25 January 2018
EMA/88475/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hemlibra

International non-proprietary name: emicizumab

Procedure No. EMEA/H/C/004406/0000

Note

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

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List of abbreviations

95/99 TI	95% confidence/99% probability tolerance interval
A280	absorbance at 280 nanometres
AC	acceptance criterion
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADE	acceptable daily exposure
ADI	acceptable daily intake
AE	adverse event
AGE	advanced glycation end-products
aPCC	activated prothrombin complex concentrates
APTT	activated partial thromboplastin time
AR	annual report
ATA	anti-therapeutic antibody
ATCC	American Type Culture Collection
ATS	attribute testing strategy
AU	absorbance unit
AUC	area under the curve
BI	bioindicator
bp	base pair
BSA	bovine serum albumin
CDR	complementarity-determining region
CH	constant domain of the heavy chain
CHO	Chinese hamster ovary
CI	confidence interval
CIP	clean-in-place
CL	constant domain of the light chain
CMV	cytomegalovirus
CoA	certificate of analysis
CPE	cytopathic effect
CPP	critical process parameter
CQA	critical quality attribute

CV	coefficient of variation
DF	diafiltration
DL	detection limit
DoE	design of experiment
DP	Drug Product
DS	Drug Substance
ESMO	equivalent in sample mean only
F/T	freeze/thaw
Fab	antigen-binding portion of immunoglobulin molecule
Fc	effector portion of the immunoglobulin molecule
FcRn	neonatal Fc receptor
HC	heavy chain
HCCF	harvested cell culture fluid
HCP	host cell proteins
IgG	immunoglobulin G
IgG1(κ)	immunoglobulin G1(κ)
IPC	in-process control
IV	intravenous
IVPCV	integrated viable packed cell volume
KPI	key performance indicator
LC	light chain
mAb	monoclonal antibody
MCB	master cell bank
MHC	major histocompatibility complex
MoA	mechanism of action
MPN	most probable number
MSV	murine sarcoma virus
MTV	mouse thymic virus
NA	not applicable
N.D.	not detected
NE	no excursion
NEM	N-ethylmaleimide
NF	National Formulary

NIR	near infrared
NT	not tested
OD	optical density
OQ	operational qualification
P	p-value (overall analysis of variance)
pCPP	potential critical process parameter
PCR	polymerase chain reaction
PCV	packed cell volume
PD	pharmacodynamics
PHCCF	pre-harvest cell culture fluid
pI	isoelectric point
PI-2	parainfluenza virus type 2
PK	pharmacokinetics
poly A	polyadenylation
PPQ	process performance qualification
PQ	performance qualification
PQS	pharmaceutical quality system
PSD	practically significant difference
PV	process validation
QA	Quality Assurance
QA	quality attribute
QbD	quality by design
QC	Quality Control
QL	quantitation limit
QPCR	quantitative polymerase chain reaction
QS	quantity sufficient
QTPP	quality target product profile
QU	Quality Unit
RH	relative humidity
RM	Reference Material
RMSE	root mean square error
rpm	revolutions per minute
RRF	risk ranking and filtering

RSD	relative standard deviation
R2	coefficient of determination
RVLP	retrovirus-like particle
SC	subcutaneous
SD	standard deviation
SDM	scale-down model
SME	subject matter expert
SST	system suitability test
T	temperature
t	time
t0	time zero
TE	Thrombo-embolic event
TEM	transmission electron microscopy
TI	tolerance interval
TMA	Thrombotic Microangiopathy
TNTC	too numerous to count
TOC	total organic carbon
TSE	transmissible spongiform encephalopathy
UF	ultrafiltration
UFDF	ultrafiltration and diafiltration
UV	ultraviolet
VF	virus filtration
VH	variable domain of the heavy chain
VHP	vaporised hydrogen peroxide
VL	variable domain of the light chain
WCB	working cell bank
WFI	water for injection

Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Limited submitted on 22 June 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Hemlibra, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Hemlibra is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.

Hemlibra can be used in all age groups

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that emicizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 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.

Applicant's request for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance emicizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 25 June 2015, 23 July 2015 and 21 July 2016. The Scientific Advice pertained to insert quality, non-clinical and clinical aspects of the dossier.

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

- The application was received by the EMA on 22 June 2017.
- Accelerated Assessment procedure was agreed-upon by CHMP on 18 May 2017.
- The procedure started on 13 July 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 September 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 September 2017. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 28 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 10 October 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 9 November 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 December 2017.
- During the CHMP meeting on 12 December 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 December 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 18 January 2018.
- During the meeting on 25 January 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Hemlibra on 25 January 2018.

2. Scientific discussion

2.1. Problem statement

The development of inhibitors is the most severe treatment-related complication of haemophilia A. Current treatment option for haemophilia A patients who developed inhibitors is immune tolerance induction (ITI). However, ITI fails to eradicate inhibitors in approximately 20-40% of treated patients (Franchini et al. 2012). It is also time intensive and burdensome, particularly for children, who frequently require surgical implantation of central venous lines. When FVIII can no longer be used to control bleeding, patients with inhibitors may be treated with agents who bypass FVIII, known as bypassing agents (BPA). But these products are not as effective as FVIII, with patients suffering frequent bleeds, mainly into target joints, that are difficult to control even with large doses of bypassing agents. BPAs are also short-acting and may need to be administered frequently, particularly for prophylactic treatment, with long IV infusion times. This can sometimes cause compliance issues. Increased bleeding resulting from suboptimal disease management leads to pain and disability through progression of joint disease, notwithstanding the impact on quality of life (Hay and DiMichele 2012; Kempton and White 2009; Kreuz et al. 1995).

Overall, there is an unmet medical need for new, more convenient and efficacious treatment options for patients with Haemophilia A with inhibitors.

2.1.1. Disease or condition

Haemophilia A is a X-linked recessive bleeding disorder characterised by congenital underproduction of or dysfunction of FVIII. It accounts for approximately 80% of all cases of haemophilia.

Haemophilia A can be classified into severe, moderate or mild haemophilia depending on the % normal level of active clotting factor remaining (< 1%: severe haemophilia; 1–5% moderate and 5-40% with mild haemophilia). This classification is however less relevant for the population of patients who developed inhibitors.

The main bleeding sites in patients with haemophilia A are usually intra-articular, intramuscular, subcutaneous, gastrointestinal, mucocutaneous, and/ or intracranial. Repeated intra-articular bleeds are a major contributor to decreased quality of life, as the joint damage associated with multiple haemarthroses may progress to haemophilic arthropathy.

2.1.2. Epidemiology

The incidence of haemophilia A is approximately 1 in 5,000 live-born male births or 1 out of every 10,000 live births (Centers for Disease Control and Prevention [CDC] 2016; National Institutes of Health [NIH] 2017; Franchini and Mannucci 2013; WFH 2016b). In the European Union, this equates to around 510 newborns with haemophilia A in 2015 (based on an estimated 5.1million children born in EU-28 (Eurostat 2015). The prevalence of haemophilia A varies with the reporting country, with a range of 5.4-14.5 cases per 100.000 males. Haemophilia A occurs in all races and ethnic groups. Because it is an X-linked, recessive disease, it is predominantly occurring in males. Females are usually asymptomatic carriers.

The epidemiology of inhibitors in haemophilia A is reported as an overall inhibitor prevalence of 5–7%. When limited to patients with severe disease the prevalence is much higher at 12–13%. The incidence of new FVIII inhibitors in patients with severe FVIII deficiency is approximately 30%.

Inhibitors are less common in patients with mild or moderate haemophilia occurring in approximately 3–13% of patients (World Federation of Hemophilia [WHF] 2016a). Most patients develop an inhibitor within a relatively short time of exposure days. A bimodal peak of inhibitor risk in early childhood and old age has been identified lately (all reviewed in Witmer C *et al*; Ther Adv Hematol (2013) 4(1) 59–72).

2.1.3. Clinical presentation, diagnosis and prognosis

Factor VIII inhibitors can be detected either with routine laboratory testing or by clinical presentation. An inhibitor is clinically suspected when a patient experiences bleeding that does not adequately respond to haemostatic therapy (Witmer C *et al*; Ther Adv Hematol (2013) 4(1) 59–72).

Patients with inhibitors are recognised as having the most severe clinical course among those affected by haemophilia, mainly due to suboptimal disease management. These patients experience frequent bleeds that are difficult to control even with large doses of bypassing agents, with bleeds which can be life threatening.

2.1.4. Management

For the proposed patient population who developed inhibitors, permanent eradication of inhibitors is usually first choice. Immune tolerance induction (ITI) involves administration of factor VIII in a small dose to begin with and gradually increasing the dose so that the individual's immune system learns to tolerate the FVIII and ceases to produce inhibitors. However, an optimal regimen for ITI remains to be defined and the length of treatment is based on individual responses, ranging from months to years and comes with high treatment burden. ITI has a success rate of 60% to 80% (Mariani et al. 2003; Hay and DiMichele 2012; Santagostino et al. 2009).

When FVIII can no longer be used to control bleeding, patients with inhibitors may be treated with bypassing agents. The two principal products available for this are:

- recombinant factor VIIa (rFVIIa, NovoSeven) and
- activated prothrombin complex concentrate (aPCC, or factor eight inhibitors bypassing agent [FEIBA]).

BPAs are short-acting and may need to be administered often, with long IV infusion times (25-50 minutes for FEIBA) and/or require frequent administration for prophylaxis (daily or every other day for FEIBA). Frequent administration is time-consuming and burdensome for people with haemophilia A and their caregivers.

NovoSeven is indicated for episodic use only, while FEIBA is approved for episodic and prophylactic use.

It is recommended that prophylaxis be considered for patients whose condition has failed to respond to ITI and who have recurrent significant bleeding (i.e. a target joint or life-threatening haemorrhages) (Young, G *et al*, 2011; Haemophilia 17: e849–e857). Still the haemostatic effect of bypassing agents used prophylactically is suboptimal. Data have shown that patients on aPCC prophylaxis achieve an ABR of 7.9 (Antunes *et al*; 2014), and patients who take rFVIIIa prophylactically experience 2-3 bleeds/month (Konkle *et al*; 2007). These are higher numbers of bleeds than patients without inhibitors on FVIII concentrates who can achieve a median ABR of approximately 0-2 with optimal prophylaxis.

Despite the availability of prophylaxis regimens for patients who develop FVIII inhibitors, the majority of patients are currently treated with episodic regimens, in part due to the treatment burden of prophylaxis regimens.

About the product

Emicizumab is a novel bispecific monoclonal antibody which mimics coagulation factor VIII and, therefore, is capable of promoting the activation of FX by FIXa, resulting in downstream haemostasis at the site of bleeding in patients with haemophilia A who have decreased or no circulating levels of FVIII.

Emicizumab has no structural relationship or sequence homology to factor VIII and, as such, does not induce or enhance the development of direct inhibitors to factor VIII.

The applied and approved indication is the following:

Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors.

Hemlibra can be used in all age groups.

The recommended dose is 3 mg/kg once weekly for the first 4 weeks (loading dose), followed by 1.5 mg/kg once weekly (maintenance dose), administered as a subcutaneous injection.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on:

- There is unmet medical need for new, more efficacious, but equally convenient treatment options for patients with Haemophilia A with inhibitors.
- The request for accelerated assessment has overall been adequately substantiated. The data package will allow robust evaluation of the claimed indication.
- Based on the evidence submitted, a clinically meaningful benefit is assumed, whilst the safety concerns particularly around DDIs have been characterised and risk minimisation measures proposed, to be evaluated as part of the RMP.
- The proposed full extrapolation of efficacy and safety for the youngest age group (0-2 years of age) is noted. The acceptability of this exercise will be part of the review process but is not considered to jeopardise an overall assumed positive benefit:risk for the remaining age groups within the proposed indication.
- If licensed, Emicizumab, with its weekly s.c. dosing schedule and an improved efficacy profile over existing inhibitor treatment options, which are limited, has the potential to provide substantial therapeutic advantage to patients with Haemophilia A and inhibitors.
- It has the potential to change medical practice, as it decreases treatment burden by elimination of daily IV treatments at home with its subsequent risks, while reducing bleeding rates and improving quality of life.

