mg/kg every 4 weeks, and from week 5 on 3 or 6 mg/kg.

Although the Q2W and Q4W regimens were studied in patients ≥ 12 years of age, the PK consistency across age supports extrapolation of these regimens to the whole age range of the paediatric population. The availability of several efficacious dosing regimens for emicizumab will allow individualization of the regimen to the patients' needs and lifestyle

Overall, the clinical efficacy, safety and exposure-response relationships confirm the appropriateness of 3 mg/kg QW for the first 4 weeks, followed by either 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W in the overall population of patients (children, adolescents and adults) with haemophilia A with or without inhibitors to FVIII. Hence, the proposed new posology can be recommended.

Study BH30071 (HAVEN-3)

Design and conduct

Study BH30071 (HAVEN-3) is a randomised, multi-centre, open-label study. The study enrolled 152 patients with severe congenital haemophilia A (intrinsic FVIII level < 1%) aged 12 years or older and with a body weight ≥ 40 kg. Other inclusion criteria were: a negative test for factor VIII inhibitors (and with evidence of lack of the presence of an inhibitor for the last 5 years); documentation of treatment and bleeding episodes over the last 24 weeks; ≥5 bleeds in the last 24 weeks for those on episodic treatment; acceptable laboratory tests. All subjects were male. Out of 152 patients in total, 8 were 12-18yrs and 5 were over age 65yrs. 3 subjects reported a past history of inhibitors. 94 subjects had a history of episodic treatment in the last 24 weeks and 73 reported on prophylactic treatment for that period.

The study had 4 arms. Patients who received episodic treatment with FVIII prior to study entry and experienced at least 5 bleeds over the 24 weeks prior to study entry (equivalent to annualized bleeding rate [ABR] ≥ 10) were randomized in a 2:2:1 ratio to the following regimens:

- Emicizumab prophylaxis at 3 mg/kg QW SC for 4 weeks, followed by 1.5 mg/kg QW SC (**Arm A**), 36 subjects
- Emicizumab prophylaxis at 3 mg/kg QW SC for 4 weeks, followed by 3 mg/kg Q2W SC (**Arm B**), 35 subjects
- No prophylaxis control arm (**Arm C**), 18 subjects

Randomization was stratified according to the number of bleeds patients experienced over the last 24 weeks prior to study entry (< 9 or ≥ 9 bleeds [equivalent to annualised bleed rate = 18]). Patients who were randomized to the no prophylaxis arm (control arm, Arm C) could switch to receive emicizumab prophylaxis at 3 mg/kg Q2W maintenance dose after completing 24 weeks in the study. Patients who received FVIII prophylaxis prior to study entry were enrolled in **Arm D** [63 subjects] to receive emicizumab prophylaxis at 3 mg/kg QW SC for 4 weeks, followed by 1.5 mg/kg QW SC.

All patients reported receiving treatment with FVIII in the 24 weeks prior to enrolment. The median number of bleeds in the 24 weeks prior to enrolment was between 11.5 and 16.5 in the randomized patients, and 2.0 in Arm D.

Efficacy data and additional analyses

Bleed rate was defined as the number of bleeds over the efficacy period. A bleed was counted in the primary analysis if it was treated with coagulation factors and fulfilled the adapted International Society on Thrombosis and Haemostasis (ISTH) criteria.

The number of bleeds was also annualized for each patient using the following formula:

ABR = (Number of bleeds / Total number of days during the efficacy period) x 365.25.

Endpoints were assessed using a negative binomial regression model. A bleed was considered to be a "treated bleed" if it was directly followed (i.e. there was not an intervening bleed) by a haemophilia medication reported to be a "treatment for bleed", irrespective of the time between the treatment and the preceding bleed.

Over 94% of subjects have over 24 weeks of study time

Emicizumab prophylaxis with the maintenance dose of 1.5 mg/kg QW resulted in a 96% reduction in rate of treated bleeds compared with no prophylaxis (annualised bleed rate cohort A/ cohort C ratio = 0.04; p < 0.0001); similarly, emicizumab prophylaxis with the maintenance dose of 3 mg/kg Q2W led to a 97% reduction in rate of treated bleeds, compared with no prophylaxis (annualised bleed rate cohort B / cohort C ratio = 0.03; p < 0.0001). The study met its main endpoint.

For 36 subjects exposed to 1.5mg/kg ecicizumab qw sc, the negative binomial model-based annualised bleed rate for treated bleeds was 1.5 (95% CI: 0.89, 2.47) and for all bleeds was 2.5 (95% CI: 1.63, 3.90).

For 35 subjects exposed to 3mg/kg ecicizumab q2w sc, the negative binomial model-based annualised bleed rate for treated bleeds was 1.3 (95% CI: 0.75, 2.27) and for all bleeds was 2.6 (95% CI: 1.63, 4.29).

For 18 subjects who did not receive prophylaxis, the negative binomial model-based annualised bleed rate for treated bleeds was 38.2 (95% CI: 22.86, 63.76) and for all bleeds was 47.6 (95% CI: 20.45, 79.59).

The proportion of patients experiencing zero treated bleeding episodes while on emicizumab prophylaxis was 55.6% and 60.0% in Arms A and B, respectively, compared to 0% in Arm Ccontrol. The proportion of patients with 0-3 treated bleeds was 91.7% and 94.3% in Arms A and B, respectively, compared to 5.6% in Arm C control.

The annualised bleed rate of all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds showed similar reductions to those reported for the annualised bleed rate of all bleeds i.e. data were supportive.

HAVEN-3 did not include subjects with inhibitors. In order to justify its claim for use of the posology of 3mg/kg q2w for subjects with inhibitors, the MAH conducted an extrapolation exercise.

The MAH has conducted an intra-patient comparison of bleeds whilst exposed to emicizumab versus bleeds whilst on standard care (data obtained via the non-intervention study BH29768. The intra-patient exercise is not considered a fair comparison. Patients in the non-intervention study had markedly reduced compliance with treatment compared to the emicizumab exposed population whose treatment was administered in a health facility and under supervision. The above results are viewed in a general sense only.

The MAH arranged endpoints in a hierarchy with penalty if an analysis did not pass stated criteria [as is the case for the intra-patient comparison] and so results of various quality of life questionnaires are noted in a general sense only; results would not give rise to any particular concern.

The MAH conducted a survey of patient preference. Whilst results of the survey suggest that there was overwhelming preference for the current product, it is recognised that the study took place with an open-label, uncontrolled design and so the opinion of subjects is highly likely to have been unduly influenced as a result. Results of the preference survey are viewed in a general sense and are considered to be broadly supportive of the claims of the MAH.

Study BO39182 (HAVEN-4)

Design and conduct

Study BO39182 (HAVEN-4) is a multi-centre, open-label study. The study enrolled 48 patients with severe congenital haemophilia A (intrinsic FVIII level < 1%) aged 12 years or older and with a body weight ≥ 40 kg. Subjects were either with or without the presence of inhibitors to FVIII.

7/48 subjects took part in a run-in PK study. The main efficacy analysis was of the 41/48 subjects who did not take part in the PK run-in study.

All patients were male. Most (75.6%) were White. The median age of enrolled patients was 39.0 years (range: 14 – 68 years). Most (92.7%) were adults aged ≥ 18 years and 3 patients (7.3%) were aged <18 years. There were 3 patients (7.3%) ≥65 years of age in the study.

11 patients (28.9%) on study had a history of FVIII inhibitor diagnosis. 6/11 patients did not test positive for FVIII inhibitors at study entry. Out of these 6 patients, 2 had undergone ITI. The mean time from FVIII inhibitor diagnosis was 234.7 months, with 9 of 11 patients diagnosed ≥ 72 months prior to study entry.

30 patients (73.2%) were categorised as being on prior prophylactic treatment, mainly short acting FVIII (23 patients, 76.7%). Episodic treatment in the 24 weeks prior to the study start was recorded for 19 patients (11 patients who were on episodic treatment and 8 patients who were on prophylactic treatment), mostly short acting FVIII (14 patients, 73.7%).

The median number of bleeds in the last 24 weeks prior to study entry was 5.0 (range: 0-90).

Subjects in the main cohort were administered emicizumab prophylaxis at 3 mg/kg QW SC for 4 weeks followed by 6 mg/kg Q4W SC.

Efficacy data and additional analyses

Bleed rates and analyses were as described for study HAVEN-3. The MAH submitted an updated study report during the evaluation of this application. At the CCOD for this primary analysis, the median duration of exposure was 24.14 weeks (range: 23.6-28.1). The median number of doses received was 10.0 (range: 10-11, corresponding to a range of 6 to 7 maintenance doses of 6 mg/kg), with a median cumulative dose of 3660 mg (range: 2175-5040).

There were no missed doses (defined as > 42 days between 2 doses), and all patients received the correct amount at each dose.

Drug administrations were monitored in-clinic from weeks 1 to 25; no patients had drug administration problems.

While receiving emicizumab prophylaxis:

- The NB model-based ABR for treated bleeds was 2.4 (95% CI: 1.38, 4.28), and the median ABR was 0.0 (IQR: 0.00, 2.08).
- 23 patients (56.1%) did not experience any treated bleeds. In total, 37 patients (90.2%) experienced 0 to 3 treated bleeds.
- The model-based ABR for treated spontaneous bleeds was 0.6 (95% CI: 0.27, 1.53), and the median ABR was 0.0 (IQR: 0.00, 0.00). Most patients (n = 34, 82.9%) did not experience any treated spontaneous bleeds while receiving emicizumab prophylaxis and 97.6% of patients experienced 0 to 3 treated spontaneous bleeds.
- The model-based ABR was 1.7 (95% CI: 0.82, 3.68) for treated joint bleeds and 1.0 (95% CI: 0.31, 3.26) for treated target joint bleeds. The median ABR was 0.0 (IQR: 0.00, 1.85) for treated joint bleeds and 0.0 (IQR: 0.00, 0.00) for treated target joint bleeds
- 12 (29.3% [95% CI: 16.1, 45.5]) patients experienced 0 all bleeds (i.e. ABR = 0); 17 patients had ABR between 1 and ≤5, 7 had an ABR between 5 and ≤10 and 5 had an ABR >10 (one subject had an ABR of 37).

The MAH submitted results of a preference survey. Whilst results of the survey suggest that there was overwhelming preference for the current product, it is recognised that the study took place with an open-label, uncontrolled design and so the opinion of subjects is highly likely to have been unduly influenced as a result. Results of the preference survey are viewed in a general sense and are considered [in that general sense] to be broadly supportive of the claims of the MAH.

BH29884 (HAVEN 1)

Design and conduct

BH29884 (HAVEN 1) is a randomised, multi-centre, open-label study. The study was previously submitted to support the initial MA; the MAH has submitted an update of experience beyond 24 weeks of exposure to study product and with an additional 4 patients recruited.

The study enrolled 113 Haemophilia A patients aged ≥ 12 years with documented historical high-titre inhibitors (≥ 5 BUs) against FVIII who were treated with episodic or prophylactic bypassing agents prior to study entry, with ≥ 6 bleeds in the last 24 weeks prior to screening (if on an episodic bypassing agent regimen) or ≥ 2 bleeds in the last 24 weeks prior to screening (if on a prophylactic bypassing agent regimen). Emicizumab was administered at a weekly loading dose of 3.0 mg/kg SC for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC i.e. the update reports on extended exposure to 1.5 mg/kg/week emicizumab.

Efficacy data and additional analyses

Bleed rates and analyses were as previously described. The majority (82.3%) of patients had ≥ 48 weeks follow-up at cut-off.

Model-based annualised bleed rate (95% CI) for treated bleeds across all treatment arms in the all emicizumab-treated patients was 2.7 (1.64, 4.35), mean (95% CI) calculated annualised bleed rate was 2.8 (0.53, 8.45). These results are consistent with those reported in the Primary CSR (4.6 and 4.7 respectively).

The lower figures now reported are explained by the MAH as follows: mean calculated annualised bleed rates for treated bleeds estimated by interval decreased over time and the improvement was sustained up to Week 72.

Median calculated annualised bleed rate was zero for all endpoints (i.e., treated bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds), consistent with the Primary CSR.

The MAH has conducted an intra-patient comparison of bleeds whilst exposed to emicizumab versus bleeds whilst on standard care (data obtained via the non-intervention study BH29768). The intra-patient exercise is not considered a fair comparison. Patients in the non-intervention study had markedly reduced compliance with treatment compared to the emicizumab exposed population whose treatment was administered in a health facility and under supervision. The above results are viewed in a general sense only.

BH29992 (HAVEN 2)

Design and conduct

BH29992 (HAVEN 2) is a single-arm, multi-centre, open-label study. The study was submitted previously to support the application for a licence; the MAH now submits an update.

The study enrolled 63 paediatric patients (60 patients < 12 years of age, including 10 patients ≤ 2 years, and 3 patients ≥ 12 years of age and < 40 kg) with congenital haemophilia A with FVIII inhibitors, who were receiving bypassing agents as a previous treatment. Most (95.2%) had severe haemophilia.

All subjects were male with a mean age of 6.6yrs (range 1 – 15yrs). The study population was multi-ethnic. The average weight was 26.6kg and average height was 120cm. There was a median of 6 bleeds in the last 24 weeks prior to study entry (range: 0-155 bleeds). Upon study entry, subjects were administered a weekly loading dose of 3.0 mg/kg SC of emicizumab for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC for cohort A. [subjects are not yet recruited to cohorts B and C (cohorts added as protocol amendment 3 dated 01 Sept 2017)].