2.2. Quality aspects

2.2.1. Introduction

Emicizumab is a novel bispecific monoclonal antibody which mimics coagulation factor VIII (referred to as FVIII hereafter) and, therefore, is capable of promoting the activation of FX by FIXa, resulting in downstream haemostasis at the site of bleeding in patients with haemophilia A who have decreased or no circulating levels of FVIII.

The antibody structure is based on a human immunoglobulin G4 (IgG4) framework containing two different heavy chains (referred to as Q- and J-chains by the applicant) and light chain sequences. The bispecific antibody binds to FIXa and FX and has co-factor activity that substitutes FVIII.

The finished product is supplied as a single-use, sterile, colourless to slightly yellow solution for subcutaneous injection and contains no preservatives. The finished product is formulated as 30 mg/mL (30 mg strength) or 150 mg/mL (containing 60 mg, 105 mg, and 150 mg of emicizumab). The excipients are L-histidine, L-aspartic acid, L-arginine, and poloxamer 188 and water for injections.

2.2.2. Active Substance

General information

The recombinant humanized monoclonal antibody is produced in Chinese hamster ovary (CHO) cells and consists of one anti-FIXa heavy chain named in-house as Q chain, one anti-FX heavy chain named in-house as J chain, and two light chains (referred to as L-chain).

The Fc region of the two heavy chains (Q chain and J chain) was engineered to preferentially heterodimerize by electrostatic steering mutations. During the purification of the bispecific antibody, mispaired Homo species including J-Homo Main (antibody consists of two light chains and two J chains) and Q-Homo Main (antibody consists of two light chains and two Q chains), are removed.

Like other complex glycoproteins, emicizumab displays a certain amount of micro-heterogeneity in terms of different degrees of glycosylation and modifications of amino acids. Both heavy chains, Q chain and J chain, also have a single conserved glycosylation site.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Emicizumab is produced using a suspension-adapted CHO cell line. The source is the working cell bank (WCB), which is derived from the master cell bank (MCB). The cell culture process for the production of emicizumab active substance involves three stages: the seed train, the inoculum train, and the production culture. The seed train is used to provide a continuous source of cells for the production of multiple batches and is started by thawing one vial of the working cell bank (WCB). The inoculum train is used to expand the cell population for introduction into the production stage. The production stage is used to produce emicizumab, which is secreted into the culture fluid. During production, cell viability and productivity are enhanced by addition of nutrients. The production culture is harvested by separating the secreted molecule from cells and cell debris.

From each production run, a single batch of harvested cell culture fluid (HCCF) is produced and can be traced back to the WCB vial used to initiate the manufacturing process.

Following the cell culture steps, harvest is initiated from the production bioreactor. Following completion of the cell culture production stage, the secreted emicizumab in the pre-harvest cell culture fluid (PHCCF) is separated from cells and cellular debris. The harvested cell culture fluid (HCCF) is cooled and stored. Once the contents of the bioreactor are processed, water for injections may be flushed to recover any residual product.

The emicizumab purification process consists of chromatography steps and additional steps for removal and inactivation of potential viral contaminants. The final step in the active substance purification process is concentration of the product and buffer exchange using ultrafiltration and diafiltration (UFDF). Protein concentration and buffer composition are adjusted to the active substance specification by addition of a stock solution containing histidine and arginine buffer and poloxamer 188. The active substance solution is filtered into appropriate storage containers.

Cell substrate, genetic stability, cell banks

The generation of the production cell line and the expression vectors has been described in detail.

Emicizumab is manufactured in a Chinese Hamster Ovary (CHO) cell line which is regarded as well established. Sufficient details have been provided on the source and history of the cell substrate. The preparation of the expression constructs for the three different antibody chains (Q/J/L chains) has been appropriately described and vector maps have been provided.

Control of materials

The details on the raw materials used in the fermentation and purification process as well as the quality standards e.g. compendial or non-compendial (in-house) specifications have been presented. The pharmacopoeial raw materials and reagents comply with their respective monographs. The non-pharmacopoeial materials are accepted on the basis of the specification indicated.

Control of critical steps and intermediates

To ensure the quality of emicizumab active substance, in-process controls (IPCs) have been established. Depending on criticality, some of the IPCs are tested against acceptance criteria; for other IPCs, alert levels and action limits have been defined and these are acceptable. All IPC tests and limits applied to the cell culture and purification processes have been provided.

Process validation

Development, characterization, and validation of the emicizumab process are based on a Quality by design (QbD) approach. The applicant has emphasized that emicizumab follows essentially the same concepts as previously approved for other Roche antibodies. The QbD strategy has been discussed in detail.

The applicant has built a series of risk assessment tools aimed at analyzing, categorizing, and ensuring appropriate mitigation and management of risk to product efficacy and safety related to the production process. In combination, these elements form a comprehensive risk and science based program to assess the criticality of product attributes and rationally design a process and product control strategy.

• Identification of critical quality attributes (CQAs) for the active substance and finished product using CQA risk ranking and filtering (RRF) was refined iteratively during development as more product knowledge was accumulated;

• Process design, assessment of potential critical process parameters (pCPPs) to be included in process validation (PV) studies, and analysis and categorization of study results to identify CPPs were refined continuously over the process development life cycle;

• The product and process understanding and risk assessment outcomes were used as inputs to a final assessment that determines the Attribute Testing Strategy (ATS), which was coupled to a robustness assessment.

Process validation strategy

The manufacturing process for emicizumab active substance has been evaluated and validated to define acceptable process parameter ranges that ensure consistent product quality. Development and PV of the emicizumab active substance process are built upon a comprehensive science- and risk-based approach, which incorporates process and product understanding developed from emicizumab-specific studies. The applicant has generated risk assessments for the identification of potential critical process parameters (pCPPs), PV and linkage studies, as well as the tool applied to define the CPPs.

The PV section includes studies conducted using qualified scale-down models and manufacturing-scale equipment. Site-specific studies include PV studies that were conducted at manufacturing scale. These studies demonstrate manufacturing process consistency for relevant product quality attributes and key performance indicators (KPIs) when producing emicizumab in the commercial facility. Site- and scale-independent PV studies to support the identification of CPPs and the definition of acceptable process parameter ranges are generally conducted in qualified scale-down models of the manufacturing-scale unit operations.

The commercial active substance manufacturing process, validated site-specific at commercial scale (G2.1 process), was shown to be reproducible and produces active substance with acceptable quality. Data generated from seven consecutive batches all meet the predefined validation study acceptance criteria as well as the proposed commercial acceptance criteria. All batches were manufactured consecutively according to the production plan. This is acceptable.

Moreover, the results of 30 manufacturing batches demonstrate process consistency. Consistent removal of J/Q homo variants and other product- or process-related impurities was demonstrated. Deamidation in complementarity-determining regions (CDRs) and non-CDRs were consistent and within controlled levels.

The G2.1 commercial process is able to consistently reduce host cell proteins (HCP) and leached protein A to acceptable low levels. In conclusion, the evaluation of G2.1 batches confirms that process-related impurities and product variants are controlled and reduced to acceptable levels.

Moreover, the validation of site-specific process hold times was successfully performed.

Manufacturing process development

Summary of emicizumab control strategy

The control strategy comprises the elements of batch release, in-process controls (IPCs) with acceptance criteria, stability testing, and the monitoring program. These elements are part of the Attribute Testing Strategy (ATS). The control strategy further comprises control of raw materials, environmental control, procedural controls, control of process parameters, and additional IPCs.

One of three possible outcomes is identified for each quality attribute:

1. Control system testing

2. Monitoring program

3. No testing

Once a testing strategy has been defined for each attribute, an overall assessment is performed to determine the robustness of the proposed testing strategy. The recommended testing strategy for each of the emicizumab active substance quality attributes using the ATS RRF tool and the robustness assessment has been listed by the applicant.

The applicant has utilized their risk ranking and filtering (RRF) tool for the attribute testing strategy (ATS). The applicant's evaluation of quality attributes appears comprehensive and the classification of scores seems reasonable.

Comparability

During clinical development, four different active substance manufacturing processes were established. The four process versions are referred to as G1 process, G1.2 process, G2 process and G2.1 process. The G2.1 process is used for the manufacture of material for pivotal clinical studies and is established as the commercial process.

The comparability assessment between clinical trials phases included a large number of analytical procedures including various functional assays, e.g. biological activity and an FcRn binding assay. No relevant differences in structure, mass, potency, and purity were observed.

Characterisation

Sufficient data on the physicochemical, biological, and immunochemical characteristics of emicizumab has been provided:

- Physicochemical characterisation, which describes studies on the elucidation of the structural information of emicizumab, including primary structure, post-translational modifications, and higher-order structure. In addition, detailed characterisation of emicizumab structural variants, including molecular size and charge variants, has been provided provided.
- Biological and immunochemical characterization, which studies emicizumab's ability to bind FIXa and FX.
- CQA assessment, which references the used tools and a summary of the CQAs.

FcRn binding properties of the emicizumab active substance process performance qualification (PPQ) batches were analysed and demonstrated that the batches are comparable.

The identification of CQAs for emicizumab has been described in sufficient detail and the potential impurities have been analysed and are considered sufficiently controlled.

Specification

The proposed active substance specification includes control for pharmaceutical characteristics, identity, purity, bacterial endotoxins, bioburden, content, and potency. Overall, the test items included in the specifications are considered adequate and in line with relevant guidance.

Analytical methods

Descriptions of analytical procedures for active substance lot release, and validation summaries have been provided.

Batch analysis

Batch data for active substance lots used during clinical development and for product manufactured at the commercial manufacturing facility have been provided. The batch analyses data demonstrate that the results were within the specifications and that emicizumab active substance is reproducibly manufactured.

Reference standards

The two-tiered (primary and secondary/working) reference standard system, including the details on the batch selection, preparation, storage, qualification, and stability of emicizumab reference standards has been appropriately described. Also, the history of the reference standards and qualification of future reference standards have been described in sufficient detail. The characterisation results obtained confirmed compliance with the acceptance criteria proposed for active substance and corroborate suitability as reference standards.

Container closure system

The proposed bags appear suitable as container closure system. Adequate extractable and leachable (E&L) studies were conducted. No leachables were found above acceptable limits. The information provided was sufficient.

Stability

Primary stability data to support the commercial shelf life assignment are derived from stability studies of the following active substance batches:

-Three PPQ batches (used for process validation) manufactured at the commercial facility using the G2.1 commercial manufacturing process and scale, and stored at the recommended storage condition;

-Seven clinical batches manufactured at the commercial facility using the G2.1 commercial manufacturing process and scale, and stored at the recommended storage condition;

-One technical batch manufactured at the commercial facility using the G2.1 commercial manufacturing process and scale, and stored at the recommended storage condition.

For all batches, all stability results have remained within the proposed acceptance criteria, therefore supporting the claimed shelf life at the recommended conditions.

Stability-indicating profile

A panel of analytical procedures was developed and validated that profiles the stability characteristics of emicizumab. Validation of the commercial analytical procedures and their stability-indicating properties have been adequately described. The analytical procedures to assess the stability of emicizumab include methods to determine potency, purity, and physicochemical changes. This set of analytical procedures ensures that changes in quality, quantity, and potency of emicizumab will be detected.