Efficacy data and additional analyses

Bleed rates and analyses were as previously described. The primary efficacy data is presented for the annualised bleed rate in patients <12 years population with at least 12 weeks of treatment (n=59). The median duration of the efficacy period was 29.6 weeks (range: 18.4-63.0)

51 of the 59 patients (86.4%) had 0 treated bleeds (annualised bleed rate =0) while receiving emicizumab prophylaxis. Eight patients (13.6%) had 11 treated bleeds, all but 1 were traumatic. No patient reported >2 treated bleeds.

58 of 59 patients (98.3%) had reported 0 treated spontaneous bleeds (annualised bleed rate =0). One patient (1.7%) experienced 1 treated spontaneous bleed (annualised bleed rate of 0.85, efficacy period=431 days), categorized as “other” (left hip).

53 of 59 patients (89.8%) reported 0 treated joint bleeds (annualised bleed rate =0). Treated joint bleeds were reported by 6 patients with individual annualised bleed rates ranging from 0.88 to 4.54.

57 of 59 patients (96.6%) reported 0 treated target joint bleeds (annualised bleed rate =0). Treated target joint bleeds were reported by 2 patients whose individual annualised bleed rates were 1.86 (efficacy period=196 days) and 4.54 (efficacy period=161 days).

The MAH reported on an intra-patient comparison exercise. The intra-patient comparison exercise is generally supportive towards a claim of efficacy [yet such a comparison of real-world experience versus experience in clinical studies is not considered a ‘fair comparison’ upon which to make clinical / scientific judgement].

Additional expert consultation

An ad hoc expert group meeting was convened on the 25th January 2019 to discuss the following points relating to the clinical need in mild and moderate haemophilia A patients:

1. 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?

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. There may be a need for some with mild haemophilia A (but there is a need to show a benefit in the moderate population first).

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; insensitivity to physiological control mechanisms of thrombin generation such as those based on thrombomodulin-APC system) 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.

2. What would be the characteristics of patients with mild or moderate congenital haemophilia A without inhibitors to FVIII who are likely to benefit from exposure to Hemlibra?

There were different views on the subgroup of non-severe haemophilia patients who might benefit from prophylaxis treatment. There was general agreement that currently, routine prophylaxis to be investigated for Hemlibra would include:

- Moderate haemophilia A patients with FVIII levels ≤ 5% (based on den Uijl et al., 2011) and who had a first spontaneous intra-articular bleed before the age of 5 years

or

- Moderate haemophilia A patients with FVIII levels ≤ 5% who were already started on a prophylaxis regimen with a long-term prophylaxis intention

However, it was acknowledged that practices may vary and compliance with frequent i.v. administrations is an issue.

3. In the absence of a formal clinical trial of use of Hemlibra in the management of patients with mild or moderate congenital haemophilia A without inhibitors to FVIII; are the laboratory and pre-clinical data submitted by the company thus far adequate to address concerns over unknown, unpredictable risk and clinical safety in this sub-group of patients?

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.

4. Is a formal clinical trial in subjects with mild or moderate congenital haemophilia A without inhibitors to FVIII preferred and what aspects of safety would require particular attention?

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 of thrombosis and thrombotic microangiopathy, such as plasma concentrations of prothrombin fragment F1 + 2, soluble fibrin, D-dimer, and thrombin-antithrombin complex, 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 new born children was also raised.

Finally, the need for generating data in patients needing surgery was also expressed as relevant.

Third party intervention

The CHMP received a letter from another company (hereinafter referred to as “third party”) on 09 August 2018 in which a number of concerns were raised with regards to the studies used by the MAH to support its application.

The MAH was invited to comment on the issues raised by the third party and submitted its response on 19 September 2018.

The main issue pertain to the intra-patient comparisons to by-passing agents in studies HAVEN-1 and HAVEN-2 and HAVEN-3 and in addition the 3rd party highlighted several deficiencies with regards to the study design of HAVEN-3.

CHMP Conclusion

The third party has raised numerous points of contention that are considered to fall within the points already raised by the CHMP.

It is acknowledged that direct evidence provides the best evidence of relative clinical effect in order to avoid bias and so render fair comparison. From a statistical point of view, randomised trials would have been preferred.

It is appreciated that subjects in the non-intervention studies would have been managed at different centres by different physicians with different preference for management. It is considered that the analysis of ‘usual care’ as all being equivalent or essentially the same would confound analysis and lead to the introduction of uncertainty.

The SmPC for Hemlibra describes annualised bleed rates (ABR) for ‘all bleeds’, ‘treated bleeds’, ‘treated spontaneous bleeds’, ‘treated joint bleeds’ and ‘treated target joint bleeds’ for the HAVEN studies i.e. the attending physician has access to this data and so is able to make an informed decision. An attending physician will be aware of the subjective nature that patients have in treating bleeds.

Overall, the main points raised of contention have been resolved by addressing the limitations of the comparisons for the HAVEN studies in section 5.1 of the SmPC for awareness of the physician.

Assessment of paediatric data on clinical efficacy

It is considered that data on the paediatric population within the HAVEN studies along with the extrapolation reasoning of the company permit acceptance of the claim of efficacy in the paediatric population without inhibitors.

2.4.3. Conclusions on the clinical efficacy

The clinical efficacy has been demonstrated in adult and paediatric subjects with severe congenital Haemophilia A and without inhibitors present.

Clinical efficacy has not been demonstrated in subjects with mild or moderate grades of congenital Haemophilia A without inhibitors.

2.5. Clinical safety

Introduction

Overview of Studies Contributing to Safety Information

The current submission includes clinical data from two new pivotal Phase III studies:

- results of the primary analysis of Study BH30071 (also known as Study HAVEN 3) in adult and adolescent patients (≥ 12 years of age) with haemophilia A without inhibitors that evaluated QW and Q2W dosing regimens, results of an interim analysis of Study BO39182 (also known as Study HAVEN 4) in adult and adolescent patients (≥ 12 years of age) with or without inhibitors that evaluated Q4W dosing regimen.

In addition, the current submission includes updated results (QW dosing) from the previously submitted:

- Study BH29992 (also known as Study HAVEN 2) in children and infants < 12 years of age with inhibitors (now comprising results from 60 patients < 12 years of age, of which 5 patients are < 2 years of age) and
- Study BH29884 (also known as Study HAVEN 1) in adult and adolescent patients (≥ 12 years of age) with inhibitors

Updated long-term data from ongoing Phase I/II extension Study ACE002JP (extension of ACE001JP Part C) in adults and adolescents ≥ 12 years of age with haemophilia A with or without inhibitors is also included in the current submission.

An overview of the studies now submitted is given in the following table:

Table 67: Summary of studies contributing to safety evaluation

Patient Population	Dosing Regimen(s)	Analysis/Clinical Cutoff Date (*No. of patients*)/Safety Observation Period (*weeks*)
Phase III Studies		
BH30071: Open-label, multicenter, global, randomized study		
Patients aged ≥ 12 years with severe hemophilia A (intrinsic FVIII level < 1%) without FVIII inhibitors **Arm A, Arm B, and Arm C:** patients (previously on episodic FVIII) randomized 2:2:1 to receive emicizumab prophylaxis QW (Arm A), Q2W (Arm B), or no prophylaxis (Arm $C_{control}$). **Arm D:** Non-randomized arm for patients previously on prophylactic FVIII who received QW emicizumab prophylaxis.	Arm A, B, and D: Patients receive loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 1.5 mg/kg QW (Arm A)[a], 3 mg/kg Q2W (Arm B)[a], or 1.5 mg/kg QW (Arm D)[b]. Arm $C_{control}$: Patients receive no prophylaxis, allowed to switch to receive emicizumab prophylaxis after at least 24 weeks on no prophylaxis[a] referred as Arm C_{emi} (loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 3 mg/kg Q2W).	**Primary analysis (study ongoing)** Data cutoff: 15 Sep 2017 Enrolled: N = 152, exposed to emicizumab = 151 Randomized: Arm A: N = 36 Arm B: N = 35 Arm C: N = 18 Non-randomized: Arm D: N = 63 **Safety Observation Period** Median = 32.6 weeks (range: 14.4–50.6) (N = 152)

BO39182: Open-label, multicenter, global, non-randomized study		
Patients aged ≥12 years with hemophilia A with or without FVIII inhibitors.	Expansion Part: Patients receive a loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 6 mg/kg Q4W[a]. PK run-in part: Patients receive a dose of 6 mg/kg Q4W[a]. No loading dose was given in PK run-in part[a].	**Primary Analysis (study ongoing)** Data cutoff: 15 Dec 2017 Enrolled and exposed to emicizumab: N=48 (41 in expansion part, 7 in PK run-in)[c] **Expansion Part** **Follow-up Efficacy Period** Median=25.6 weeks (range: 24.1–29.4) (N=41) **PK Run-In Part** **Safety Observation Period** Median=43.7 weeks (range: 41.7–45.7) (N=7)
BH29992: Open-label, multicenter, global, single-arm study		
Pediatric patients with inhibitors from birth to<12 years of age, with allowance of patients 12–17 years of age who weigh<40 kg[d].	Patients receive loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 1.5 mg/kg QW[e].	**Interim Analysis (study ongoing)** Data cutoff: 05 Oct 2017 Enrolled and exposed to emicizumab: N=63 <12 years N=60 (including 10 patients ≤ 2 years of which 5 patients<2 years) ≥12 years and<40kg: N=3 **Safety Observation Period** Median=29.3 weeks (range: 8.3–63.0) (N=63)

BH29884: Phase III, Open-label, multicenter, global, randomized study		
Patients ≥ 12 years of age with inhibitors to FVIII **Arms A and B:** patients previously on episodic BPA randomized 2:1 to receive emicizumab prophylaxis (Arm A) vs. no prophylaxis (Arm $B_{control}$). **Arm C:** Non-randomized emicizumab arm for patients previously on BPA prophylaxis. **Arm D:** Non-randomized emicizumab arm for patients previously on episodic or prophylactic BPA	Arm A, C, and D: Patients receive loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 1.5 mg/kg QW[a]. Arm $B_{control}$: Patients receive no prophylaxis, allowed to switch to receive emicizumab prophylaxis after at least 24 weeks on study, referred as Arm B_{emi} (loading dose of emicizumab 3 mg/kg QW for 4 weeks prior to starting maintenance of 1.5 mg/kg QW)[a].	**Updated analysis (study ongoing)** Data cutoff: 08 Sep 2017 Enrolled: N = 113, exposed to emicizumab = 112 Randomized: Arm A: N = 35; Arm B: N = 18 Non-randomized: Arm C: N = 49; Arm D: N = 11 **Safety Observation Period** Median = 72.3 weeks (range: 0.1–94.4) (N = 113)

Phase I/II Study		
ACE002JP: conducted in Japan, Phase I/II, open-label extension study of patients from Study ACE001JP Part C with possible dose up-titration to other treatment groups *Results of ACE001JP Part C were analyzed with its extension Study ACE002JP. All references to "Study ACE002JP" in this document should be understood to mean ACE001JP Part C and ACE002JP collectively.*		
Patients with hemophilia A with and without inhibitors from Part C of Study ACE001JP.	Group 1: patients receive loading dose of emicizumab 1 mg/kg prior to starting maintenance of 0.3 mg/kg QW maintenance dose[f] Group 2: patients receive loading dose of emicizumab 3 mg/kg loading dose prior to starting maintenance of 1 mg/kg QW maintenance dose[f] Group 3: patients receive no loading dose prior to starting maintenance of 3 mg/kg QW maintenance dose[f]	**Interim Analysis (study ongoing)** *(includes data from ACE001JP Part C)* Data cutoff: 31 Aug 2017 (includes data from ACE001JP Part C) N = 18 (3 groups of 6 patients each)[g] **Safety Observation Period** Median = 158 weeks (range: 12.3–225 weeks), 197 weeks (4.1–204 weeks), and 174 weeks (12.1–178 weeks) in the 0.3, 1, and 3 mg/kg QW

AE = adverse event; EQ-5D-5L = EuroQoL-Five Dimension-Five Levels; FVIII = factor VIII; Haem-A-QoL = hemophilia-specific quality of life index for adults; Haemo-QoL SF = hemophilia-specific quality of life index for adolescents Short Form; HRQoL = health-related quality of life; NIS = non-interventional study; PK = pharmacokinetics; SC = subcutaneous.

For the reanalysis of immunogenicity data presented in this summary more recent clinical cutoff dates were used for the Studies BH30071 (07 Feb 2018), BO39182 (30 Apr 2018), BH29992 (30 Apr 2018), and BH29884 (03 Apr 2018). The rest of the data is based on the cutoff dates mentioned in this table.

[a] Patients had the opportunity to increase their dose to 3 mg/kg QW if they had completed at least 24 weeks on study drug, met the specific criteria, and received approval from the Medical Monitor.

[b] Patients had the opportunity to increase their dose to 3 mg/kg QW after the second qualifying bleed, with approval from the Medical Monitor.

[c] Only safety and PK assessment of Q4W emicizumab regimen was performed in the PK run-in part (n=7). These patients were not included in efficacy assessment. Safety and efficacy were assessed in expansion part consisting of 41 patients.