Based on the stability results the claimed shelf life for the active substance at the recommended storage conditions is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Emicizumab finished product is supplied as a sterile, colourless to slightly yellow solution for single-use subcutaneous injection and contains no preservatives.

Each single-use, 3 mL vial contains 30 mg, 60 mg, 105 mg, or 150 mg (nominal value) of emicizumab at target pH 6.0. The finished product is formulated as 30 mg/mL (30 mg strength) or 150 mg/mL (containing 60 mg, 105 mg, and 150 mg of emicizumab). The 60 mg, 105 mg, and 150 mg finished products have identical formulations, differing from each other only in the fill volume (0.4 mL; 0.7 mL and 1 mL respectively).

The 30 mg strength consists of 30 mg/mL emicizumab in a vial at a nominal fill volume of 1.0 mL. The 30 mg finished product has an identical composition to the active substance and the 150 mg/mL finished products, except for a 5-fold lower emicizumab concentration. The 30 mg finished product is intended for low-body weight/paediatric patients, and the lower concentration is intended to facilitate the handling from a liquid volume perspective.

The primary packaging components used for the manufacture of emicizumab finished product consist of a 3 mL USP/Ph. Eur./JP Type I glass vial, sealed with a rubber stopper and crimped with an aluminum cap fitted with a plastic flip-off disk.

Pharmaceutical development

The finished product formulation for the 150 mg/mL strength is identical to the active substance formulation. Concentration and composition of formulated emicizumab occurs at the active substance stage. No further compounding or dilution is performed during finished product manufacturing. The 30 mg finished product formulation is identical to the active substance formulation, except for a five-fold lower concentration of active ingredient achieved by dilution with formulation buffer at the finished product manufacturing stage.

Phase I clinical trials were conducted with a single-use formulation, designated as F01 and containing 80 mg/mL emicizumab. For subsequent pivotal clinical trials, the formulation was adapted by increasing the protein concentration while keeping all other formulation components and concentrations unchanged. Two strengths of this formulation were used in clinical trials; the only difference between them is the fill volume, namely 60 mg (0.4 mL, Product F04) and 150 mg (1.0 mL, Product F03). The commercial finished product strengths are the same as those used for pivotal clinical trials, with the addition of a 105 mg strength (F02), that was not used in clinical trials. An additional formulation (Product F05), containing 30 mg/mL emicizumab in the identical formulation composition, was developed for clinical and commercial use in low-body weight/paediatric patients and was used in pivotal clinical trials.

The results of formulation development studies conducted prior to pivotal studies provided the data and rationale for the selection of an appropriate formulation. These studies were followed by a multivariate formulation robustness study to address potential critical formulation parameters.

The multivariate formulation robustness study demonstrated that the relevant quality attributes of emicizumab are acceptable at the edges of these composition ranges. A multivariate stability study was then conducted using several formulation parameters as input factors, as these factors had been identified to have a potential impact on critical quality attributes (CQAs) during finished product storage. In summary, the active substance and finished product shelf lives are adequately supported even at the edges of the allowed formulation composition ranges.

Manufacture of the product and process controls

The finished product was developed using a Quality by Design approach with risk assessment tools to define critical quality attribute acceptance criteria (CQA-ACs), CPPs, and the control strategy.

The process description is based on a batch size range (i.e., volume of bulk finished product solution). The vials, stoppers, vessels, and filters as well as the connective tubing are cleaned and sterilized prior to use. The finished product solution is filtered through an in-line 0.22 µm sterilizing-grade filter.

The manufacture of finished product includes the following main process steps:

-Pooling of several containers of the active substance and mixing

-Bioburden reduction filtration of the bulk finished product solution

-Sterile filtration of the finished product solution; vial filling and stoppering

-Capping and crimping

-Final inspection of vials

-Labelling and secondary packaging

A summary of the acceptable ranges derived from the process design and validation studies have been provided. The ranges are justified by process design studies, process validation studies, and media fill runs.

Controls of critical steps and intermediates

An overview of the CPPs and IPCs that control the critical steps and, thus, ensure appropriate routine control of the entire manufacturing process has been provided.

Apart from microbiological attributes and some other process parameters, finished product process design and validation studies have demonstrated that the emicizumab finished product manufacturing process is robust.

Validation studies have been performed to ensure that the sterilization and depyrogenation processes for product-contacting equipment are effective. Media fill runs are routinely performed and demonstrate the effectiveness of aseptic processing operations and the suitability of the technical setup. Filter validation was performed to demonstrate microbial retention under worst-case processing conditions.

Process validation / verification

The validation of the finished product manufacturing process included the manufacture of several consecutive PPQ runs representing the full range of batch sizes for commercial manufacturing.

The process validation campaign was conducted using active substance batches from the G2.1 process manufactured according to the commercial active substance manufacturing process and scale.

The finished product (FP) registration batches (used as primary stability batches) and PPQ batches (used for formal process validation) for the 30 mg, 60 mg, 105 mg, and 150 mg FP were manufactured at the commercial manufacturing facility.

Three registration batches for the 60 mg FP and three registration batches for the 150 mg strength were manufactured. The purpose of the registration batches is to support the shelf life claim for the commercial finished products.

For the 30 mg strength, three batches were manufactured at the commercial manufacturing facility, serving the double purpose of registration batches and PPQ batches. As registration batches, these batches support the shelf-life claim for the commercial finished product. As PPQ batches, the same batches validate the finished product manufacturing process.

Furthermore, the batch sizes (prepared volume of bulk finished product solution) of the PPQ batches were defined to cover the minimum and the maximum of the commercial manufacturing batch size range. During the validation campaign, process parameters for each process step were operated at the target operating conditions or at the edges of the allowed ranges.

The information provided in this section is sufficient and acceptable.

Product specification

The finished product specification includes relevant parameters in accordance with ICH Q6B and the Ph. Eur. monograph on parenteral preparations.

Analytical procedures

Both pharmacopoeia-based and emicizumab-specific analytical procedures are used to test the commercial batches of the finished product for release and/or stability.

Detailed descriptions of the analytical procedures have been provided. The suitability of these analytical procedures for their intended use was either verified or validated.

Batch analysis

The evaluation of the emicizumab registration and PPQ finished product batches against the proposed commercial specifications has been provided. PPQ batches are used for the finished product manufacturing process validation. Registration batches are manufactured using the finished product commercial manufacturing process at the commercial facility. Finished product registration batches are different from PPQ batches and are used to derive primary stability data that support the shelf life claim for the finished product.

All batch analysis results meet the specifications that were in effect at the time of testing and release for each batch.

In addition, all available release data from emicizumab finished product batches produced during the registration and PPQ campaigns were re-evaluated against the proposed commercial release specification and results meet the commercial release specification acceptance criteria.

Overall, the batch testing results are consistent.

Container closure

The primary packaging components used for the manufacture of emicizumab finished product consist of a 3 mL colourless USP/Ph. Eur./JP Type I glass vial, sealed with a rubber stopper, crimped with an aluminium cap fitted with a plastic flip-off disk. All primary packaging materials are of suitable quality for packaging sterile liquid products and comply with relevant pharmacopoeial requirements.

The container closure system has been sufficiently described. Packaging materials are of standard quality and comply with relevant Ph. Eur. requirements.

Stability of the product

A shelf life of 24 months at 2°C-8°C, protected from light, is proposed for the finished product. Batches were examined under long-term storage conditions at 5±3°C, and accelerated stability studies were performed at 25±2°C /60% relative humidity. The batches were also studied under stress conditions at 40±2°C /75% relative humidity.

In addition, stability of the finished product when exposed to light has been investigated for the 60 mg and for 30 mg emicizumab FP in the manufacturing-scale container closure material (3 mL USP/Ph. Eur./JP Type I glass vial). Stability after intensive light exposure was determined by comparing the results of an unprotected, exposed sample in the primary packaging (unlabelled vial) to the results for vials stored in the secondary packaging. The photo stability study demonstrates that finished product in unprotected vials should not be exposed to intense light for prolonged periods and that the vials should be stored in the carton.

Overall, the stability data looks consistent and satisfactory. Stability acceptance criteria were met. Based on the results from the primary stability studies, as well as data from photo stability study, temperature excursion studies, in-use stability study, and freeze/thaw stability study, the claimed shelf life of 2 years when stored at 2°C to 8°C is acceptable. Based on the in-use stability results once removed from the refrigerator, unopened vials can be kept at room temperature (below 30°C) for up to 7 days.

Comparability exercise for finished medicinal drug product

During clinical development and up to the definition of the commercial presentation, the changes that were introduced into emicizumab finished product concerned the emicizumab concentration and the fill volume, whereas the primary packaging and the nature and concentration of the excipients were left unchanged throughout clinical development.

No change in finished product manufacturing process and in-process controls was made between G1, G2, and G2.1-derived finished products, except for the fill volume.

The comparability between G1, G2, and G2.1 processes was demonstrated during clinical development on the active substance level, by assessing results from release testing and extended characterization available at the time of comparability assessment. In addition, and also as part of clinical development, a comparative stress stability study was performed on finished product level including finished product manufactured using active substance derived from G1, G2, and G2.1 processes. Overall, the G2.1 material was shown to be comparable with G1 and G2 materials in terms of product quality and safety as shown by release testing, extended characterization, and comparative stress stability.

The comparability between G1, G2, and G2.1-derived finished products during clinical development also included a comparison of relevant finished product release data available at the time of comparability assessment. With the introduction of G2.1-derived finished product with different fill volumes, the suitability for intended use was also confirmed during clinical development by comparing relevant finished product release data available at the time of comparability assessment.

The assessment performed during clinical development, and based on comparative finished product release data, demonstrated that G1, G2, and G2.1-derived finished products have comparable quality and that there is no impact of the fill volume on finished product quality.

Adventitious agents

No substances of human or animal origin are used during manufacture, and the safety of the cell substrate has been suitably demonstrated. No virus like particles were detected other than retrovirus-like particles which were identified as intracytoplasmic A and C-type particles, which are known to be present in CHO cells. An acceptable estimation of the number of retrovirus particles per dose was provided.

The applicant has conducted viral clearance studies and selected the model viruses in accordance with ICH Q5A. The small scale models used were suitably validated. No impact on viral clearance was seen with any process parameter within the ranges tested. Clearance studies were based on worst case setting. The studies show an acceptable viral clearance potential of the manufacturing process.

Column sanitisation procedures were suitably validated. All study reports and analytical validation results were submitted.

The information provided is considered sufficient and satisfactory.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information presented in the quality sections of the emicizumab dossier is very detailed and of high quality. Relevant guidelines and Ph. Eur. monographs have been taken into account. The development of the manufacturing process and the control strategy is based on a QbD approach and is generally considered justified. A very similar approach has already been found acceptable for other authorised Roche monoclonal antibodies. The QbD approach used for the development and control of the manufacturing process has been extensively explained in this application. The control strategy is considered sufficient to guarantee consistent quality of emicizumab. Specification limits and analytical methods are suitable to control the quality of the active substance and finished product.

The stability program is in general considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Sufficiently detailed data and documents have been provided indicating that the quality of the active substance and finished product are well controlled.

Information about the active substance and finished product was of acceptable quality. The manufacturing processes of the active substance and finished product have been adequately described and have been satisfactorily validated. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

2.3. Non-clinical aspects

2.3.1. Introduction

To support the registration of Hemlibra, a series of *in vitro* studies were performed to characterise the binding of emicizumab to activated and non-activated Factor IX and X and the effects on Factor X activation, Factor IX activation, prothrombin activation, thrombin generation and activated partial thromboplastin time (aPTT).