[d] Two new cohorts in patients < 12 years of age have been added to the study (protocol amendment 3) to investigate 3.0 mg/kg Q2W and 6.0 mg/kg Q4W dosing regimens. The enrollment to these additional cohorts took place after the cut-off of the analysis of the Interim CSR.

[e] Patients had the opportunity to increase their dose to 2.25 mg/kg QW in first instance followed by 3 mg/kg QW if they experienced more than two spontaneous bleeding events during a 12-week treatment period at a given dose.

[f] Patients in Group 1 and Group 2 had the opportunity to increase their dose to 1 mg/kg QW and 3 mg/kg QW, respectively, following approval by the study's Efficacy and Safety Evaluation Committee based on evaluation of laboratory test values, vital signs, 12-lead ECG results, adverse events, pharmacokinetics, pharmacodynamic response, serum cytokine concentrations, and number of bleeding episodes during a treatment period of at least 12 weeks (12 consecutive administrations) at the subject's maximum dose. The same evaluation process was used to determine whether any patient in Group 1 having been escalated to 1 mg/kg QW (Group 2), may subsequently be escalated to 3 mg/kg QW (Group 3).

[g] Results include 2 patients from Study ACE001JP Part C who did not enter extension Study ACE002JP.

Serious adverse events, medication errors and off-label use were monitored in the following additional studies or compassionate use requests:

- Study MO39129 (also known as STASEY study), a single-arm, multi-centre, open-label Phase IIIb clinical study enrols patients aged 12 years or older with haemophilia A who have persistent inhibitors against FVIII at enrolment. This study is being conducted to enhance the safety data that have been obtained as part of the clinical development program. At the cut-off of 18 Oct 2017, only 7 patients were exposed to emicizumab for a maximum duration of 6 weeks.
- US Early Access Program (ML39356): At the cut-off of 18 Oct 2017, 28 patients (including 3 paediatric patients) received emicizumab
- Compassionate Use Requests (MO29988): At the cut-off of 18 Oct 2017, 6 patients have received emicizumab under single case compassionate use requests: 2 in Belgium, 1 in France, 1 in Lithuania, 1 in the UK, and 1 in Australia

Safety monitoring in the emicizumab clinical studies (BH30071, BO39182, BH29992, BH29884, and ACE002JP) consisted of collection of adverse events, serious adverse events, laboratory tests (standard haematology and blood chemistry), pharmacodynamic parameters, anti-emicizumab antibodies, anti-FVIII antibodies (inhibitor titres) and physical observations / measurements (vital signs, electrocardiograms).

The Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 was used to classify.

Patients who withdrew from treatment at any point in Studies BH30071, BO39182, BH29992, and BH29884 were required to return for a safety follow-up visit 24 weeks after the last administration of emicizumab and expected to continue to record their bleeds and haemophilia medications exposure during this period.

In these studies, the World Health Organization (WHO) toxicity grading scale was used for assessing AE severity (WHO 2003), as shown:

Table 68: adverse event severity grading scale for events not specifically listed in WHO toxicity grading scale

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

In Study ACE002JP, the safety follow-up period started 3 weeks after the scheduled date of the last emicizumab treatment and then for up to 34 weeks more, dependent upon dosing scheme.

In Study ACE002JP, the severity of AEs was assessed according to the following criteria:

- Mild: does not interfere with the subject's normal activities
- Moderate: interferes with the subject's normal activities
- Severe: completely prevents the subject's normal activities and inevitably requires intervention or discontinuation of treatment with emicizumab

Selected adverse events for emicizumab included:

- injection site reactions
- thromboembolic events
- thrombotic microangiopathy
- systemic hypersensitivity reactions (including anaphylaxis and anaphylactic reactions)

For studies BH30071, BO39182, BH29992, and BH29884: a sandwich enzyme-linked immunosorbent assay (ELISA) method was used to analyse anti-therapeutic antibodies in plasma. The sensitivity of the method was 6.04 ng/mL. The assay precision for:

- Study BH30071 was 4.0% to 4.9%,
- Study BH29884 was 2.6% to 5.4%,
- Study BO39182 was 2.7% to 4.4%,
- and for Study BH29992 was 3.8% to 5.9%.

In Study ACE002JP, anti-emicizumab antibodies were measured using electrochemiluminescence and ELISA.

Pooling of data

Safety data from Studies BH30071, BO39182, BH29992, and BH29884 with the three maintenance dosing regimens proposed for the label (1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W) are pooled and are referred to as the “all exposure population” (N = 373).

[Updated safety data from Study ACE002JP are presented separately because this was a study of only 18 subjects exposed to a different dosing regimen from the main studies]

Table 69: Data contributing to analysis of safety

Study and Analysis	Data Contributing to Analysis[a]
BH30071 Primary Analysis	Patients aged ≥12 years with severe hemophilia A (intrinsic FVIII level <1%) without inhibitors against FVIII **Randomized patients:** patients randomized to receive emicizumab prophylaxis (Arms A and B) vs. no prophylaxis (Arm $C_{control}$) **Arms A, B, C_{emi}[b], D**: all patients who received ≥1 dose of emicizumab
BO39182 Interim Analysis	Patients aged ≥12 years with hemophilia A with or without FVIII inhibitors All patients who received ≥1 dose of emicizumab[c]
BH29992 Interim analysis	Children with hemophilia A with inhibitors <12 years of age and 12–17 years of age who weighed <40 kg All patients who received ≥1 dose of emicizumab
BH29884 Updated Analysis	Adults and adolescent patients with hemophilia A with inhibitors ≥12 years of age **Arms A, B_{emi}, C, D**: all patients who received ≥1 dose of emicizumab[d]
ACE002JP Interim Analysis	Japanese adult and adolescent patients with hemophilia A ≥12 to <60 years of age (with and without inhibitors) **Cohorts 1-3**: all patients who received ≥1 dose of emicizumab
Pooled Analysis	
Studies BH30071, BO39182, BH29992, BH29884	All patients who received ≥1 dose of emicizumab

[a] Includes also data after up-titration, for patients who were up-titrated
[b] Arm C_{emi} only patients who switched from no prophylaxis to emicizumab Q2W were included
[c] Includes patients from PK run-in and expansion cohorts
[d] Arm B_{emi} only patients who switched from no prophylaxis to emicizumab QW were included

Patient exposure

Overall extent of exposure

373 patients have received at least one dose of emicizumab, with an overall exposure of 298.4 patient-years.

Table 70: Emicizumab exposure by study

APPROVED Summary of Study Drug Exposure, Safety Population
Protocols: BH30071, BO39182, BH29992, BH29884
Cutoff Date: BH30071 - 15SEP2017; BO39182 - 15DEC2017; BH29992 - 05OCT2017; BH29884 - 08SEP2017
Snapshot Date: BH30071 - 14NOV2017; BO39182 - 14FEB2018; BH29992 - 16NOV2017; BH29884 - 23OCT2017

	BH30071 (N=150)	BO39182 (N=48)	BH29992 (N=63)	BH29884 (N=112)	Total (N=373)
Number of treated patients	150	48	63	112	373
Duration of Exposure (Weeks)					
Mean (SD)	30.32 (10.95)	27.10 (6.11)	36.79 (16.30)	61.92 (19.25)	40.49 (20.32)
Median	29.79	24.14	29.14	62.00	34.14
Min - Max	0.1 - 50.1	23.6 - 44.1	8.3 - 63.0	3.4 - 94.3	0.1 - 94.3
Total Patient Years	87.2	24.9	44.4	132.9	289.4
Duration of Exposure (Weeks)					
0 - 4	7 (4.7%)	0	0	2 (1.8%)	9 (2.4%)
5 - 12	4 (2.7%)	0	1 (1.6%)	1 (0.9%)	6 (1.6%)
13 - 24	27 (18.0%)	35 (72.9%)	18 (28.6%)	2 (1.8%)	82 (22.0%)
25 - 36	69 (46.0%)	6 (12.5%)	24 (38.1%)	9 (8.0%)	108 (29.0%)
37 - 52	43 (28.7%)	7 (14.6%)	0	10 (8.9%)	60 (16.1%)
> 52	0	0	20 (31.7%)	88 (78.6%)	108 (29.0%)
Number of doses					
Mean (SD)	27.5 (11.6)	10.3 (0.6)	37.6 (16.3)	62.2 (19.2)	37.4 (23.0)
Median	27.0	10.0	30.0	63.0	31.0
Min - Max	1 - 50	10 - 12	9 - 64	4 - 95	1 - 95
Total cumulative dose (mg)					
Mean (SD)	4312.60 (1797.57)	3705.09 (728.18)	1842.83 (1388.02)	7441.13 (2788.36)	4756.67 (2798.58)
Median	4155.75	3682.50	1380.00	7140.00	4261.50
Min - Max	340.5 - 11151.0	2175.0 - 5145.0	277.2 - 6903.0	838.5 - 16233.0	277.2 - 16233.0

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Patient-years is the sum over patients' emicizumab exposure time (time intervals between the start and end of emicizumab treatment).
A dose is a day with injection of emicizumab. A dose can be given with 1 or more injections.
Emicizumab dose is given in mg/kg using the most recent body weight.
Includes also data after up-titration, for patients who were up-titrated.

The duration of exposure to emicizumab and number of patients exposed varied between studies. Overall, the median duration of exposure was 34.1 weeks (range: 0.1-94.3 weeks). Patients in BH29884 had the longest median exposure (62 weeks, with 78.6% of patients with more than 52 weeks of exposure). Patients in BO39182 had the shorter median exposure (24.1 weeks).

41 of 373 patients (11.0%) missed ≥1 dose of study product. Of these, 33 patients were in Study BH29884, and 8 patients were in Study BH30071.

14 of 373 received emicizumab injections that deviated from the planned dose (<90% or >110%), for either the loading or maintenance doses.

No patients in Studies BO39182 and BH29992 had missed doses or dose deviations.

Exposure to Non-Emicizumab Haemophilia A Medication

Although prophylaxis with non-emicizumab haemophilia A medication was prohibited or limited to first week for patients on prior FVIII prophylaxis, short-term, focused prophylaxis before activity or before procedure/surgery was allowed. Drugs intended to control or prevent bleeds were administered in the studies.

Table 71: Number of patients exposed to non-emicizumab haemophilia medications administered while on study

	BH30071 (N=150)	BO39182 (N=48)	BH29992 (N=63)	BH29884 (N=112)	Total (N=373)
aPCC	0	0	2 (3.2%)	29 (25.9%)	31 (8.3%)
rFVIIa	0	1 (2.1%)	14 (22.2%)	46 (41.1%)	61 (16.4%)
FVIII	89 (59.3%)	26 (54.2%)	0	3 (2.7%)	118 (31.6%)

Most patients used non-emicizumab haemophilia A medications for treatment of bleeds (39.4%) rather than preventative doses before activity (23.3%) or for procedure/surgery (7.2%).

Procedures and Surgeries While Receiving Emicizumab Prophylaxis

Although patients who had planned major surgeries were excluded from the studies, enrolled patients underwent unplanned or minor surgeries and procedures in Studies BH30071, BO39182, BH29884, and BH29992 while receiving emicizumab. Perioperatively, investigators decided based on clinical judgment, whether and how much hemostatic support was needed; no guidance was provided by the Sponsor with the exception of protocol amendments. Limited information regarding patients who underwent surgical procedures is available, as these studies were not designed to proactively collect such details.

All invasive medical procedures were categorized as minor surgical procedures. Gastroenterological endoscopies, and endodontic procedures were also included as they have the potential to result in bleeding.

In Study BH30071, 18 patients underwent a total of 80 procedures, with 1 patient having 44 procedures. 16 [minor] procedures / surgeries were performed in 11 patients without peri-operative FVIII use and did not result in a bleed.

- 1 patient had one or more procedures / surgeries that resulted in a bleed and were associated with peri-operative FVIII use.
- 1 patient who underwent an orthopedic surgery received prophylactic FVIII treatment and did not experience a bleed due to the surgery.

In Study BO39182, 6 patients underwent a total of 10 procedures. 4 patients underwent six [minor] procedures / surgeries without prophylactic or peri-operative hemophilia medication.

- One patient underwent 3 procedures of hematoma evacuation and received prophylactic FVIII for all 3 procedures.
- Another patient underwent a cystoscopy and received prophylactic FVIII prior to the procedure. Both patients who received prophylactic FVIII did not experience post-procedural bleeds.

In Study BH29992, 12 patients underwent a total of 12 procedures. Ten [minor] procedures / surgeries were performed in 10 patients without peri-operative bypassing agent use and did not result in a bleed.

- One patient who had a CVAD removal received a prophylactic dose of rFVIIa
- one patient had an appendectomy for which he received a single prophylactic dose of aPCC.

Neither of these procedures led to a bleed.

In Study BH29884, 27 patients underwent a total of 45 procedures. [minor] Procedures / surgeries were performed in 15 patients without peri-operative bypassing agent use and did not result in a bleed. Twelve patients had one or more procedures/surgeries that were associated with peri-operative bypassing agent use. These included a total hip replacement, central line catheter placement, port removal, tooth extractions and right knee arthroscopy/synovectomy and debridement of arthrofibrosis and chondroplasty. Of these 12 patients, 3 patients reported bleeding due to their procedures; specifically, the procedures were total hip replacement, tooth extraction of molar, and right knee arthroscopy/synovectomy and debridement of arthrofibrosis and chondroplasty.

Adverse events

Overview of Adverse Events

The overall AE profile for emicizumab in all exposed patients is shown in the following table:

Table 72: Summary of adverse event profile

APPROVED Safety Summary, Safety Population
Protocols: BH30071, BO39182, BH29992, BH29884
Cutoff Date: BH30071 - 15SEP2017; BO39182 - 15DEC2017; BH29992 - 05OCT2017; BH29884 - 08SEP2017
Snapshot Date: BH30071 - 14NOV2017; BO39182 - 14FEB2018; BH29992 - 16NOV2017; BH29884 - 23OCT2017

	BH30071 (N=150)	BO39182 (N=48)	BH29992 (N=63)	BH29884 (N=112)	Total (N=373)
Total number of patients with at least one AE	127 (84.7%)	37 (77.1%)	54 (85.7%)	96 (85.7%)	314 (84.2%)
Total number of AEs	557	194	331	465	1547
Total number of patients with at least one					
AE with fatal outcome	0	0	0	1 (0.9%)	1 (0.3%)
Serious AE	12 (8.0%)	2 (4.2%)	10 (15.9%)	19 (17.0%)	43 (11.5%)
AE leading to withdrawal from treatment	1 (0.7%)	0	0	3 (2.7%)	4 (1.1%)
AE leading to dose modification/interruption	2 (1.3%)	0	0	6 (5.4%)	8 (2.1%)
Grade >=3 AE	15 (10.0%)	2 (4.2%)	7 (11.1%)	14 (12.5%)	38 (10.2%)
Related AE	46 (30.7%)	13 (27.1%)	12 (19.0%)	33 (29.5%)	104 (27.9%)
Local injection site reaction	39 (26.0%)	10 (20.8%)	11 (17.5%)	17 (15.2%)	77 (20.6%)
Adverse events of special interest					
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	0	0	0	1 (0.9%)	1 (0.3%)
Thromboembolic event (TE)	0	0	0	3 (2.7%)	3 (0.8%)
TE event related to aPCC and emicizumab	0	0	0	2 (1.8%)	2 (0.5%)
Thrombotic microangiopathy (TMA)	0	0	0	3 (2.7%)	3 (0.8%)
TMA event related to aPCC and emicizumab	0	0	0	3 (2.7%)	3 (0.8%)

Investigator text for AEs encoded using MedDRA version 20.1. 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.
The numbers for systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the Sampson Criteria include all patients that experienced indicative symptoms.

314 patients (84.2%) had at least one AE, and 43 patients (11.5%) reported SAEs.

[One patient in Study BH29884 had an AE with fatal outcome (SAE of rectal haemorrhage), which was previously reported.]

There were not any further cases of thrombotic microangiopathy and thromboembolic events related to the drug-drug interaction between aPCC and emicizumab (known events).

There was a higher rate of injection site reactions in BH30071 compared with the other studies. Injection site reactions were observed at any dose across the treatment and did not appear to be limited to the first few doses.

The overall safety profile of emicizumab is consistent with that reported previously.

Adverse events

In total, 314 patients (84.2%) had at least one AE. The SOCs with the highest incidence of reported AEs were as follows:

- Infections and Infestations (48%) -- the most common preferred terms were nasopharyngitis, upper respiratory tract infections, and influenza
- General Disorders and Administration Site Conditions (35.7%) -- the most common preferred terms were injection site reaction and pyrexia
- Musculoskeletal and Connective Tissue Disorders (29%) -- most common preferred term was arthralgia
- Injury, Poisoning and Procedural Complications (23.9%) -- the most common preferred term was contusion
- Gastrointestinal Disorders (21.2%) -- the most common preferred term was diarrhoea.

The most common SOCs / preferred terms were similar between studies. Adverse events reported in ≥ 5% of patients overall are summarised below:

Table 73: summary of all adverse events with an incidence of at least ≥ 5%

APPROVED Adverse Events with Incidence >=5% in any study by Preferred Term, Safety Population
Protocols: BH30071, BO39182, BH29992, BH29884
Cutoff Date: BH30071 - 15SEP2017; BO39182 - 15DEC2017; BH29992 - 05OCT2017; BH29884 - 08SEP2017
Snapshot Date: BH30071 - 14NOV2017; BO39182 - 14FEB2018; BH29992 - 16NOV2017; BH29884 - 23OCT2017

MedDRA System Organ Class MedDRA Preferred Term*	BH30071 (N=150)	BO39182 (N=48)	BH29992 (N=63)	BH29884 (N=112)	Total (N=373)
GASTROINTESTINAL DISORDERS					
DIARRHOEA	5 (3.3%)	1 (2.1%)	5 (7.9%)	8 (7.1%)	19 (5.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
INJECTION SITE REACTIONS	39 (26.0%)	10 (20.8%)	11 (17.5%)	17 (15.2%)	77 (20.6%)
PYREXIA	3 (2.0%)	2 (4.2%)	9 (14.3%)	8 (7.1%)	22 (5.9%)
INFECTIONS AND INFESTATIONS					
NASOPHARYNGITIS	18 (12.0%)	11 (22.9%)	14 (22.2%)	28 (25.0%)	71 (19.0%)
UPPER RESPIRATORY TRACT INFECTION	16 (10.7%)	5 (10.4%)	9 (14.3%)	13 (11.6%)	43 (11.5%)
INFLUENZA	9 (6.0%)	0	5 (7.9%)	7 (6.3%)	21 (5.6%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					
CONTUSION	7 (4.7%)	1 (2.1%)	9 (14.3%)	3 (2.7%)	20 (5.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS					
ARTHRALGIA	28 (18.7%)	10 (20.8%)	3 (4.8%)	17 (15.2%)	58 (15.5%)
NERVOUS SYSTEM DISORDERS					
HEADACHE	16 (10.7%)	7 (14.6%)	8 (12.7%)	21 (18.8%)	52 (13.9%)

Investigator text for AEs encoded using MedDRA version 20.1. 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 AEs' rows, multiple occurrences of the same AE in an individual are counted separately.
*Injection site reactions are reported by high level term.
AEs with Incidence >=5% are selected on the 'Total' column.

Injury, Poisoning and Procedural Complications were more frequently reported in Study BH29992 (41.3%) compared with other studies, with AEs of contusion (14.3%), skin abrasion (11.1%), fall (7.9%), ligament sprain (6.3%), laceration (4.8%) being also more frequently reported. Overall, the relatively higher frequency of injuries in this paediatric study is expected, because children are more prone to injury than adults, as they tend to be more physically active.

In contrast, long-term joint destruction is known to be more frequent in adults with haemophilia A than in children and consistent with this, there a was low frequency of arthralgia in children (4.8%), as expected in this age group.

Study BH30071: the proportion of patients treated with emicizumab who experienced any AE was 84.7% and the incidence of the SOC infections and infestations was 40.7%.

Study BO39182: In the PK run-in part, all 7 patients exposed to emicizumab experienced an AE. The most common by SOC was musculoskeletal and connective tissue disorders (71.4%). In the expansion part, the most common AEs by SOC were general disorders and administration site conditions (31.7%), musculoskeletal and connective tissue disorders (31.7%) and nervous system disorders (19.5%).

Nasopharyngitis (26.8%) was the most commonly reported AE, followed by injection site reaction (22.0%). Seven patients (17.1%) reported an AE immediately after injection; most commonly ISR. Injection site pain and presyncope were reported in 1 patient each (2.4%). With the exception of injection site pain, these AEs were all assessed as related to emicizumab treatment.

Serious adverse event / deaths / other significant events

Deaths

One patient in Study BH29884 died due to an SAE of rectal haemorrhage; the patient also experienced thrombotic microangiopathy (case previously reported). There were 2 deaths reported in a compassionate use program (MO29988), narratives are submitted.

Other Serious Adverse Events

Study BH30071:

Emicizumab Prophylaxis versus No Prophylaxis

Five SAEs were reported in 5 patients across treatment arms, each experienced 1 SAE: 1 of 18 patients in Arm C control, 1 of 36 patients in Arm A, and 3 of 35 patients in Arm B.

Three SAEs of haemorrhages were reported: haematoma (Grade 3, recovered/resolved) in Arm C control, and epistaxis (Grade 2, recovered/resolved) and putamen haemorrhage (Grade 4, recovering/resolving; treatment with emicizumab was not interrupted and the patient continued on emicizumab without recurrence of the event) in Arm B.

Device loosening (Grade 3, recovered/resolved) and femur fracture (Grade 3, recovered/resolved) were reported in Arms A and B, respectively.

None of the SAEs were reported as being related to emicizumab treatment.

None of the patients were withdrawn from treatment as a consequence of the reported SAEs.

Among all patients treated with emicizumab, a total of 12 patients reported 14 SAEs. In addition to the 4 SAEs reported for 4 patients randomized to Arms A and B and described above, 8 patients in Arm D reported 10 SAEs (groin pain, rhabdomyolysis, synovitis, infection, subperiosteal abscess, wound infection, epistaxis, acute coronary syndrome, Mallory-Weiss syndrome, and suicidal ideation), which included 2 serious

haemorrhages. In addition, 1 SAE of nephrolithiasis was reported for 1 patient in Arm D 34 days after up-titration.

None of the SAEs were reported as being related to emicizumab treatment.

None of the patients were withdrawn from treatment as a consequence of the reported SAEs.

Study BO39182

Two SAEs were reported.

- One patient in the PK run-in cohort had an SAE of hypertension. This patient had a previous medical history of hypertension. The SAE was reported as unrelated to emicizumab treatment and it resolved. The emicizumab dose was not modified or interrupted due to the SAE.
- One patient in the expansion cohort had an SAE of rhabdomyolysis. The SAE was not considered to be related to emicizumab and the outcome was reported as recovered/resolved. The emicizumab dose was not interrupted, nor was the patient withdrawn from treatment, due to this SAE.

Study BH29992

Twelve SAEs were reported by 10 patients (15.9%), none of which were assessed as related to emicizumab treatment. All but 1 SAE (asthma, not related) resolved. The emicizumab dose was not modified or interrupted due to these SAEs.

Study BH29884

Overall, 19 patients (17.0%) reported a total of 29 SAEs. Five patients experienced SAEs of hemarthrosis, 3 patients experienced thrombotic microangiopathy, and 2 patients experienced device related infections. All other SAEs were reported once in single patients. Overall, 6 SAEs considered related to emicizumab treatment were reported in 5 patients (4.5%) as described previously. Of these, 3 SAEs of thrombotic microangiopathy considered related to emicizumab treatment were reported in 3 patients (2.7%). All other treatment-related SAEs (cavernous sinus thrombosis, skin necrosis, and thrombophlebitis superficial) were each reported in only 1 patient.

Other Significant Adverse Events

Injection site reaction was the most common AE, experienced by 77 of 373 patients (20.6%):

Table 74: Summary of local injection site reactions

APPROVED Summary of Local Injection Site Reactions, Safety Population
Protocols: BH30071, BO39182, BH29992, BH29884
Cutoff Date: BH30071 - 15SEP2017; BO39182 - 15DEC2017; BH29992 - 05OCT2017; BH29884 - 08SEP2017
Snapshot Date: BH30071 - 14NOV2017; BO39182 - 14FEB2018; BH29992 - 16NOV2017; BH29884 - 23OCT2017

MedDRA System Organ Class MedDRA Preferred Term	BH30071 (N=150)	BO39182 (N=48)	BH29992 (N=63)	BH29884 (N=112)	Total (N=373)
Total number of patients with at least one adverse event	39 (26.0%)	10 (20.8%)	11 (17.5%)	17 (15.2%)	77 (20.6%)
Overall total number of events	84	27	26	40	177
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
Total number of patients with at least one adverse event	39 (26.0%)	10 (20.8%)	11 (17.5%)	17 (15.2%)	77 (20.6%)
Total number of events	84	27	26	40	177
INJECTION SITE REACTIONS	39 (26.0%)	10 (20.8%)	11 (17.5%)	17 (15.2%)	77 (20.6%)

Investigator text for AEs encoded using MedDRA version 20.1. 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 events' row in which multiple occurrences of the same AE are counted separately.

All injection site reactions were non-serious, and Grade 1 or 2 in intensity. Most Injection site reactions (94.9%) were well tolerated and as they did not require treatment. Injection-site reactions were observed at any dose across the treatment and did not appear to be limited to the first few doses. There were no discontinuations or dose modifications/interruptions due to injection site reactions. All injection site reactions resolved without sequelae.

No cases with events consistent with systemic hypersensitivity, anaphylactic, or anaphylactoid reactions were reported.

There were not any new reports of thromboembolic events or thrombotic microangiopathy.

Safety related to drug-drug interactions and other interactions

The aggregate analyses performed previously with BH29884 data were repeated for all studies and included new treatment analyses for FVIII, as well as updated analyses for aPCC and FVIIa.

Aggregate Treatment Event Analyses for Activated Prothrombin Complex Concentrate

The majority of patients exposed to aPCC were in BH29884 (29 of 31 patients [93.5%]), only 2 patients were exposed in BH29992, and no patients were exposed to aPCC in BH30071 and BO39182, as they were mainly non-inhibitor patients.

As a first step, the Sponsor conducted an aggregate analysis of treatment events of the use of aPCC. The analysis looked at all doses received by patients, irrespective of the purpose, and counted all doses of aPCC as one “treatment event” until there was a 36-hour, infusion free break. For the purposes of this analysis, an “event” describes the use of aPCC, not bleeds or patients. Treatment events were linked to the thromboembolic event or thrombotic microangiopathy AEs if they overlapped fully or partially with the AE or where the end date of the treatment event occurred within 3 days prior to the AE start.