In addition, the haemostatic potency of emicizumab was evaluated *in vivo*, in the *Cynomolgus monkey*.

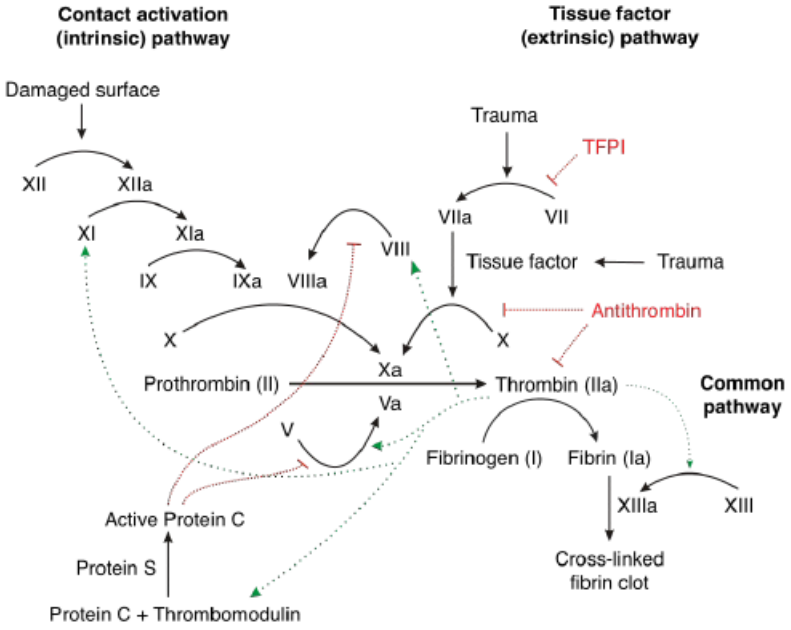
The potential for emicizumab to promote Fc effector function was also investigated.

2.3.2. Pharmacology

FVIII is a glycoprotein found in plasma that, in its activated form, serves as a co-factor for FIXa and FX, facilitating the reaction whereby FX is catalysed to FXa. After coagulation is initiated by the complex of exposed tissue factor (TF) and activated factor VII (FVIIa) in the plasma and a small amount of thrombin is produced, FVIII undergoes enzymatic cleavage by thrombin and is converted into activated FVIII (FVIIIa). Because it enhances the FIXa–induced FX activation reaction by 200,000-fold; FVIIIa plays a critical role in accelerating the explosive coagulation reaction during the propagation phase of the blood coagulation reaction process. A dysfunction at this central point in haemostasis is therefore associated with severe bleeding complications of a broad spectrum of locations.

An overview of the coagulation system with its activation (solid and dotted arrow headed lines) and inhibition pathways (bar-headed lines) is presented in Figure 1.

Figure 1: **Coagulation Pathway**

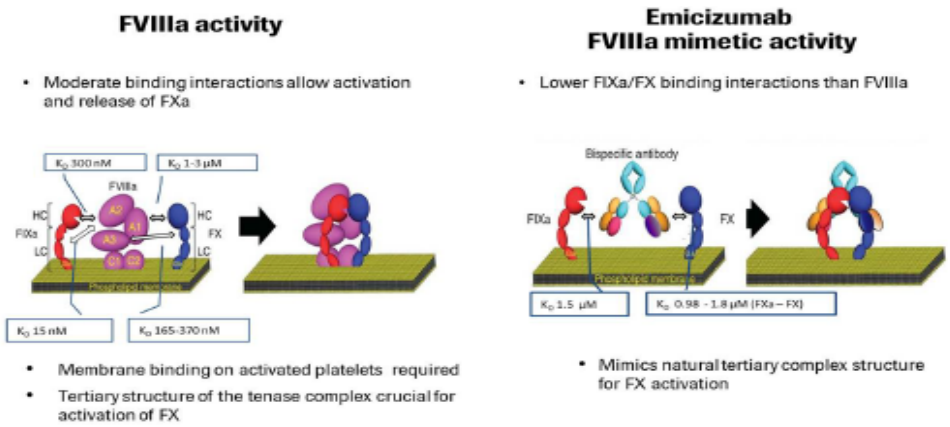


TFPI=tissue factor pathway inhibitor.
Image by [J. Dunckley, 2007].

Hemlibra is a humanised monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure, produced by recombinant DNA technology in Chinese hamster ovary cells. Hemlibra bridges activated factor IX and factor X mediating the activation of the latter. This is normally the function of coagulation factor VIII, which is missing in haemophilia A patients. This bispecific antibody restores the function of missing activated factor VIII that is needed for effective haemostasis. In patients with haemophilia A, haemostasis can be re-established irrespective of the presence of FVIII inhibitors, as Hemlibra shares no sequence homology with FVIII. The figure below summarises the interactions of FVIIIa (part A) or emicizumab (part B) with FIX/FIXa and FX/FXa.

The mode of action of emicizumab and how it compares to that of FVIIIa, is shown in Figure 2.

Figure 2: Schematic Illustration of the Mode of Action of FVIIIa and Emicizumab



FIXa=activated factor IX; FVIIIa=activated factor VIIIa; FX=factor X; FXa=activated FX; Gla=gamma-carboxyglutamate acid-rich; HC=heavy chain; K_D=dissociation constant; LC=light chain.

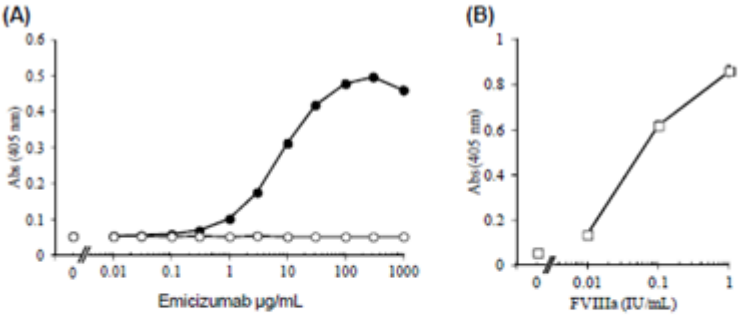
Primary pharmacodynamic studies

The *in vitro* data presented demonstrate that emicizumab has a moderate bispecific target binding affinity for activated and non-activated FIX and FX in the micromolar range.

Characterisation of the binding epitopes revealed that emicizumab binds to the EGF1 domain of FIX/FIXa and to the EGF2 domain of FX/FXa. Although EGF domains are expressed in other vitamin K-dependent coagulation-related proteins, emicizumab did not bind FVII, FXII, or Protein C, demonstrating clear binding specificity for FIX/FIXa and FX/FXa.

The applicant characterised the functional activity of emicizumab and investigated the effect on human FX activation. The data demonstrate that emicizumab promotes activation of FX by FIXa in the absence of FVIIIa and thus it has the potential to functionally restore haemostatic activity.

Figure 3: Effect of Hemlibra on activation of factor X by activated factor IX



Abs = absorbance; FVIIIa = activated factor VIII; hFIXa = human activated factor IX; hFX = human factor X.
(A): Effect of emicizumab on activation of hFX by hFIXa. (B): Effect of FVIIIa on activation of hFX by hFIXa. Absorbance corresponds to relative FX activation.
Mean ± SD (n = 3), calculated from three measurements.SD too small to be visualized.
Filled circles (●) indicate FIXa mediated FX activation by emicizumab, open circles (○) indicate effects of emicizumab in the absence of FIXa. Open squares (□) indicate the effect of FVIIIa.

The Michaelis-Menten kinetics of substrate FX were calculated to assess the catalytic efficiency of emicizumab. In comparison to FVIIIa, the estimated Michaelis-Menten constant (K_m) of emicizumab was lower, indicating stronger binding interaction to FIXa and FX, but the catalytic efficiency (kcat/K_m) to promote the turnover of the reaction was only ~9% of the catalytic efficiency of FVIIIa.

Table 1: Kinetics of FIXa-Catalyzed FX Activation

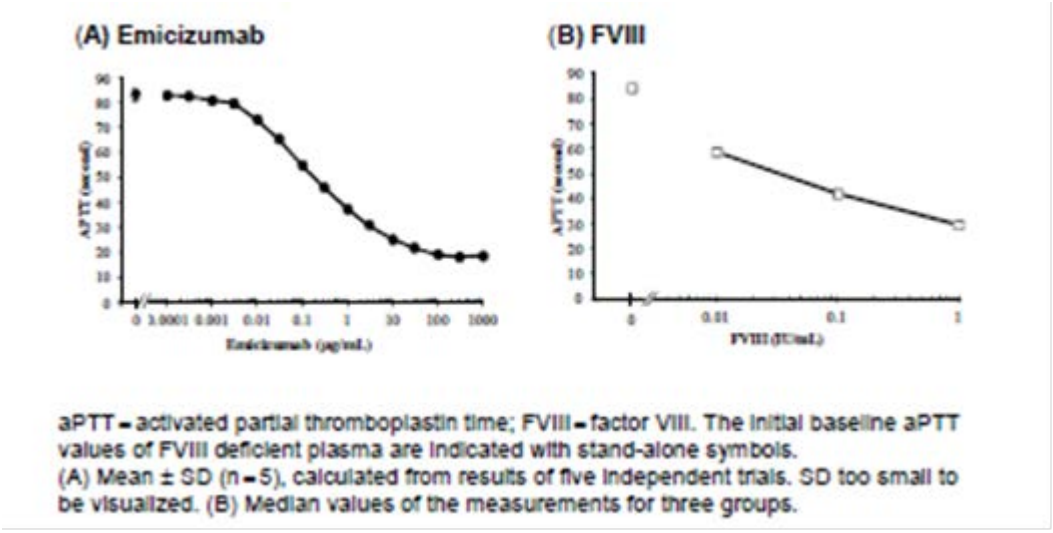
Condition	K_m (uM)	V_{max} (nM min^{-1})	k_{cat} (min^{-1})	k_{cat}/K_m	Fold increase k_{cat}/K_m
FIXa+FX+PL	0.0986	0.0257	0.000643	0.00652	1
+ emicizumab	0.00505	2.88	2.88	570	87400
+FVIIIa	0.0195	126	126	6460	991000

k_{cat} = Catalytic rate constant; k_{cat}/K_m = Catalytic efficiency; K_m = Michaelis-Menten constant; V_{max} = Maximum velocity; PL = phospholipid.

Emicizumab was tested in an aPTT clotting test in human congenital FVIII-deficient plasma with normal levels of von Willebrand factor activity and pathologically prolonged aPTT clotting time at baseline. Emicizumab caused a concentration-dependent reduction in aPTT and reduced it down to normal range, exhibiting procoagulant activity with a minimum effective concentration of 0.01

µg/mL (interference with the assay likely to contribute). When compared with the normalised aPTT of FVIII at physiological concentrations of 1 IU/mL, aPTT normalisation was reached with emicizumab concentrations of around or below 10 µg/mL. Hence, emicizumab demonstrated functional FVIIIa mimetic activity and showed its potential to effectively restore dysfunctional haemostasis in FVIII-deficient human plasma.