The aim was to examine whether the cumulative dose of aPCC within a given time interval was linked to the occurrence of these AEs. The first 7 days of emicizumab exposure and data in safety follow-up period (30

days after discontinuation of emicizumab prophylaxis) were excluded for the purposes of this analysis, due to low emicizumab concentration at these times.

Based on this analysis, there were 22 patients who experienced a total of 82 treatment events of the use of aPCC, of which 80 were in BH29884 and 2 in BH29992. This shows that, while a minority of emicizumab-treated patients with FVIII inhibitors used concomitant aPCC, many of the patients did have more than one aPCC treatment event.

The majority of aPCC treatment events lasting for < 24 hours (57.3%) had cumulative doses ranging between 50-100 U/kg and in total 84.1% lasting < 24 hours.

Two patients experienced at least 1 thromboembolic event linked to an aPCC treatment event. Three patients experienced a total of 3 thrombotic microangiopathy events linked to a treatment event.

A categorical analysis looked at the average exposure to aPCC over 24 hours and the total duration of the aPCC treatment events. Of the 82 aPCC treatment events, 8 consisted of an average 24-hour aPCC dose > 100 U/kg and lasted for 24 hours or more.

Five of these 8 events were associated with thromboembolic and thrombotic microangiopathy events.

Table 75: Categorical analysis of average daily exposure and duration of treatment with activated prothrombin complex concentrate

Duration of aPCC Treatment per 24-hour Intervals	Average Dose of aPCC over 24 hours (U/kg/24 hours)				
	<50	50–100	101–150	>150	Any Dose
<24 hours	9	47	8	5	69
24–<48 hours	0	3	1[d]	0	4
48–<72 hours	0	0	3[a,c]	1[b]	4
72–<96 hours	0	1	2	1[e]	4
≥ 96 hours	1	0	0	0	1
All	10	51	14	7	82

aPCC: activated prothrombin complex concentrate

a Thrombotic microangiopathy

b Cavernous sinus thrombosis

c Thrombotic microangiopathy

d Skin necrosis/thrombophlebitis

e Thrombotic microangiopathy

Note: Only subjects receiving aPCC at any point after 7 days of Emicizumab exposure are included (N=22). Treatment events are included where the treatment event overlaps fully or partially with the thromboembolic event / thrombotic microangiopathy event or where the end date of the treatment event falls into the 3 days prior to the thromboembolic event / thrombotic microangiopathy event start.

This analysis confirms that all thromboembolic and thrombotic microangiopathy events related to aPCC were associated with an average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more.

An additional categorical analysis looked at the distribution of cumulative doses of treatment events and compared those consisting of a single dose of aPCC with those consisting of multiple doses. The conclusions of this updated analysis remain consistent with the previous submission. A total of 24 single dose events (29.3%) had more than one infusion, all of which had a cumulative dose > 100 U/kg. All of the treatment events associated with thromboembolic or thrombotic microangiopathy events consisted of multiple aPCC doses.

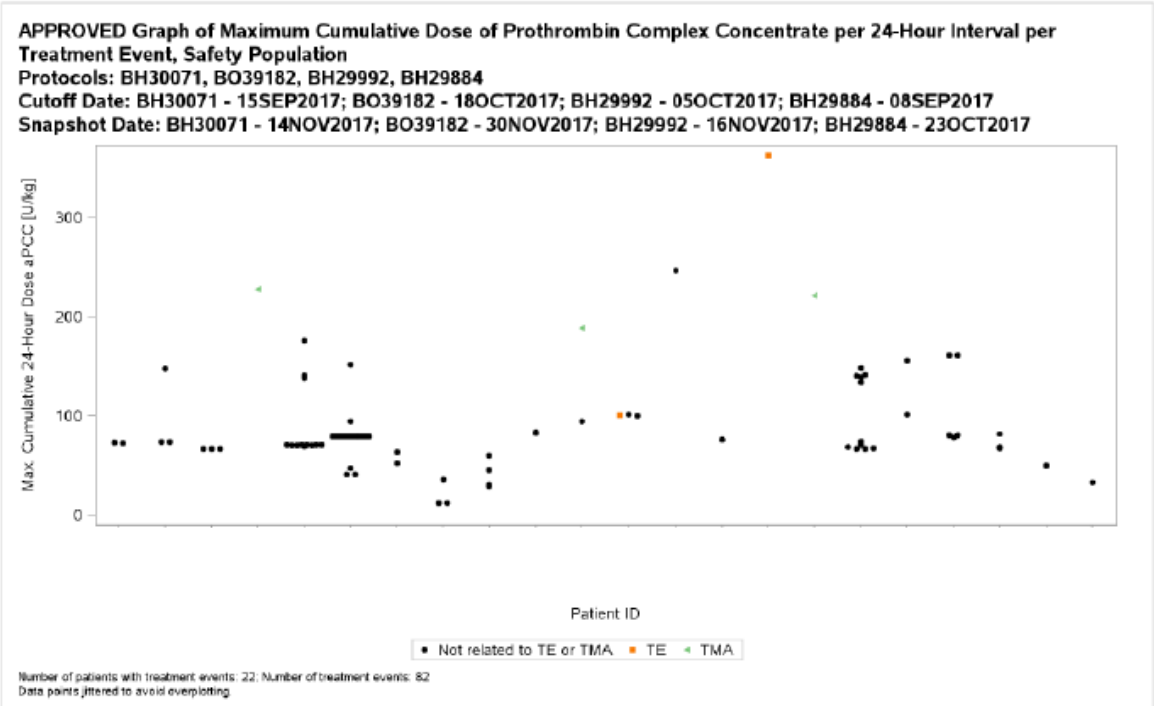
Table 76: Cumulate dose of activated prothrombin complex concentrate by number of infusion

	Cumulative Dose				
Number of infusions	<50 U/kg	50–64 U/kg	65–79 U/kg	80-100 U/kg	>100 U/kg
1	9	3	22	20	2
>1	0	0	0	0	24[a,b,c,d,e]

aPCC: prothrombin complex concentrate
a Thrombotic microangiopathy
b Cavernous sinus thrombosis
c Thrombotic microangiopathy
d Skin necrosis/thrombophlebitis
e Thrombotic microangiopathy
Note: Only subjects receiving aPCC at any point after 7 days of Emicizumab exposure are included (N=22). Treatment events are included where the treatment event overlaps fully or partially with the thromboembolic event / thrombotic microangiopathy event or where the end date of the treatment event falls into the 3 days prior to the thromboembolic event / thrombotic microangiopathy event start.

In order to inform dosing guidance over a defined time period, an additional analysis looked at the maximum cumulative 24-hour dose of aPCC per treatment event. The methodology used for this analysis was described previously. The conclusions of this updated analysis remain consistent with the previous submission. The 3 thrombotic microangiopathy events and the 2 thromboembolic events related to aPCC were associated with at least one instance of maximum cumulative aPCC dose being > 100 U/kg within a 24-hour interval during the contemporaneous treatment event.

Figure 41: Maximum cumulative dose of activated prothrombin complex concentrate per 24 hour interval per treatment event



Three of 4 treatment events with a maximum cumulative 24-hour dose of > 200 U/kg aPCC within a 24-hour interval were associated with thromboembolic or thrombotic microangiopathy events.

Similar analyses were performed for treatment events with rFVIIa. The conclusions of this updated analysis remain consistent with the previous submission. There were 57 patients who experienced a total of 227

treatment events of the use of rFVIIa, of which 205 were in BH29884, 20 in BH29992, and 2 in BO39182. Most rFVIIa treatment events (34.4%) had cumulative doses ranging between 90-180 µg/kg and 77.5% lasting < 24 hours. Of 227 treatment events of co-exposure to rFVIIa and emicizumab in 57 participants, 185 included an average rFVIIa dose ≥ 90 mg/kg/day, of which 49 events lasted ≥ 24 hours. No treatment events with rFVIIa were associated with thromboembolic events. No treatment events where rFVIIa was administered alone were associated with thrombotic microangiopathy events.

New analyses were performed for treatment events with FVIII (including high FVIII doses). There were 86 patients who experienced a total of 278 treatment events of the use of FVIII, of which 215 were in BH30071, 59 in BO39182, and 4 in BH29884.

Table 77: Categorical analysis of average daily exposure and duration of treatment with Factor VIII

APPROVED Number of Treatment Events per Average Daily Exposure of Factor VIII, Safety Population
Protocols: BH30071, BO39182, BH29992, BH29884
Cutoff Date: BH30071 - 15SEP2017; BO39182 - 15DEC2017; BH29992 - 05OCT2017; BH29884 - 08SEP2017
Snapshot Date: BH30071 - 14NOV2017; BO39182 - 14FEB2018; BH29992 - 16NOV2017; BH29884 - 23OCT2017

Population: Total(N=373), included patients: N=86

	Average Dose (Factor VIII)				
	<50 IU/kg/day	50-100 IU/kg/day	101-150 IU/kg/day	>150 IU/kg/day	Any Dose
<24 hours	188 (67.6%)	41 (14.7%)	1 (0.4%)	1 (0.4%)	231 (83.1%)
24 - <48 hours	22 (7.9%)	5 (1.8%)	1 (0.4%)	1 (0.4%)	29 (10.4%)
48 - <72 hours	3 (1.1%)	2 (0.7%)	0	0	5 (1.8%)
72 - <96 hours	2 (0.7%)	2 (0.7%)	0	0	4 (1.4%)
>=96 hours	8 (2.9%)	0	1 (0.4%)	0	9 (3.2%)
All	223 (80.2%)	50 (18.0%)	3 (1.1%)	2 (0.7%)	278 (100%)

Percentages are based on all treatment events.
Note: Only subjects receiving Factor VIII at any point after 7 days of Emicizumab exposure are included.
Factor VIII includes Factor VIII long acting and Factor VIII short acting.

The majority of FVIII treatment events (70.5%) had cumulative doses < 50 IU/kg and 83.1% lasting < 24 hours. Of 278 treatment events of co-exposure to FVIII and emicizumab in 86 participants, 55 included an average FVIII dose ≥ 50 IU/kg/24 hours, of which 12 events lasted ≥ 24 hours.

Summary of Aggregate Treatment Event Analyses

The aggregate treatment event analyses showed that a high cumulative dose of aPCC administered concomitantly with emicizumab was associated with an increased risk of development of thromboembolic or thrombotic microangiopathy events. Specifically, all patients who developed thromboembolic or thrombotic microangiopathy events related to aPCC and emicizumab have received on average a cumulative amount of > 100 U/kg/24 hours of aPCC for a period of 24 hours or more.

The Sponsor concludes that there is sufficient evidence to support a drug-drug interaction between aPCC and emicizumab.

No patients who received concomitant FVIII or rFVIIa alone at any dose or duration developed thromboembolic or thrombotic microangiopathy. Similarly, patients who were co-exposed to a maximum cumulative dose of aPCC ≤ 100 U/kg within a 24-hour interval did not develop thromboembolic or thrombotic microangiopathy events.

Discontinuation due to adverse events

In Study BH30071, 1 patient in Arm B discontinued treatment after 51 days in the study due to multiple low grade AEs (7 AEs: depressed mood, headache, insomnia, lethargy, nightmare, pruritus and alopecia). None of the AEs were reported as serious, and all AEs were Grade 1 or 2 in intensity. None of the AEs required treatment, and all were reported as resolved.

[3 patients were previously reported for Study BH29884].

2 patients (1.3%) in study BH30071 had an adverse event leading to modification or interruption of study treatment (gastroenteritis led to one missing dose and synovitis led to an up-titration).

[6 patients were previously reported for Study BH29884].

Laboratory finding

Overall, there were no changes of clinical significance in haematology or chemistry laboratory parameters in the emicizumab clinical studies.

The company has updated its analysis system to detect antibodies; the company acknowledges that the ADA incidence reports in the Phase III studies could have been underestimated. The sensitivity of the ADA assay has been optimized using disease-specific samples to calculate cutpoints in line with CHMP guidelines for immunogenicity testing.

The overall incidence of ADA across four pivotal Phase III studies was 3.5% (14 of 398) and comparable across studies. Thirteen patients had treatment-induced ADAs and 1 patient had a treatment-boosted response:

Table 78: Incidence of anti-emicizumab antibodies across Phase III studies

APPROVED Overall Anti-Therapeutic Antibody Status, Safety Population
Protocols: BH30071, BO39182, BH29992, BH29884
Cutoff Date: BH30071 - 07FEB2018; BO39182 - 30APR2018; BH29992 - 30APR2018; BH29884 - 03APR2018
Snapshot Date: BH30071 - 19JUL2018; BO39182 - 19JUL2018; BH29992 - 19JUL2018; BH29884 - 19JUL2018

	BH30071 (N=151)	BO39182 (N=48)	BH29992 (N=88)	BH29884 (N=112)	Total (N=399)
Number of patients with at least one post-baseline assessment	151	48	88	111	398
Number of patients with missing baseline assessment	6	1	1	4	12
Number of ATA negative patients					
Negative	142 (94.0%)	43 (89.6%)	80 (90.9%)	107 (96.4%)	372 (93.5%)
Negative (treatment unaffected)	3 (2.0%)	3 (6.3%)	4 (4.5%)	2 (1.8%)	12 (3.0%)
All negative (neg+neg unaffected)	145 (96.0%)	46 (95.8%)	84 (95.5%)	109 (98.2%)	384 (96.5%)
Number of ATA positive patients					
Positive (treatment boosted)	1 (0.7%)	0	0	0	1 (0.3%)
Positive (treatment induced)	5 (3.3%)	2 (4.2%)	4 (4.5%)	2 (1.8%)	13 (3.3%)
All positive (boosted+ induced)	6 (4.0%)	2 (4.2%)	4 (4.5%)	2 (1.8%)	14 (3.5%)

ATA = Anti therapeutic antibodies (also referred to as ADA, or anti-drug/ anti-emicizumab antibodies).
Classification according to Shankar et al. (2014).
Missing baseline assessments are considered as NEGATIVE for derivation of overall anti-therapeutic antibody status.
Percentages are based on the number of patients with at least one post-baseline assessment.

The PK profiles of the 14 ADA-positive patients were examined; of these, 3 (0.75%) had ADAs with neutralizing potential, which was further supported by reduced PD effect. Of these 3 patients, 1 discontinued from emicizumab treatment due to lack of efficacy (Study BH29992). This was reported as an SAE (neutralising antibodies positive). The second patient discontinued due to personal preference and the third patient has not experienced any bleeds (treated or untreated) up to the CCOD and is continuing emicizumab treatment on study.

No cases of anaphylaxis or hypersensitivity were reported in ADA-positive patients. There was no trend towards increased frequency or severity of injection site reactions (ISRs) after patients tested positive for ADAs.

There were no clinically significant changes in ECG parameters from baseline.

Vital signs

There were no clinically significant changes from baseline in vital signs parameters.

Safety in special populations

Overall, there were no appreciable differences in the AE profile of emicizumab between the various age groups (infants, children, adolescents, and adults):

Table 79: Overview of adverse events by age group

APPROVED Safety Summary by Age Group, Safety Population
Protocols: BH30071, BO39182, BH29992, BH29884
Cutoff Date: BH30071 - 15SEP2017; BO39182 - 15DEC2017; BH29992 - 05OCT2017; BH29884 - 08SEP2017
Snapshot Date: BH30071 - 14NOV2017; BO39182 - 14FEB2018; BH29992 - 16NOV2017; BH29884 - 23OCT2017

	0 - < 2 years old (N=5)	2 - < 12 years old (N=55)	12 - < 18 years old (N=47)	18 - < 65 years old (N=253)	>= 65 years old (N=13)	Total (N=373)
Total number of patients with at least one AE	4 (80.0%)	48 (87.3%)	42 (89.4%)	210 (83.0%)	10 (76.9%)	314 (84.2%)
Total number of AEs	10	309	207	975	46	1547
Total number of patients with at least one						
AE with fatal outcome	0	0	0	1 (0.4%)	0	1 (0.3%)
Serious AE	0	9 (16.4%)	5 (10.6%)	28 (11.1%)	1 (7.7%)	43 (11.5%)
AE leading to withdrawal from treatment	0	0	0	4 (1.6%)	0	4 (1.1%)
AE leading to dose modification/interruption	0	0	2 (4.3%)	6 (2.4%)	0	8 (2.1%)
Grade >=3 AE	0	6 (10.9%)	4 (8.5%)	28 (11.1%)	0	38 (10.2%)
Related AE	1 (20.0%)	11 (20.0%)	15 (31.9%)	76 (30.0%)	1 (7.7%)	104 (27.9%)
Local injection site reaction	1 (20.0%)	10 (18.2%)	11 (23.4%)	55 (21.7%)	0	77 (20.6%)
Adverse events of special interest						
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	0	0	1 (2.1%)	0	0	1 (0.3%)
Thromboembolic event (TE)	0	0	0	3 (1.2%)	0	3 (0.8%)
TE event related to aPCC and emicizumab	0	0	0	2 (0.8%)	0	2 (0.5%)
Thrombotic microangiopathy (TMA)	0	0	1 (2.1%)	2 (0.8%)	0	3 (0.8%)
TMA event related to aPCC and emicizumab	0	0	1 (2.1%)	2 (0.8%)	0	3 (0.8%)

Investigator text for AEs encoded using MedDRA version 20.1. 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.
The numbers for systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the Sampson Criteria include all patients that experienced indicative symptoms.

Overall, the majority of patients were White (246 of 373 [65.9%]); there were no appreciable differences in the AE profile of emicizumab as a function of race. There were no clinically meaningful differences in AE profile when stratified by baseline inhibitor status:

Table 80: Overview of adverse events by inhibitor status

APPROVED Safety Summary by Inhibitor Status, Safety Population
Protocols: BH30071, BO39182, BH29992, BH29884
Cutoff Date: BH30071 - 15SEP2017; BO39182 - 15DEC2017; BH29992 - 05OCT2017; BH29884 - 08SEP2017
Snapshot Date: BH30071 - 14NOV2017; BO39182 - 14FEB2018; BH29992 - 16NOV2017; BH29884 - 23OCT2017

	Inhibitor Patients (N=183)	Non-Inhibitor Patients (N=190)	Total (N=373)
Total number of patients with at least one AE	155 (84.7%)	159 (83.7%)	314 (84.2%)
Total number of AEs	829	718	1547
Total number of patients with at least one			
AE with fatal outcome	1 (0.5%)	0	1 (0.3%)
Serious AE	29 (15.8%)	14 (7.4%)	43 (11.5%)
AE leading to withdrawal from treatment	3 (1.6%)	1 (0.5%)	4 (1.1%)
AE leading to dose modification/interruption	6 (3.3%)	2 (1.1%)	8 (2.1%)
Grade >=3 AE	21 (11.5%)	17 (8.9%)	38 (10.2%)
Related AE	47 (25.7%)	57 (30.0%)	104 (27.9%)
Local injection site reaction	30 (16.4%)	47 (24.7%)	77 (20.6%)
Adverse events of special interest			
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	1 (0.5%)	0	1 (0.3%)
Thromboembolic event (TE)	3 (1.6%)	0	3 (0.8%)
TE event related to aPCC and emicizumab	2 (1.1%)	0	2 (0.5%)
Thrombotic microangiopathy (TMA)	3 (1.6%)	0	3 (0.8%)
TMA event related to aPCC and emicizumab	3 (1.6%)	0	3 (0.8%)

Investigator text for AEs encoded using MedDRA version 20.1. 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.
The numbers for systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the Sampson Criteria include all patients that experienced indicative symptoms.
Patients from BH300071 are classified as Non-Inhibitor patients, Patients from BH29992 and BH29884 are classified as Inhibitor patients, Patients from BO39182 are inhibitors if they had >=0.6BU inhibitor in the past and assigned to BPA in the last 24 weeks prior to study.

Additional information overall, the majority of patients were treated with 1.5 mg/kg QW emicizumab (274 of 373 patients). There were no appreciable differences in the AE profile of emicizumab as a function of dosing regimen.

Table 81: Summary of overall safety profile by treatment regimen

APPROVED Safety Summary by dosing regimen, Safety Population
Protocols: BH30071, BO39182, BH29992, BH29884
Cutoff Date: BH30071 - 15SEP2017; BO39182 - 15DEC2017; BH29992 - 05OCT2017; BH29884 - 08SEP2017
Snapshot Date: BH30071 - 14NOV2017; BO39182 - 14FEB2018; BH29992 - 16NOV2017; BH29884 - 23OCT2017

	1.5mg/kg QW emicizumab (N=274)	3mg/kg Q2W emicizumab (N=51)	6mg/kg Q4W emicizumab (N=48)	Total (N=373)
Total number of patients with at least one AE	239 (87.2%)	38 (74.5%)	37 (77.1%)	314 (84.2%)
Total number of AEs	1189	164	194	1547
Total number of patients with at least one				
AE with fatal outcome	1 (0.4%)	0	0	1 (0.3%)
Serious AE	38 (13.9%)	3 (5.9%)	2 (4.2%)	43 (11.5%)
AE leading to withdrawal from treatment	3 (1.1%)	1 (2.0%)	0	4 (1.1%)
AE leading to dose modification/interruption	8 (2.9%)	0	0	8 (2.1%)
Grade >=3 AE	32 (11.7%)	4 (7.8%)	2 (4.2%)	38 (10.2%)
Related AE	78 (28.5%)	13 (25.5%)	13 (27.1%)	104 (27.9%)
Local injection site reaction	58 (21.2%)	9 (17.6%)	10 (20.8%)	77 (20.6%)
Adverse events of special interest				
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	1 (0.4%)	0	0	1 (0.3%)
Thromboembolic event (TE)	3 (1.1%)	0	0	3 (0.8%)
TE event related to aPCC and emicizumab	2 (0.7%)	0	0	2 (0.5%)
Thrombotic microangiopathy (TMA)	3 (1.1%)	0	0	3 (0.8%)
TMA event related to aPCC and emicizumab	3 (1.1%)	0	0	3 (0.8%)

Investigator text for AEs encoded using MedDRA version 20.1. 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.
The numbers for systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the Sampson Criteria include all patients that experienced indicative symptoms.
1.5 mg/kg/QW: BH30071, BH29992 and BH29884; 3 mg/kg/Q2W: BH30071, 6mg/kg/Q4W: BO39182.

Reproductive system

No clinical studies that assessed the reproductive and developmental toxicity of emicizumab have been conducted to date.

Overdose

There were no AEs associated with deviation from the planned dose (there were subjects who received >110% dose).

Presented below are ADRs experienced by emicizumab-treated patients based on Phase III studies,. No new ADRs were reported.

Table 82: Summary of adverse drug reactions in patients treated with emicizumab

MedDRA System Organ Class Adverse reaction (preferred term, MedDRA)	Number of Patients (N=373)	Percent of Patients
General Disorders and Administration Site Conditions		
Injection site reaction	77	21%
Pyrexia	22	6%
Nervous System Disorders		
Headache	52	14%
Gastrointestinal Disorders		
Diarrhea	19	5%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	58	16%
Myalgia	13	4%
Blood and Lymphatic System Disorders		
Thrombotic microangiopathy	3	<1%
Infections and Infestations		
Cavernous sinus thrombosis	1	<1%
Skin and Subcutaneous Tissue Disorders		
Skin necrosis	1	<1%
Vascular Disorders		
Thrombophlebitis superficial	1	<1%

MedDRA=Medical Dictionary for Regulatory Activities

ADRs observed in Study ACE002JP (injection site reaction, headache, diarrhea) were also observed in the Phase III program; therefore, this study contributes no unique ADRs to the pooled safety analysis.

Additional studies

- As of 18 October 2017, there was no SAE reported in the 7 patients who received emicizumab for a maximum duration of 6 weeks in Study MO39129 (a phase IIIb study).
- As of 18 October 2017, there was no SAE reported in the 28 patients (including 3 paediatric patients) who received emicizumab under the US early access programme.
- As of 18 October 2017, of the 6 patients who received emicizumab under single-case compassionate use requests, 5 patients experienced a total of 5 SAEs all of which were considered to be unrelated to emicizumab treatment. There were no deaths.

Post marketing experience

Emicizumab was first approved on 16 November 2017 (US approval). It was subsequently approved in the EU and Australia. Post-marketing data regarding its use was presented in the first global PSUR submitted in July 2018. The next PSUR will be submitted in January 2019.

2.5.1. Discussion on clinical safety

No new aspects of clinical safety have been shown within the clinical studies now submitted. New events of thromboembolic microangiopathy are not reported.

Overall, emicizumab exposure its associated risks are comparable across different dosing regimens and the safety profile is expected to be similar in children (and adults) receiving emicizumab weekly, every two or every four weeks. This conclusion is further confirmed by the similar safety profile observed across the 3 regimens. Also of note, the Cmax of all three regimens is lower than that observed with emicizumab 3 mg/kg QW in Study ACE002JP, where the study drug has been well-tolerated over an approximately 4 year period.

The MAH has updated its analysis system to detect anti-drug antibodies and has found that there were patients who developed antibodies. One such patient withdrew from study because of loss of efficacy related to development of neutralising antibodies.

The available emicizumab safety data indicate that, in itself, the presence of inhibitors is not associated with AEs or specific safety concerns in patients receiving emicizumab.

The types of AEs observed in Study BH29884 and Study BH30071 were similar (with the exception of thromboembolic events or thrombotic microangiopathy; see below), and there were no new or unexpected AEs in patients without inhibitors.

The main observed safety event with emicizumab is the occurrence of thrombotic microangiopathy or thromboembolic events, which were reported when an average cumulative amount of > 100 U/kg/24 hours of aPCC was administered for 24 hours or more, to patients receiving emicizumab prophylaxis. Notably, these events are not related to the presence of inhibitors, and a similar co-exposure of a patient without inhibitors would be expected to have an identical risk for these events. However, this is a hypothetical scenario as bypassing agents are not used for the treatment of patients without inhibitors.

The lack of effect of inhibitor status on the emicizumab safety profile is expected, since neither the underlying disease nor the mechanism of action of emicizumab is affected by FVIII inhibitors. However, as patients with inhibitors require treatment with bypassing agents, whereas patients without inhibitors are treated with FVIII, an important difference between these two groups of patients is the potential interaction between emicizumab and the concomitant medications each group typically receives.