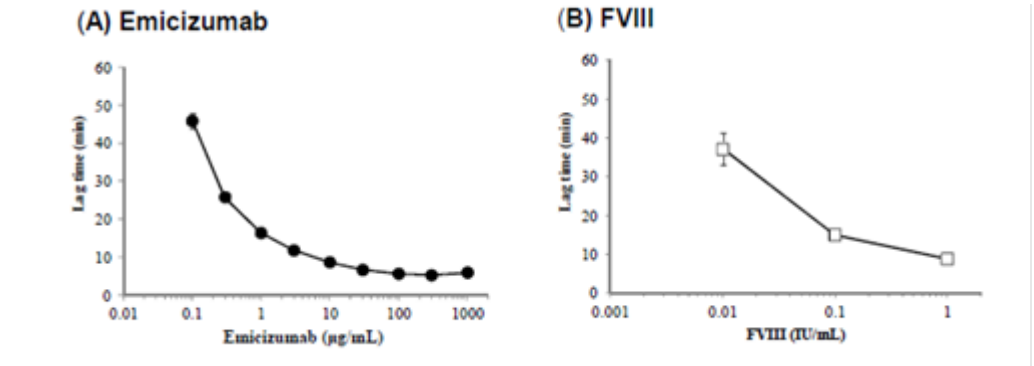
Figure 4: Effect of CH5534262 on activated partial thromboplastin time in haemophilia plasma

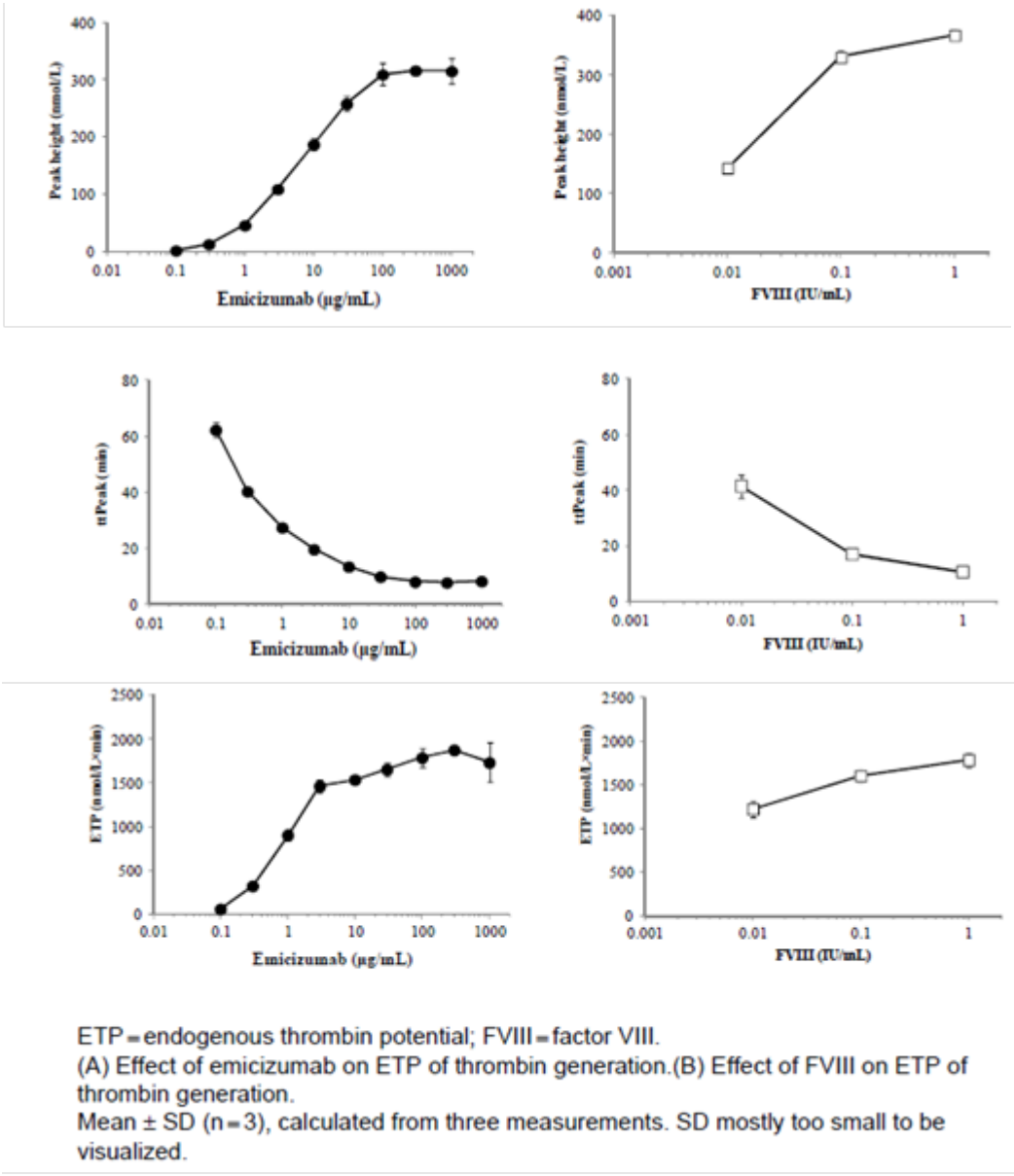


aPTT = activated partial thromboplastin time; FVIII = factor VIII. The initial baseline aPTT values of FVIII deficient plasma are indicated with stand-alone symbols.
(A) Mean ± SD (n = 5), calculated from results of five independent trials. SD too small to be visualized. (B) Median values of the measurements for three groups.

A thrombin generation assay was performed to quantify the total amount of thrombin generated after activation, permitting analysis of the kinetics of and capacity for thrombin formation and thus giving further insight into the initiation, propagation and termination phases of coagulation. Hence, the potential to generate thrombin was also investigated. In FVIII-deficient human plasma, emicizumab promotes concentration-dependent thrombin generation in the presence of FXIa. The shortening of the time to onset of thrombin generation (lag time) suggests an effect on the initial phase of coagulation, a finding consistent with the reduction of aPTT. More importantly, emicizumab also promotes thrombin generation during the propagation phase of coagulation, as indicated by the increase in peak free thrombin concentration (peak height) and endogenous thrombin forming capacity. In inhibitor-positive plasma emicizumab (1 nM to 1 µM) showed increased thrombin peak height and reduced APTT in a manner that was comparable to its activity in inhibitor-negative plasma.

Figure 5: Effect of emicizumab on thrombin generation induced by activated factor XI in haemophilia A plasma





ETP = endogenous thrombin potential; FVIII = factor VIII.
(A) Effect of emicizumab on ETP of thrombin generation.(B) Effect of FVIII on ETP of thrombin generation.
Mean ± SD (n = 3), calculated from three measurements. SD mostly too small to be visualized.

A study was conducted to investigate whether binding of emicizumab to FIX and FX inhibits activation. Emicizumab significantly inhibited activity in three FIX- and FX-dependent reaction steps:

- FX activation by FIXa/FVIIIa (N3 reaction). For this reaction pathway, emicizumab has bifunctional binding activity and the inhibition was particularly pronounced at 10 µg/mL
- FX activation by FVIIa/TF (N5 reaction) and
- Prothrombin activation by FXa/FVa (N6 reaction).

Given the potential inhibitory effects on 3 FIX/FX-dependent reactions as reported *in vitro*, two *in vivo* investigative studies were conducted to evaluate the potential for high local exposure of emicizumab to inhibit blood coagulation.

No evidence of local inhibitory activity or exacerbation of local or systemic bleeding at areas of high local emicizumab exposure was observed. SC administration of high doses of emicizumab (up to 30 mg/kg; 118 or 120 mg/mL) to *Cynomolgus* monkeys with acquired haemophilia A did not exacerbate bleeding at the injection site compared to vehicle. This was confirmed in a second study

where SC administration of 10 mg/kg (80 mg/mL formulation) did not exacerbate bleeding even in the presence of trauma-injury. Taken together, the anticoagulant potential of emicizumab identified in a series of *in vitro* tests (at 100 µg/mL) did not translate into a risk of systemic bleeding *in vivo*.

In an enzyme assay using purified *Cynomolgus* monkey, rat and mouse FIXa and FX, emicizumab was found to cross-react only with the corresponding clotting factors of *Cynomolgus monkeys*. Binding of monkey FIX and FX to emicizumab was comparable to emicizumab binding to hFIX and hFX; however, the responses for human FX were slightly higher than that observed for monkey FX (e.g. response at 160 nM FX: 13 ± 0.2 for cy vs 25.7 ± 0.2 for human). The difference in binding activity translated to a difference in the capacity to generate thrombin; whereby the concentrations of emicizumab required to reproduce the activity of a given concentration of porcine FVIII was higher in monkey FVIII-neutralised plasma when compared to human FVIII-neutralised plasma. However, it is evident that the observed difference was attributed to inter-animal variability as opposed to inter-species differences.

Emicizumab significantly inhibited *Cynomolgus monkey* FX activation by FIXa/FVIIIa (IC_{50} 0.17 mg/mL), FX activation by FVIIa/tissue factor (IC_{50} 0.57 mg/mL) and prothrombin activation by FXa/FVa (IC_{50} 0.75 mg/mL); it is noted that the IC_{50} values for *Cynomolgus monkey* were consistently higher 8.1, 4.4 and 3.3-fold higher than those observed for the purified human factors, respectively. However, the inhibition of FX activation in the monkey was not translatable to the *in vivo* situation and hence the difference in the observed potency was not deemed to be relevant. Moreover, the difference in the capacity of emicizumab to generate thrombin in monkey plasma was generally comparable to that observed in human plasma as outlined previously.

An acute model of haemophilia A was established in the monkey whereby FVIII-deficiency was induced (on Day 0) via a single IV injection of the mouse hybridoma VIII-2236 antibody. Trauma-induced bleeding caused a reduction in haemoglobin levels, bruising on the skin surface, an increase in APTT (indicator of FVIII depletion), but no effect on prothrombin time (PT) during the observation period (Days 0 to 3). Pre-treatment with emicizumab (0.3, 1, 3, 10, 50 and 200 mg/kg SC) on Day -4 caused a dose-dependent attenuation of the Hb loss, skin bruising and APTT prolongation, whereby the higher doses caused maximum restoration of some of the parameters. Similarly, intravenous treatment with emicizumab at 0.3 to 3 mg/kg caused a dose-dependent attenuation of haemostatic dysfunction when administered after bleeding induction.

In a chronic haemophilia A model, *Cynomolgus* monkeys were given weekly injections of the chimeric mouse-monkey anti primate FVIII-neutralising antibody. This model bears a closer resemblance to human hereditary haemophilia A with characteristic spontaneous bleeding; however, it is acknowledged that the bleeding sites are not identical to those which present clinically. Emicizumab, when administered subcutaneously at a starting dose of 3.97 mg/kg on Day 0 and then from Day 7 onwards at 1 mg/kg/week, prevented spontaneous intra-articular bleeding and other bleeding symptoms similar to haemostatic complications in human haemophilia A (e.g. bruising on the skin surface, haematuria). It is noted however, that there was no significant difference per se in the mean Hb levels when compared the emicizumab to the control group at each timepoint over the 8-week period; this may be due to the observed variability in the vehicle group.

Secondary pharmacodynamic studies

The Fc receptors, FcγRI, FcγRIIa (167Arg and 167His), FcγRIIIa (176Phe and 176Val), FcγRIIIb (Neutrophil antigen 1 and 2) and C1q protein are known to mediate Fc effector function.

The binding activity of emicizumab was compared to the IgG4 antibody, natalizumab with absent/low Fc effector functionality and that of the IgG1 antibody rituximab which has full Fc effector functionality. The binding to the Fcγ receptors evaluated was generally similar to that observed with the IgG4 antibody, natalizumab, with the exception of the fact that observed binding to the inhibitory receptor, hFcγRIIb with emicizumab was higher. When comparing the binding activities for emicizumab vs. rituximab, again, it was only the binding to the inhibitory Fc receptor, FcγRIIb that exceeded that observed for the reference antibody rituximab. Interestingly, the binding profiles observed with *Cynomolgus* monkey Fcγ receptors was generally in line with that observed for human; hence, the monkey is considered suitable for the evaluation of potential Fc effector functions *in vivo*.

The low binding activity of emicizumab to C1q protein was similar to that of natalizumab and suggests that the proposed product is unlikely to induce complement-dependent cytotoxicity. Taken together these data are suggestive of a low potential for Fc effector function.

The extent of the binding activity of emicizumab to FcRn is comparable to natalizumab and this binding is consistent with its long half-life.

Safety pharmacology programme

Separate safety pharmacology studies were not performed which is acceptable and in accordance with the ICH S6 (R1) guideline.

The safety pharmacology endpoints were evaluated during the repeated-dose toxicity studies described in Section 2.3.4 of this report. No effects on the CNS, respiratory or CNS were identified.

Pharmacodynamic drug interactions

Interactions with FVIII and by-passing agents

The currently available medicines for the 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 procoagulant 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 by-passing 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. Under the extrinsic pathway-triggered 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).

In vivo effects of emicizumab in combination with FVIII and by-passing agents

The effect of co-administration of emicizumab and bypassing agents (rFVIIa and aPCC) on thrombus formation was investigated in a *Cynomolgus* monkey model of FVIII-neutralised haemophilia A/venous stasis. No thrombi were seen in either the jugular vein or the femoral vein in the untreated control group and the 3 mg/kg emicizumab-only group. Thrombus formation was observed in the rFVIIa and aPCC groups. There was no significant difference between these two groups, although a tendency towards a higher thrombus weight was seen in the aPCC group. The sum of thrombus weights in the combination dose groups increased above the levels noted in the rFVIIa and aPCC groups, although the individual measured thrombi did not exceed the levels observed with either compound alone. The platelet counts, fibrinogen concentration, FDP concentration and D-dimer concentration do not indicate enhanced systemic coagulation or fibrinolysis in any group.

In vivo effects of emicizumab ± in combination with FVIII and Bypassing Agents

The effect of emicizumab on thrombus formation was compared to that of rFVIIa and FVIII treatment in a model of venous stasis in normocoagulative *Cynomolgus* monkeys. Almost no thrombus formation was observed at the site of stasis in the untreated control group. In contrast, thrombus weight increased significantly at the site of stasis in the positive control group that received 120 µg/kg rFVIIa IV. Thrombi also formed at the stasis site in the groups that received emicizumab (1 and 2 mg/kg IV) or FVIII (25 U/kg); however, the total thrombus weights in these groups were not markedly higher than those in the rFVIIa group. Immediately after IV injection of 1 or 1+2 mg/kg emicizumab, the mean ± SD plasma concentrations were 23.3 ± 6.3 µg/mL and 49.4 ± 9.8 µg/mL, respectively.

Interference with various diagnostic assays

Emicizumab greatly shortens aPTT even at concentrations far below the clinical effective concentrations. Thus, emicizumab may also interfere with any other aPTT-based diagnostic test, such as the FVIII one-stage activity assay, whereas assays of the extrinsic coagulation cascade, such as PT, are not significantly affected.

The aim of the interference studies was to evaluate the effects of emicizumab on a variety of *in vitro* assay systems used as diagnostics related to haemostasis and coagulation. 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.

2.3.3. Pharmacokinetics

The pharmacokinetics of emicizumab were studied in mice and in *Cynomolgus* monkeys. The monkey was identified as the most relevant species as it was shown to cross react with emicizumab. In the vast majority of the nonclinical studies, emicizumab was administered via the SC route administration as this mimics the proposed clinical route.

The analytical methods used for the toxicokinetic analyses for the pivotal toxicity studies were sufficiently validated. The analytical methods (ELISA) used had sufficient selectivity and reproducibility to determine emicizumab in *Cynomolgus monkey* plasma over the range of 0.01

µg/mL to 0.4 µg/mL. The narrow range was noted however no effects on the determination were observed by diluting up to 40,000-fold.

An electro chemiluminescence immunoassays was developed for the analysis of anti-drug antibodies (ADA) in monkey plasma. Upon review of the analytical report, it was noted that on Day 2, intra-day precision values, were not adopted because electro-chemiluminescent (ECL) signals were high and inter-day precision, C.V. (%), did not meet the acceptance criteria. However, two additional assays were performed to confirm the variation of ECL signals. This deviation is not considered to affect the overall interpretation of the data generated.

In the mouse, following a single subcutaneous administration of emicizumab (1 mg/kg), Cmax occurred at 1 to 3 days post-dose, apparent T1/2 was 17.6 days and bioavailability was estimated to be 84.3%. In the monkey, following administration of emicizumab (0.06 to 6 mg/kg), apparent t1/2 was independent of dose and ranged from 23.6 to 26.5 days and bioavailability was said to be complete at 102%. Exposures (Cmax and AUC) increased in a dose-proportional manner. The observed slow clearance is consistent with the observed FcRn affinity reported. No changes in concentrations of blood coagulation factors IX and X were noted after single SC administration of emicizumab at 0.06 to 6 mg/kg. This suggests that the binding to emicizumab does not change the turnover of FIX or FX. This is consistent with the binding affinity (low µM range) of emicizumab for FIX and FX.

Following repeated SC administration of emicizumab in the monkey, where doses of up to 30 mg/kg were administered for up to 26 weeks, exposures increased with dose and accumulated upon repeated dosing (by 2-7-fold), which is consistent with the long t1/2.

Anti-drug antibodies were detected in the single dose studies (mouse: in 1/5 animals; monkey 2/6) in the 13-week study (in 7/29 animals) and in the 26-week study (in 9/30 animals). Some of the ADA-positive animals did exhibit faster elimination of emicizumab; those demonstrating a complete loss of exposure tested positive for neutralising antibodies. However, all samples could not be assessed for neutralising activity as the high concentrations of emicizumab interfered with the antibody characterisation assay.

No studies to evaluate the distribution, metabolism, excretion or potential to cause pharmacokinetic interactions were conducted which is in line with the ICH S6 guideline (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals [EMA/CHMP/ICH/731268/1998.

Overall, the pharmacokinetic aspects of the non-clinical package are considered to be adequate.

2.3.4. Toxicology

The studies performed in support of this application are summarised in table below and it is evident that pivotal studies were conducted in accordance with Good Laboratory Practice.

Table 2: Toxicology studies performed with emicizumab

Title	GLP	Report No.
A 4-week intermittent dose (once weekly, 5 doses) intravenous administration toxicity study of CH5534262 in cynomolgus monkeys followed by a 4-week recovery period	Y	[1060140]
A 4-week intermittent dose (once weekly, 5 doses) subcutaneous administration toxicity study of CH5534262 in cynomolgus monkeys (dose range-finding study)	N	[1060168]
A 13-week subcutaneous intermittent dose (once weekly, 14 doses) toxicity study of CH5534262 in cynomolgus monkeys followed by a 13-week recovery period	Y	[1060133]
A 26-week intermittent dose (once weekly, 27 doses) subcutaneous administration toxicity study of CH5534262 in mature cynomolgus monkeys followed by a 13-week recovery period	Y	[1060134]
Preliminary study to establish the conditions for immunohistochemical reactivity of a humanized anti-human factor IX/X monoclonal antibody (CH5534262), a human bispecific antibody, and its parent antibodies, factor IX monoclonal antibody (CH5534261) and factor X monoclonal antibody (CH5534263) in control materials and selected human and cynomolgus monkey tissues.	N	[1060173]
A tissue cross-reactivity study of CH5534262 in normal human tissues	Y	[1060174]
Whole blood cytokine assay for in vitro cytokine release from human blood cells after treatment with CH5534262	N	[1060175]

Single dose toxicity

While no single dose studies were performed, No acute toxicological were noted following the first IV administration at 10, 30, or 100 mg/kg or SC administration at 1, 6, or 30 mg/kg.

Repeat dose toxicity

Intravenous study

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 when 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)(intravenous study). 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, periarteritis 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 [Study 1076956;

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 animal 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.

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.

Subcutaneous study

Emicizumab was administered SC at 0 (vehicle control), 1, 6 and 30 mg/kg to *Cynomolgus monkeys* (n=1/sex/group) QW for 4 weeks (total of 5 doses) to assess toxicity and systemic exposure.

APTT shortening was observed at all dose levels as well as elevation of coagulation FVIII activity at ≥ 6 mg/kg/week doses. These were attributed to the pharmacological effect of emicizumab. In addition, the activity of coagulation FIX and FX was elevated at 30 mg/kg/week. These observations were not considered toxicologically significant as no changes in fibrinolytic markers, such as FDP (fibrin and fibrinogen degradation products) and D-dimer, or emicizumab-related thrombotic changes were observed.

Perivascular infiltration of mononuclear cells in the subcutis at the injection sites was observed at all doses. This change was considered to be caused by high protein concentration at the injection site. Additionally, follicular hyperplasia of the axillary lymph node at the site of administration was observed in one male at 6 mg/kg/week and considered to be related to an inflammatory response at the injection site.

A dark-red area in the subcutis of individual injection sites was observed at all doses at necropsy, and correlated with slight haemorrhage observed microscopically. Slight haemorrhage in the subcutis, without a necropsy finding, was observed at an injection site in one male at 30 mg/kg/week. In the subcutis at the injection site, slight degeneration/necrosis and swelling of endothelium were noted in one female at 1 mg/kg/week and in one male and one female at 30 mg/kg/week. Additionally, slight neutrophil infiltration in the subcutis at the injection site was observed in one female at 1 mg/kg/week.

No emicizumab-related changes were observed in general condition, body weight, FOB, food consumption, ophthalmoscopy, electrocardiography, urinalysis, blood chemistry, lymphocyte subset test, cytokine measurement, bone marrow examination and organ weight.

Exposure to emicizumab during repeated administrations was maintained during the treatment period and documented with measurements of steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration) (Ctrough). Anti-emicizumab antibodies were not detected in any emicizumab-treated animals.

Table 3: No effect (animal) exposures and exposure margins

Species	Dose (mg/kg/week)	$AUC_{0-168\ ss}$ (d•µg/mL)	Exposure Margin [a]	C_{max} (µg/mL)	Exposure Margin [a]
Cynomolgus monkey	30	8755	11	1355	10

$AUC_{0-168\ ss}$ = steady-state area under the plasma concentration-time curve from 0 to 168 h; AUCτ = AUC over one dosing interval; C_{max} = maximum plasma concentration; QW = once weekly.

[a] Predicted exposure at steady state based on trough data at 24 weeks in patients dosed with 3 mg/kg QW: C_{max} = 132 µg/mL and AUC_{tau} = 783 d•µg/mL.

Genotoxicity

Genotoxicity studies were not performed as it is not expected that IgGs would interact directly with DNA or other chromosomal material in accordance with ICH S6 (R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals [EMA/CHMP/ICH/731268/1998].

Carcinogenicity

Carcinogenicity studies were not performed which is acceptable and in line with ICH S6 (R1).

Reproduction Toxicity

The effects of emicizumab on fertility were assessed in the 13-week SC GLP toxicity study in *Cynomolgus monkeys* (the animals were 3 years old at the start of dosing) and the 26-week SC GLP toxicity study in mature *Cynomolgus monkeys* (4 to 6 years old at the start of dosing). Emicizumab did not cause any toxicological changes on male or female reproductive organs at doses up to 30 mg/kg/week in either of these studies. In the 26-week study, the effect of emicizumab on fertility (sperm analysis, menstrual cycles) was also evaluated. No toxicological effects on fertility were observed in this study.