In contrast, none of the co-exposure events of emicizumab and FVIII in Study BH30071 or Study BO39182 were associated with significant AEs, thereby, establishing a favorable safety profile of this co-exposure. Although this co-exposure was not tested specifically in children, the biologic function and dosage of infused FVIII is identical in children and in adults. In fact, the only potential difference is a shorter half-life of exogenous FVIII in children (Mancuso et al. 2017), resulting in a lower exposure for a given dose.

Results from Study BH29884 and Study BH29992 demonstrate that emicizumab trough plasma concentrations are consistent across different ages. In healthy individuals, FVIII levels remain constant from birth through adulthood (Andrew et al. 1988; 1992), so in this respect the emicizumab levels are consistent with the physiologic lack of change of FVIII activity levels with age. The early physiologic maturation of FVIII

levels (Kuhle et al. 2003) suggests that a given FVIII activity is expected to provide a similar safety and efficacy in adults and in children.

Therefore the favourable safety data obtained in Study BH29992 are applicable to and representative of all paediatric patients with haemophilia A, regardless of the presence or absence of FVIII inhibitors, and that the safety profile of the combination of FVIII and emicizumab has been established in Study BH30071.

In summary, the above considerations regarding the biology of haemophilia A and the mechanism of action of emicizumab, together with the consistent PK data in Study BH29884 and Study BH30071, indicate that the presence of FVIII inhibitors does not impact the safety or efficacy of emicizumab. The efficacy and safety data obtained from Study BH29992 are equally applicable and generalisable to children with or without FVIII inhibitors.

The clinical value of this generalisation is further highlighted by the superior efficacy of emicizumab compared to FVIII prophylaxis observed in Study BH30071and by the substantial medical unmet needs of paediatric patients without inhibitors. These unmet needs include central venous access device (CVAD)-associated morbidity, delayed initiation of prophylaxis resulting in increased risk of intracranial haemorrhage, and an onerous treatment burden - all of which are addressed by emicizumab due to its long half-life and SC bioavailability.

Updates have been made to the SmPC to reflect new information on clinical safety which is considered acceptable.

The MAH has not submitted clinical data on safety in subjects with mild or moderate haemophilia and without inhibitors; this has been considered as a notable deficiency because of concern over thrombosis in subjects with appreciable endogenous FVIII activity when exposed to the current product.

Assessment of paediatric data on clinical safety

Data available from the paediatric population has not identified aspects of safety that are specific to the paediatric population. Nonetheless, it is advised to collect more detailed information on safety in the paediatric population via the proposed PASS (please see RMP section).

Additional expert consultation

See outcome of the ad hoc expert group meeting convened on the 25th January 2019 – under Discussion of Clinical Efficacy

2.5.2. Conclusions on clinical safety

Aspects of clinical safety are considered to be clinically manageable in line with the recommendations given in the SmPC.

The company has not submitted clinical data on safety in subjects with mild or moderate haemophilia and without inhibitors; considering this lack of data and because of the risk of thrombosis and TMA, no recommendation can be made to grant the indication in mild and moderate haemophilia A patients without inhibitors.

The CHMP considers the following measures necessary to address issues related to safety:

Additional safety data will be collected for the paediatric population via the proposed PASS.

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

The CHMP endorsed the Risk Management Plan version 2.4 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	Thromboembolic events (associated with emicizumab and aPCC) Thrombotic microangiopathy (associated with emicizumab and aPCC)
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 Immunogenicity
Missing information	Use in female patients, pregnancy and lactation Use in Neonates and Infants ~~Use in elderly patients~~ Long term use of emicizumab Peri-operative management of patients on emicizumab The safety of emicizumab in patients receiving ITI

aPCC = activated prothrombin complex concentrate; ITI = immune tolerance induction therapy

The missing information 'Use in elderly patients' was eligible to be removed from the list of safety concerns in view of the GVP Module V Revision 2.

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
PASS based on the EUHASS registry Ongoing ~~Planned~~	To assess the incidence of thromboembolism, thrombotic microangiopathy, and anaphylaxis in real-world conditions, in patients exposed to emicizumab and treated at centers	Thromboembolic events (associated with emicizumab and aPCC) Thrombotic microangiopathy (associated with emicizumab and aPCC)	Protocol submission (Protocol GO40162)	30 April 2018
			PASS annual report (generated by Roche, based	Within 4 months of reception of the

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	participating to the European Haemophilia Safety Surveillance System (EUHASS).	Systemic hypersensitivity, anaphylaxis, and anaphylactoid events	on the emicizumab-specific annual report)	emicizumab-specific annual report provided by EUHASS
			First PASS annual report	30 June 2020
			Final PASS annual report	30 June 2024
			PSUR/PBRER reporting	First inclusion in PSUR expected in January 2021, thereafter, in accordance with EURD list
PASS based on the HCP and patient/carer survey Initiated ~~Planned~~	Evaluate the awareness, knowledge and compliance of HCPs and patients/carers to the additional risk minimization measures (guide for HCPs, patient/carer guide, patient alert card)	Thromboembolic events (associated with emicizumab and aPCC) Thrombotic microangiopathy (associated with emicizumab and aPCC) Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab	Protocol submission	30 October 2018
			Submission of the final study report	30 April 2021 *(6 months after study completion)*
PASS based on the PedNet	Evaluation of the incidence of thromboembolic events, TMA,	Thromboembolic events (associated with	Submission of the first PASS annual report	30 September 2020

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Submission of the final study report	30 September 2022
			PSUR/PBRER reporting	First inclusion in PSUR expected in January 2021

Risk minimisation measures

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 Alert 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 HCP and patient/carer survey PASS based on the PedNET registry

Safety concern	Risk minimization measures	Pharmacovigilance activities
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 Alert 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 HCP and patient/carer survey PASS based on the PedNET registry

Safety concern	Risk minimization measures	Pharmacovigilance activities
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 Alert Card Patient/Carer Guide Guide for Laboratory Professionals	Additional pharmacovigilance activities: HCP and patient/carer survey
Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions	Routine risk minimization measures: SmPC section 4.3: Contraindications Package Leaflet section 2 What you need to know before you use 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
Immunogenicity	SmPC section 5.1: Pharmacodynamic properties *No additional measures*	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting

Safety concern	Risk minimization measures	Pharmacovigilance activities
Missing Information		
Use in female patients, pregnancy and lactation	SmPC section 4.6: Fertility, pregnancy and lactation Package Leaflet Section 2 What you need to know before you use Hemlibra *No additional measures*	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting
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
~~**Use in elderly patients**~~	~~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
Long term use of emicizumab	*No routine or additional measures*	
Peri-operative management of patients on emicizumab	SmPC section 4.2: Posology and method of administration (special populations) *No additional measures*	
The safety of emicizumab in patients receiving ITI	SmPC section 4.5:Interaction with other medicinal products and other forms of interaction *No additional measures*	

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Hemlibra (emicizumab) is included in the additional monitoring list as it is a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hemlibra is proposed for the treatment for routine prophylaxis of bleeding episodes in patients with:

- haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.
- severe haemophilia A (congenital factor VIII deficiency, FVIII<1 %) without FVIII inhibitors

Hemlibra can be used in all age groups.

3.1.2. Available therapies and unmet medical need

The standard treatment of patients with haemophilia A is intravenous FVIII replacement therapy with recombinant or plasma-derived FVIII concentrates given either episodically ("on demand") in response to the occurrence of bleeding symptoms or prophylactically on a scheduled basis to prevent bleeding. Prophylactic therapy is considered superior to episodic treatment of symptomatic bleeds. Data from clinical trials indicate that patients without FVIII inhibitors who adhere to the prescribed prophylactic FVIII regimens have satisfactory bleed control, with median annualised bleeding rates in the range of 0.9 – 4.1. Even so, MRI scans demonstrate progressive arthropathy [thought caused by subclinical bleeds] in up to two-thirds of patients who receive a primary prophylaxis regimen as standard of care. A recent survey demonstrated that prophylaxis was routinely available to adults in only 18 of 35 European countries surveyed and 50% or fewer adults received FVIII prophylaxis in 12 out of those 18 countries. Most are managed with episodic treatment. Even extended-life FVIII products need to be administered up to 3 times per week.

Up to 30% of patients with haemophilia A develop neutralising antibodies (inhibitors) against FVIII after exposure to therapeutic FVIII concentrates. The current standard of care for treatment of bleeds in haemophilia A patients with inhibitors is treatment with bypassing agents. The two products available for this are: recombinant factor VIIa (rFVIIa, NovoSeven) and activated prothrombin complex concentrate (aPCC, or factor eight inhibitors bypassing agent [FEIBA]). NovoSeven is indicated for episodic use only, while FEIBA is approved for episodic and prophylactic use in patients with high-responding inhibitors and frequent joint bleeding. These products are short-acting and may need to be administered often, with long IV infusion times and/or require frequent administration for prophylaxis.

Whilst prophylactic regimens are used for subjects with severe haemophilia, those with mild or moderate haemophilia are managed with 'on-demand' therapy. Patients with moderate or mild haemophilia A may be also managed on-demand with s/c DDAVP rather than exogenous FVIII.

For all subjects, regular venous access is needed to administer currently licensed other products.

There remains a clinical need to reduce bleeding and so reduce consequent morbidities by using products that may be easily administered.

3.1.3. Main clinical studies

Two new clinical studies were submitted in patients with and without inhibitors:

Study BH30071 (HAVEN-3), a randomised, multi-centre, open-label study. The study enrolled 152 patients with severe congenital haemophilia A (intrinsic FVIII level < 1%) aged 12 years or older and with a body weight ≥ 40 kg. Subject had a negative test for factor VIII inhibitors (and with evidence of lack of the presence of an inhibitor for the last 5 years). The study had 4 arms. Patients who received episodic treatment with FVIII prior to study entry and experienced at least 5 bleeds over the 24 weeks prior to study entry (equivalent to annualized bleeding rate [ABR] ≥ 10) were randomized in a 2:2:1 ratio. HAVEN-3 did not enrol subjects with inhibitors / 35 subjects were exposed to a maintenance dose of 3mg/kg q2w / 8 subjects were <18yrs age.

Study BO39182 (HAVEN-4) a multi-centre, open-label study. The study enrolled 48 patients with severe congenital haemophilia A (intrinsic FVIII level < 1%) aged 12 years or older and with a body weight ≥ 40 kg. Subjects were either with or without the presence of inhibitors to FVIII. 7/48 subjects took part in a run-in PK study. The main efficacy analysis was of the 41/48 subjects who did not take part in the PK run-in study. Subjects in the main cohort were administered emicizumab prophylaxis at 3 mg/kg QW SC for 4 weeks followed by 6 mg/kg Q4W SC. The median duration of the efficacy period for the 41 patients included in the efficacy analysis was 25.57 weeks (range: 24.1-29.4 weeks).

The MAH also submitted updates / final versions of the following studies that were submitted previously [as interim reports] to support the indication for subjects with inhibitors.

BH29884 (HAVEN 1) is a randomised, multi-centre, open-label study. The MAH now submits an update of experience beyond 24 weeks of exposure to study product and with an additional 4 patients recruited. The majority (82.3%) of patients had ≥ 48 weeks follow-up at cut-off.

BH29992 (HAVEN 2) is a single-arm, multi-centre, open-label study. The study enrolled 63 paediatric patients (60 patients < 12 years of age, including 10 patients ≤ 2 years, and 3 patients ≥ 12 years of age and < 40 kg) with congenital haemophilia A with FVIII inhibitors, who were receiving bypassing agents as a previous treatment. All subjects were male with a mean age of 6.6yrs (range 1 – 15yrs). The study population was multi-ethnic. There was a median of 6 bleeds in the last 24 weeks prior to study entry (range: 0-155 bleeds). Upon study entry, subjects were administered a weekly loading dose of 3.0 mg/kg SC of emicizumab for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg/week SC.

Non-interventional Study BH29768 / final analysis submitted based on date 31 Mar 2017.

Supportive Phase I/II Study ACE002JP. Eligible patients from Study ACE001JP part C (Japanese patients ≥ 12 and < 60 years of age with or without FVIII inhibitors)

3.2. Favourable effects

Bleed rates and analyses were as previously described for studies HAVEN-1 and HAVEN-2 (studies submitted previously to support initial application for a licence). A negative binomial model was used to analyse bleeds.

Haven-3:

- Emicizumab prophylaxis with the maintenance dose of 1.5 mg/kg QW resulted in a 96% reduction in rate of treated bleeds compared with no prophylaxis (annualised bleed rate cohort A / cohort C ratio = 0.04; p < 0.0001)
- Emicizumab prophylaxis with the maintenance dose of 3 mg/kg Q2W led to a 97% reduction in rate of treated bleeds, compared with no prophylaxis (annualised bleed rate cohort B / cohort C ratio = 0.03; p < 0.0001).

Haven-4:

- The negative binomial model-based annualised bleed rate for treated bleeds was 2.4 (95% CI: 1.38, 4.28) and for all bleeds was 4.5 (95% CI: 3.10, 6.60)
- 56.1%patients did not experience any treated bleeds while receiving emicizumab prophylaxis.

Haven-2:

- 86.4% patients had 0 treated bleeds (annualised bleed rate = 0) while receiving emicizumab prophylaxis

Haven-1:

- The negative binomial model of annualised bleed rate (95% CI) for treated bleeds across all treatment arms in the all emicizumab-treated patients was 2.7 (1.64, 4.35), mean (95% CI)

In all above studies, the results of all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds supported / were consistent with the data for treated bleeds.