Moreover, in the 4-week IV GLP toxicity study in *Cynomolgus* monkeys aged 3-4 years, emicizumab did not cause any toxicological changes in the reproductive organs of male or female *Cynomolgus* monkeys at doses up to 100 mg/kg/week.

No data are available with respect to potential effects of emicizumab on embryofetal development. The available data on the pharmacological action of emicizumab and the results of the general toxicity studies do not suggest that emicizumab might interfere with embryofetal development. In addition, as the vast majority of haemophilia A patients are males, this is relevant for only a small subset of patients.

Juvenile studies were not performed. However, the available 13-week SC toxicity study in monkeys of 3 years of age with once weekly dosing supports treatment of adolescent humans at 12 years of age and older [Baldrick 2010]. Toxicology studies in juvenile animals have not been conducted and are not considered meaningful for emicizumab. Fetal synthesis of clotting factors is low, begins early at about gestation week 5 and reaches measurable but low levels at week 20 until parturition [Reverdiau-Moalic *et al*. 1996]. Some components of the haemostatic system such as protein C and fibrinogen even have fetal forms with different activity to the adult forms [Jaffray and Young 2013].

Toxicokinetic data

Table 4: Animal-to-human exposure ratios from repeat-dose toxicity studies

Dose (mg/kg/week)	Species	Study ID	Animal Cmax /Co for IV(µg/mL)	Animal AUC_{0-7d} (µg.d/mL)	Animal/Human Exposure Multiple
			M	M	
IV route					
10	*Cynomolgus* monkey	4-week	406	1810	2.3
30			1430	5140	6.5
100			3550	14400	18.4
SC route					
1	*Cynomolgus* monkey	4-week	ND	35.9	0.04
		13-week	40.7	267	0.3
		26-week	52.0	339	0.4
6	*Cynomolgus* monkey	4-week	ND	204	0.2
		13-week	211	1310	1.6
		26-week	358	2360	3.0
30	*Cynomolgus* monkey	4-week	ND	1109	1.4
		13-week	1200	7360	9.3
		26-week	1340	8680	11.0

AUC and Cmax were determined at last dose (4^{th}, 13^{th}, 26^{th}) in animals.

Human exposure achieved at 24 weeks treated at 3 mg/kg QW AUC_T 783 µg.day/ml

The NOAEL dose of 30 mg/kg in the 26-week study (1060134) resulted in a steady state AUC0−168h (AUC0−168h ss) exposure of 8680 µg.d/mL. This is approximately 11-fold above the clinical exposure in a 3 mg/kg QW dosing regimen which is the regimen that is anticipated to yield the highest exposure in patients.

Local Tolerance

No local tolerance studies were performed as local tolerance was investigated during repeat-dose toxicity studies in *Cynomolgus* monkey and in model of haemophilia A in monkey. Reversible

haemorrhage, perivascular mononuclear cell infiltration and degeneration/necrosis of subcutis and swelling of endothelium in the subcutis were retrieved.

Other toxicity studies

In an *in vitro* study of cytokine release that used the whole blood of healthy adults, the levels of cytokine induced by emicizumab were comparable to those induced by panitumumab, a reference antibody with low clinical risk.

In a tissue cross-reactivity assay in normal human tissue (GLP), staining of intracytoplasmic granules was observed in liver hepatocytes and Kupffer cells, bone marrow cells (along with extracellular granules), thyroid follicular epithelium, and the adrenal cortex (inner zona reticularis). It is considered unlikely that serious adverse drug reactions will develop in humans because it is unlikely that emicizumab will enter the cytoplasm *in vivo*.

2.3.5. Ecotoxicity / environmental risk assessment

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.

2.3.6. Discussion on non-clinical aspects

Emicizumab acts as a FVIII-mimetic, whereby it promotes activation of FX by FIXa in the absence of FVIIIa. The Michaelis-Menten kinetics of this reaction were calculated to assess the catalytic efficiency of emicizumab. In comparison to FVIIIa, the estimated Michaelis-Menten constant (K_m) of emicizumab was lower, indicating stronger binding interaction to FIXa and FX, but the catalytic efficiency (k_{cat}/K_m) to promote the turnover of the reaction was only ~9% of the catalytic efficiency of FVIIIa. The applicant clarified that in contrast to FVIII, emicizumab, does not require activation by thrombin but the molecular conditions required to promote cofactor activity are nearly identical. Emicizumab has to form a correctly arranged complex with platelet-bound FIXa and FX, in order to place the FIXa protease contact region in close proximity to the FX cleavage site for subsequent FX activation. The functional activity of emicizumab is not only due to its binding constants to FIXa and FX, but also to its appropriate structure and flexibility in the non-antigen-contacting region allowing full cofactor activity. Emicizumab with its bispecific binding but only single point binding sites on both FIXa and FX cannot equally substitute the complex binding interaction and functional potency of human FVIII. The moderate binding affinity to the EGF1 and EGF2 domains allows efficient FIXa-FX crosslinking while maintaining sufficient steric flexibility within both catalytic domains for interaction and activation of FX. As emicizumab, in contrast to FVIIIa, does not directly promote the steric optimisation of the complex by additional binding interactions, the overall catalytic efficiency is expected to be lower than that of FVIIIa.

Models of haemophilia A in *cynomolgus* monkeys were established to investigate the effects of emicizumab on haemostasis under FVIII deficiency *in vivo*. While the results are supportive of the proposed use, at the time of initial application, the models were poorly characterised. However, adequate justification of the choice of parameters measured was subsequently provided.

As FVIII is a foreign substance to those who are FVIII-deficient, FVIII therapy may cause haemophilia A patients to develop antibodies to FVIII (inhibitors). Patients with inhibitors are

treated with agents which stimulate coagulation pathways that bypass the FVIII-dependent coagulation pathway. A series of *in vitro* and *in vivo* studies were therefore conducted to explore the thrombogenic risk associated with emicizumab, FVIII, FVIIa and/or activated prothrombin complex concentrates (aPCC, a heterogenous mixture of prothrombin, FIX and FX) when administered in combination.

For the thrombin generation assay, the calibrator accounts for and corrects the fluorescence quenching effect of the plasma sample and substrate depletion in order to provide an accurate thrombin concentration readout. For this to work correctly, the proportion of the plasma sample in the test well has to be exactly the same as that in the calibrator well. It is evident that 40 µL of plasma was used for the test wells and 80 µL of plasma (as recommended by the manufacturer of the kit) was used for the calibrator wells. However, the applicant clarified that equivalent volumes of plasma were used for both test and calibrator wells.

To support the clinical use of emicizumab at the maximum dose of 3 mg/kg/week, repeated SC studies of up to 26 weeks duration have been conducted in the monkey, which is supportive of the proposed use. Upon request, the applicant has confirmed that the relevant endpoints to detect effects on the central nervous system, respiratory system and reproductive function were assessed during the pivotal 26-week study and that no treatment-related effects were noted. The reported differences in APTT during the 26-week study were attributed the fact that different reagents were used (evidence in support of the variability and difference in the sensitivity of different reagents for APTT assays has been provided). In addition, the observed increase in the levels of D-dimer (fibrinolytic marker) in some animals was either small when compared to baseline, within background range, was not dose-related, and had no effect on associated parameters such as the development of thrombi (as observed during hispathological examination). The applicant has also clarified that the non-clinical batches used during the pivotal studies are representative of the final commercial product.

The age of the animals used in the 13-week and 26 week studies in the *Cynomolgus monkey* correspond to patients ≥12 years old and adolescents or older. The applicant is proposing to use the product in paediatric patients at ≤ 2 years and >2 years. It is accepted that the human coagulation cascade reaches maturity at a very young age and that juvenile studies per se are unlikely to contribute any useful data (as agreed as per CHMP Sci Advice July 2015). However, the applicant was asked to identify all of the factors likely to contribute differences in exposure in the proposed paediatric population (when compared to adults), discuss whether the existing non-clinical data support the proposed exposures in this subpopulation and provide a thorough discussion as to how the pharmacokinetic profile in paediatric patients ≤2 years and >2 years is likely to compare to that observed in the patients studied thus far. The applicant provided additional clinical data which confirmed similarity of exposure (emicizumab trough plasma concentration) between children (1 to ≤12 years), adolescents, and adults with the maintenance dose of 1.5 mg/kg/week. The applicant also provided a discussion of the changes in physiology in children and states that some uncertainty remains with respect to any potential changes in clearance/pharmacokinetic profile of monoclonal antibody in general. From a non-clinical perspective, the additional clinical PK data do support treatment of paediatric patients ≥1 year but not for patients <1 year. See clinical aspects for further information.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical perspective, the data provided support safety in the paediatric population in patients ≥1 year. Please see section 2.5.3. Discussion on clinical efficacy which provides the justification for the granting of the indication below 1 year of age.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

- Tabular overview of clinical studies

Table 5: Clinical studies contributing to efficacy evaluation in haemophilia A patients treated with emicizumab

Patient Population	Dosing Regimen	Objectives	Analysis/Clinical Cutoff Date *(No. of Patients)/Follow-up (weeks)*
Pivotal Phase III Studies			
BH29884 : Open-label, multicenter, global, randomized study, with two additional, separate therapeutic arms.			
Patients ≥12 years of age with inhibitors to FVIII **Arms A and B:** patients 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 bypassing agent prophylaxis. **Arm D:** Non-randomized emicizumab arm for patients previously on episodic or prophylactic bypassing agents 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: once weekly SC administration of emicizumab (loading doses of 3 mg/kg/week for 4 weeks, followed by maintenance dose of 1.5 mg/kg/week[a]). Arm $B_{control}$ patients receive no prophylaxis (i.e., only episodic bypassing agents) but can switch to receive emicizumab prophylaxis (Arm B_{emi}; same regimen as above) after at least 24 weeks on study.	Primary Bleed rate (with bleeds defined as those treated with coagulation factors) 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 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). Arm A and Arm C intra-patient comparisons with data from NIS BH29768 for the following parameters: treated and all bleeds. Other • Safety • PK	**Primary Analysis (study ongoing)** Data cutoff: 25 October 2016 Enrolled: N = 109 Randomized: Arm A: N = 35 Arm B: N = 18 Arm C: N = 49 Arm D: N = 7 Follow-up Efficacy: median = 24.1 weeks (range: 0.1–48.9) (N = 104) Safety: median = 24.0 weeks (range: 3.0–47.9) (N = 103)

Patient Population	Dosing Regimen	Objectives	Analysis/Clinical Cutoff Date *(No. of Patients)/Follow-up (weeks)*
BH29992 : Open-label, multicenter, global, single-arm study in children.			
Pediatric patients from birth to <12 years of age with inhibitors to FVIII, with allowance of patients 12–17 years of age who weigh <40 kg.	Once weekly SC administration of emicizumab (loading doses of 3 mg/kg weekly for 4 weeks, followed by maintenance doses of 1.5 mg/kg weekly). Possibility for individual dose up-titration based on efficacy and for population dose up-titration based on PK and efficacy[b].	To evaluate the efficacy (treated and all bleeds [bleeds treated and not treated with coagulation factors]), treated spontaneous bleed rate, treated joint bleed rate, treated target joint bleed rate; HRQoL, aspects of caregiver burden; safety; and PK, of emicizumab without any formal statistical hypothesis testing.	**Interim Analysis (study ongoing)** Data cutoff: 28 October 2016 Enrolled: N = 20 ≥2 years to < 12 years: N = 19 12–17 years: N = 1 Follow-up Efficacy: median = 12.0 weeks (range: 7.0–14.0) (N = 19) Safety: median = 12.1 weeks (range: 7.1–14.1) (N = 20)