3.3. Uncertainties and limitations about favourable effects

There are limited data on subjects with haemophilia without inhibitors in the paediatric age range. The company has conducted an extrapolation exercise for the paediatric population based on information from adults and paediatric patients with inhibitors. It is argued that the biology of haemophilia A and the mechanism of action of emicizumab, together with the consistent PK in patients with or without inhibitors, indicate that the presence of FVIII inhibitors does not impact the safety or efficacy of emicizumab, and that the mode of action of emicizumab is independent from the presence of inhibitors. Patients with congenital haemophilia A, therefore [and when considering treatment with emicizumab], constitute a single population regardless of inhibitor status. Thus, the efficacy data observed in study HAVEN 2 may be considered applicable to children without inhibitors. Therefore, in order to address the concern over the lack of data on clinical safety in the paediatric age groups, the company commits to report on clinical safety for the subsets of paediatric age groups in the PSUR (and to update the RMP accordingly). Finally, a PASS will be conducted to focus on gaining more clinical data in paediatric patients without inhibitors treated with emicizumab on a weekly basis.

There is lack of experience of long-term exposure beyond the time limits of the clinical studies submitted; the post-authorisation safety studies as described in the RMP will provide long term safety data.

There is limited experience of use around the time of surgery. Planned surgery was an exclusion criterion for studies. Most surgeries that are reported were ‘minor’. Bleeds owing to a surgery or procedure were excluded from analyses. The fact that the safety and efficacy of emicizumab have not been formally evaluated in the surgical setting has been reflected in section 4.2 of the SmPC. It is appreciated that case reports on clinical management of patients around the time of surgery would not appear to give reason to raise concern at this stage.

The MAH has not collected data on exposure of the current product to subjects with 'moderate' or 'mild' forms of haemophilia without inhibitors. Lack of information on use of the current product on subjects with 'moderate' or 'mild' forms of haemophilia without inhibitors is considered to be a notable deficiency of this application and therefore this indication cannot be granted. The MAH withdrew its claim to this proposed indication.

3.4. Unfavourable effects

5 patients developed ADAs, one of whom withdrew from the study because of acquired loss of efficacy resulting from the neutralising effect of the antibodies.

Injection site reactions were experienced by (about) 20% of all patients. This was already reflected in section 4.8 of the SmPC where the frequency of injection site reaction is very common.

Thromboembolic and thrombotic microangiopathy events reported in subject with FVIII inhibitors were ascribed to drug-drug interaction with activated prothrombin complex concentrate (aPCC). There were not any new reports of thrombotic microangiopathy or thromboembolic disease; the MAH has extended its analysis and finds that all patients who developed thromboembolic or thrombotic microangiopathy events related to aPCC and emicizumab have received on average a cumulative amount of > 100 U/kg/24 hours of aPCC for a period of 24 hours or more and concludes that there is sufficient evidence to support a drug-drug interaction between aPCC and emicizumab. Although it is unlikely that emicizumab and aPCC would be used together in patients without inhibitors, the known interaction raises concern over possible association with other coagulation factors and that use of other coagulation factors will have to be done with caution. The current warning as described in section 4.4 of the SmPC applies for the use of emicizumab and aPCC in patients without inhibitors.

Laboratory tests in relation to haemostasis are not / may not be informative in the presence of emicizumab. Emicizumab affects assays for aPTT and all assays based on aPTT, such as one-stage FVIII activity. Life-threatening bleeding due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab has been classified as an important potential risk. As a routine risk minimization measure, appropriate warnings are included in section 4.4 of the SmPC which states that aPTT-based coagulation laboratory test results in patients who have been treated with emicizumab prophylaxis should not be used to monitor emicizumab activity, to determine dosing for factor replacement or anti-coagulation, or measure FVIII inhibitor titers. Additional risk minimisation measures include educational materials aimed at patients, healthcare professionals and laboratory professionals.

Some subjects did not experience breakthrough bleeds whilst exposed to emicizumab; some subjects continue to experience bleeds in spite of full compliance with treatment. The MAH has not been able to identify any pre-existing factors that may predict those who would continue to experience breakthrough bleeds. The MAH has added information on the management of breakthrough bleeds and management of patients at the time of surgery in sections 4.4 and 5.1 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Further analysis of the MAH on the cause of thrombotic microangiopathy is reassuring yet there remains high concern that the pathophysiology of this adverse event has not been fully elucidated. Further, patients with haemophilia A without inhibitors treated in prophylaxis could have undercurrent bleeding treated with FVIII. *In vitro* pharmacodynamics interactions of emicizumab in combination with FVIIII have been tested. At FVIII concentrations of 1UI/ml, emicizumab marginally shortened lag time and tt Peak, and had almost no effect on peak height, indicating that emicizumab competes with FVIII on FIX, FX binding. It appears that

emicizumab with FVIII may result in non-additive coagulation potential. The MAH has not investigated drug-drug interaction with medicinal products used in the management of moderate (or mild) haemophilia such as DDAVP. The posology recommendation as well as the warning statement as stated in section 4.2 and 4.4 of the SmPC and already part of the initial MA are still considerate adequate to minimise these risks.

Whilst it is acknowledged that subjects were exposed to exogenous FVIII activity at the time of breakthrough bleeds, this was for short term only; clinical safety in the context of long term use of the current product in subjects with background FVIII activity is not established. There are not any data on the long-term safety aspects of haemophilia, such as arthropathy. The post-authorisation safety studies will provide more information on the long term use of emicizumab.

There are no data on subjects with 'mild' or 'moderate' congenital Haemophilia A without inhibitors who have appreciable FVIII activity; considering that it is not been established whether or not these subjects will be more at risk at events such as thrombosis or thromboembolic disease, the indication in mild and moderate haemophilia A patients without inhibitors cannot be granted. The MAH withdrew its claim to this proposed indication.

3.6. Effects Table

Table 83: Effects Table for emicizumab:

Effect	Short Description	Uncertainties/ Strength of evidence
Favourable Effects for the ITT population at 24 weeks in study HAVEN-3		
negative binomial model-based annualised bleed rate for **all treated bleeds** (excluding bleeds owing to surgery / procedures)	For 36 subjects exposed to 1.5mg/kg ecicizumab qw sc, ABR = 1.5 (95% CI: 0.89, 2.47). 96% reduction compared with no prophylaxis (annualised bleed rate cohort A / cohort C ratio = 0.04; p < 0.0001)	• Efficacy data around time of major surgery limited • Limited efficacy data for subjects <18yrs • Long-term follow-up data not available • No subjects with mild or moderate congenital Haemophilia A • Supported by sensitivity analyses and sub-group analyses • Efficacy data consistent for all types of bleeding endpoints collected
	For 35 subjects exposed to 3mg/kg ecicizumab q2w sc, ABR = 1.3 (95% CI: 0.75, 2.27) 97% reduction compared with no prophylaxis (annualised bleed rate cohort B / cohort C ratio = 0.03; p < 0.0001)	
	For 18 subjects who did not receive prophylaxis ABR = 38.2 (95% CI: 22.86, 63.76)	
negative binomial model-based annualised bleed rate for **all bleeds** (excluding bleeds owing to surgery / procedures)	For 36 subjects exposed to 1.5mg/kg ecicizumab qw sc ABR = 2.5 (95% CI: 1.63, 3.90) 95% reduction compared with no prophylaxis (annualised bleed rate cohort A / cohort C ratio = 0.05; p < 0.0001)	
	For 35 subjects exposed to 3mg/kg ecicizumab q2w sc ABR = 2.6 (95% CI: 1.63, 4.29) 94% reduction compared with no prophylaxis (annualised bleed rate cohort B / cohort C ratio = 0.06; p < 0.0001)	

Effect	Short Description	Uncertainties / Strength of evidence
	For 18 subjects who did not receive prophylaxis ABR = 47.6 (95% CI: 20.45, 79.59)	
Favourable Effects – study HAVEN-4 -- up to 24 weeks exposure interim reported		
Zero bleeds	41 patients in main study cohort [open label, uncontrolled] 56.1% patients did not experience any treated bleeds while receiving emicizumab prophylaxis. 90.2% (n = 37) of patients experienced 0 to 3 treated bleeds.	• interim data • Limited efficacy data for subjects <18yrs • No subjects with mild or moderate congenital Haemophilia A • Results consistent with other studies submitted • Limited exposure time
negative binomial model-based annualised bleed rate for **treated bleeds**	ABR = 2.4 (95% CI: 1.38, 4.28)	
negative binomial model-based annualised bleed rate for **all bleeds**	ABR = 4.5 (95% CI: 3.10, 6.60)	
Favourable Effects – study HAVEN-1		
Negative binomial model-based annualised bleed rate (95% CI) for treated bleeds across all treatment arms	82.3% of patients had ≥ 48 weeks follow-up at study cut-off ABR = 2.7 (1.64, 4.35)	• Results are consistent / lower compared to those reported in the Primary CSR • Analysis by time intervals shows reduction in bleeds over time • All subjects have FVIII inhibitors
Favourable Effects – study HAVEN-2		
Zero bleeds	Data on 59 paediatric subjects with at least 12 weeks exposure reported [open label, uncontrolled] 51/59 patients (86.4%) had 0 treated bleeds (annualised bleed rate =0) while receiving emicizumab prophylaxis. 58/59 patients (98.3%) had reported 0 treated spontaneous bleeds (annualised bleed rate =0)	• Results consistent with other studies submitted • All subjects have FVIII inhibitors • Limited exposure time

Effect	Short Description	Uncertainties / Strength of evidence
Unfavourable Effects (all safety population)		
	• Novel aspects of safety not detected. • New instances of thrombotic microangiopathy not detected • Patients may still experience bleeding episodes whilst exposed to the current product.	• Laboratory assays may be unreliable in presence of current product • Uncertain if drug antibody assays are reliable
		• Long term effectiveness of risk mitigations measures not yet established. • Underlying cause of thromboembolic microangiopathy remains open

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Reduction in the number of bleeds, as reported with exposure to emicizumab, is an important clinical outcome. The MAH itself notes that data from published clinical trials indicate that patients without FVIII inhibitors who adhere to the prescribed prophylactic FVIII regimens have satisfactory bleed control, with median annualised bleeding rates in the range of 0.9 – 4.1. Even so, MRI scans demonstrate progressive arthropathy [thought caused by subclinical bleeds] in up to two-thirds of patients who receive a primary prophylaxis regimen as standard of care.

Exposure to emicizumab appears to match the annualised bleeding rates already reported for prophylactic FVIII in the context of a clinical trial. There remains the issue of wider use outside the context of a clinical study and how compliance is affected by that.

Emicizumab has notable aspects of clinical risk, in particular haemorrhage, thromboses and thrombotic microangiopathy. Some reassurance over the cause of thrombotic microangiopathy events and how they may be prevented was provided by the MAH. However, there are no data on subjects with ‘mild’ or ‘moderate’ congenital Haemophilia A without inhibitors who have appreciable FVIII activity. Considering that it is not been established whether or not these subjects will be more at risk at events such as thrombosis or thromboembolic disease, the indication in mild and moderate haemophilia A patients without inhibitors cannot be granted.

Clinical management of breakthrough bleeds and management of patients in the peri-operative period (especially major surgeries) whilst exposed to emicizumab remain areas of limited experience; this has been adequately reflected in section 4.2 of the SmPC.

Association with a PCC should be avoided. Association with FVIII factors in case of undercurrent bleedings in haemophilia A patient without inhibitors does not seems to be synergic but competitive. It is advised that

interaction with other medicinal products and especially those with a pro-thrombotic profile be more fully investigated; this will be addressed in the post-authorisation safety study (please see RMP).

Emicizumab interacts with laboratory assay for aPTT and all assays based on aPTT. Since the extension of indication will concern a lot of patients, it will be very challenging to ensure a broad communication to healthcare professionals involved in assays and haemophilia A monitoring. (Paediatricians, haematologists, general practitioners, pharmacists etc...). A dedicated PASS will be conducted in order to assess the HCP and patient/carer survey.

3.7.2. Balance of benefits and risks

It is considered that data to support benefit outweighs risk in subjects with severe congenital haemophilia A without inhibitors at maintenance posologies of 1.5mg/kg/qw sc. 3.0mg/kg/q2w sc and 6.0mg/kg/q4w sc/

It is considered that the lack of data in mild and moderate forms of congenital haemophilia A prevent a positive recommendation for these indications.

3.8. Conclusions

The overall B/R of Hemlibra 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, IIIA and IIIB

Extension of Indication to include routine prophylaxis of bleeding episodes in patients with severe haemophilia A (congenital factor VIII deficiency, FVIII<1 %) without FVIII inhibitors. In addition, two additional posology recommendations for adults and children with haemophilia A with and without factor VIII inhibitors are recommended. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information of the pivotal trials. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor corrections and clarity to sections 4.4, 4.5 and 4.6 of the SmPC.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include routine prophylaxis of bleeding episodes in patients with severe haemophilia A (congenital factor VIII deficiency, FVIII<1 %) without FVIII inhibitors. In addition, two additional posology recommendations for adults and children with haemophilia A with and without factor VIII inhibitors are recommended. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information of the pivotal trials. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor corrections and clarity to sections 4.4, 4.5 and 4.6 of the SmPC.

Summary

Please refer to Scientific Discussion Hemlibra-H-C-4406-II-02