Patient Population	Dosing Regimen	Objectives	Analysis/Clinical Cutoff Date *(No. of Patients)/Follow-up (weeks)*
Supportive Phase I and I/II Studies			
ACE001JP Part C : Conducted in Japan, open-label, inter-individual, SC multiple ascending dose study in patients with hemophilia A with and without inhibitors. *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.*			
Japanese patients with hemophilia A ≥12 and <60 years of age enrolled in cohorts with escalating doses of emicizumab.	Cohort C-1: 1 mg/kg loading dose followed by 0.3 mg/kg/week for 12 weeks Cohort C-2: 3 mg/kg loading dose followed by 1 mg/kg/week for 12 weeks Cohort C-3: 3 mg/kg/week for 12 weeks	**Part C:** To investigate the tolerability, safety and relationship between emicizumab dose and the number of bleeding episodes in Japanese patients with hemophilia A.	**Final Analysis (study completed)** N = 18 (3 groups of 6 patients each) Follow-up Efficacy: median = 12 weeks (range: 4–12) Safety: median = 12 weeks (range: 12–48)

Patient Population	Dosing Regimen	Objectives	Analysis/Clinical Cutoff Date *(No. of Patients)/Follow-up (weeks)*
ACE002JP : conducted in Japan, open-label extension of Study ACE001JP Part C (C-1, C-2, and C-3) with possible dose up-titration[c] to other treatment groups			
Patients from Part C of Study ACE001JP.	Group 1: 0.3 mg/kg/week maintenance dose Group 2: 1 mg/kg/week maintenance dose Group 3: 3 mg/kg/week maintenance dose	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: 30 September 2016 *(includes data from ACE001JP Part C)* N = 18[d] (3 groups of 6 patients each) Follow-up Efficacy: range 4.1–177 weeks Safety: median = 174 weeks (range: 172–177), 149 weeks (4.1–156), and 126 weeks (12.1–131) in the 0.3, 1, and 3 mg/kg/week groups, respectively

Patient Population	Dosing Regimen	Objectives	Analysis/Clinical Cutoff Date *(No. of Patients)/Follow-up (weeks)*
Supportive 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[e]:** patients without FVIII inhibitors ≥12 years of age.	Dosing and duration of routine treatment are at the discretion of the investigator in accordance with local clinical practice and local labeling.	To document the number and type of bleeds in hemophilia A patients with FVIII inhibitors under routine clinical practice and to estimate the number of bleeds over time. To document treatment for hemophilia A (episodic bypass or prophylaxis bypass) in hemophilia A patients with FVIII inhibitors. To collect information on HRQoL (monthly) and health status (monthly and at the time of a bleed) in patients with hemophilia A with FVIII inhibitors under routine clinical practice. To collect information on safety (AEs) in patients with hemophilia A with FVIII inhibitors under routine clinical practice.	**Interim Analysis for Cohort A and preliminary analysis for Cohort B (study ongoing)** Data cutoff: 02 September 2016 Cohort A: N = 103 Cohort B: N = 24 Follow-up Cohort A Efficacy: median = 26.0 weeks (range: 4.1–52.4) Follow-up Cohort B Efficacy: median = 14.9 weeks (range: 5.3–22.1)

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 children 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/week if they had completed at least 24 weeks on study drug, met protocol-defined dose up-titration criteria based on suboptimal efficacy, and received approval from the Medical Monitor (see CSR BH29884).

[b] Patients had the opportunity to increase their dose if they had completed at least 12 weeks at a given dose, met protocol-defined dose up-titration criteria based on suboptimal efficacy, and received approval from the Medical Monitor (see CSR BH29992).

[c] Patients in C-1 and C-2 had the opportunity to have their dose escalated 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 subject in C-1 having been escalated to 1 mg/kg/week, may subsequently be escalated to 3 mg/kg/week (see CSR ACE002JP).

[d] Including 2 patients from Study ACE001JP who did not enter extension Study ACE002JP.

[e] Cohort C includes patients without FVIII inhibitors and is not included in this submission.

Data Sources: CSR BH29884 (t_udst01_il03_ip22asl_ip11asl_ALL2, t_ext01_02_il03_ip22_ip11_SAP2); CSR BH29992 (t_ext01_02_mde_TRT1, t_ext01_01_mde_TRT); CSR ACE001JP (Figure 10.1-2, Table 12.1-1); CSR ACE002JP (Table 10.1-1, Table 12.1.2-2 and Table 11.4.3.1-2); CSR BH29768 (t_ext01_01_vl01_ALLA, t_ext01_01_vl02_ALLB).

2.4.2. Pharmacokinetics

Clinical pharmacokinetic data have been obtained from 6 clinical trials.

The pharmacokinetic data submitted are from a single ascending dose study (ACE001JP Parts A and B), a multiple ascending dose study (ACE001JP Part C) conducted in healthy volunteers and its extension Study ACE002JP, which recruited patients with haemophilia A; a relative and absolute

bioavailability/site of administration study (JP29574) appreciating manufacturing changes prior to initiation of the Phase III trials.

Pharmacokinetic data are available for 108 healthy subjects and 141 patients with haemophilia.

In addition, sparse plasma sampling for PK and PD analyses were performed in all patients in the Phase III studies.

Phase I trial ACE001JP

Part A: Placebo-controlled, randomized, double-blind, inter-individual, subcutaneous single ascending dose study in healthy Japanese adult male volunteers (5 dose level: 0.001, 0.01, 0.1, 0.3 and 1mg/kg with each 6 subjects per group plus 2 subjects on placebo/ dose level).

Part B: Placebo-controlled, randomized, double-blind, inter-individual, subcutaneous single ascending dose study in healthy Caucasian adult male volunteers (3 dose level: 0.1, 0.3 and 1mg/kg with each 6 subjects per group plus 2 subjects on placebo/ dose level).

Part C: Open-label, inter-individual, subcutaneous multiple-ascending dose study in Japanese patients with haemophilia A (3 dose level including loading doses: 1 and 0.3; 3 and 1; only 3 mg/kg with each 6 subjects per group).

The dose escalation was done in a stepwise approach. PK samples were collected in Part A and B pre-administration, 8hrs, 24, 48, 72, 96 hrs, days 6 to 8, 11, 15, weekly until week 8, biweekly until week 12, then every 4 weeks until week 24. This was the same for Part C, but continued 4 weekly beyond week 24 until week 48. PD samples in Part A and B were collected pre-administration, day 3, 5, 8, followed by every other week until week 16; weeks 20, 24, and extended to week 36 and 48 in Part C.

Extension study ACE002JP: open label extension of Part C of the ACE001JP study (see also Section 3.6 Supportive studies)

This study is an open-label extension of Part C of the ACE001JP study, hence also conducted as an unblinded study without any control group. PK and PD samples were collected at the same timepoints as Part C of study ACE001JP and 4 weekly post-Week 24 (arbitrary) and every 12 weeks as well as at last observation. For more details on this study see Section 2.5 Supportive Studies.

Study JP29574: randomized, open-label, parallel group study in healthy adult male Japanese subjects

This study evaluated the relative and absolute bioavailability of Hemlibra across preparations and injection sites of subcutaneous Hemlibra in 60 healthy adult Japanese males in a randomized, open-label, parallel-group design. It was conducted at CPC Clinical Trial Hospital at Medipolis Research Institute (Japan). The study was initiated after changes to the drug substance manufacturing process, including the master cell bank (see also Quality AR; old: G1; new: G2.1) and changes in the preparation concentration prior to initiation of the pivotal studies using the new preparation (old: 80 mg/mL; new: 150 mg/mL).

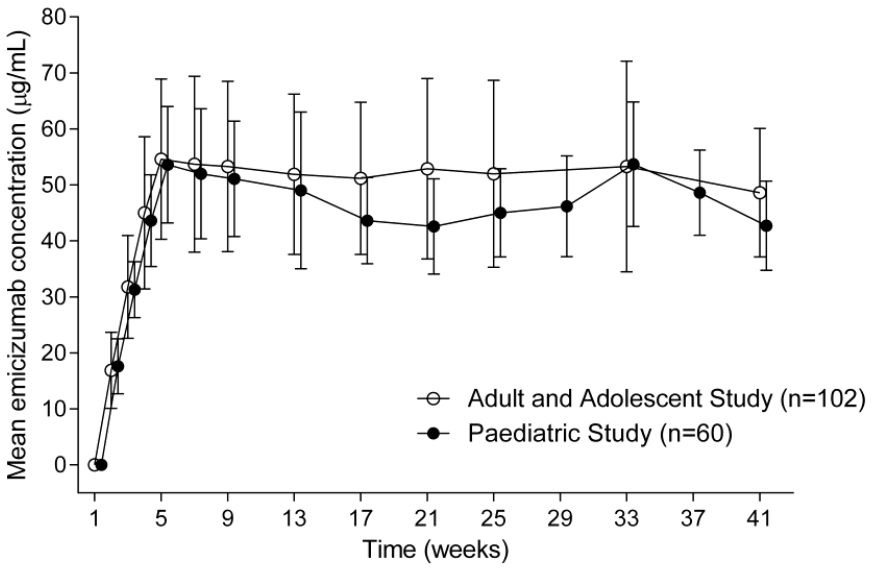
The primary objective for this study was to investigate the safety, pharmacokinetics, and relative bioavailability of single subcutaneous doses of the old and new preparations of Hemlibra; the safety, pharmacokinetics, and relative bioavailability of single subcutaneous doses of the new Hemlibra preparation when administered to the abdomen, upper arm, and thigh; and to investigate the absolute bioavailability of subcutaneous dosing of the new Hemlibra preparation. With the secondary objectives similar to the primary but relating to the PD responses.

Absorption

Following subcutaneous administration in haemophilia A patients, the absorption half-life was 1.7 days.

Following multiple subcutaneous administrations of 3 mg/kg once weekly for the first 4 weeks in haemophilia A patients, mean (±SD) trough plasma concentrations of emicizumab increased to achieve 54.6±14.3 µg/mL at Week 5. Trough plasma concentrations of approximately 50 µg/mL were sustained thereafter with weekly dosing of 1.5 mg/kg Figure 6.

Figure 6: Studies BH29884 (adult and adolescent study) and BH29992 (paediatric study): mean emicizumab trough plasma concentrations (µg/mL)



The predicted mean (±SD) Ctrough and Cmax at steady state were 52.2±13.5 µg/mL and 56.5±13.5 µg/mL, respectively. The mean (±SD) ratio of Cmax/Ctrough at steady state was 1.07±0.03.

In healthy subjects, the absolute bioavailability following subcutaneous administration of 1 mg/kg was between 80.4% and 93.1% depending on the injection site. Similar pharmacokinetic profiles were observed following subcutaneous administration in the abdomen, upper arm, and thigh. Emicizumab can be administered interchangeably at these anatomical sites.

Distribution

Plasma protein binding

Because emicizumab is a monoclonal antibody, traditional protein binding studies were not conducted.

Volume of distribution

Following a single intravenous dose of 0.25 mg/kg emicizumab in healthy subjects, the volume of distribution at steady state was 106 mL/kg (i.e. 7.4 L for a 70 kg adult).

The apparent volume of distribution (V/F), estimated from the population PK analysis, in haemophilia A patients following multiple subcutaneous doses of emicizumab was 11.4 L.

Metabolism

Antibodies are thought to be internalised in endothelial cells bound to the neonatal Fc receptor and rescued from metabolism by recycling. They are degraded in the reticulo-endothelial system to small peptides and amino acids, which are then used by the body for protein de-novo synthesis (Tabrizi et al. 2006; Roskos et al. 2004).

Emicizumab is an IgG antibody and as such is likely to broken down by proteolytic enzymes to amino acid and peptides which either excreted by kidney or re-used in protein synthesis; in line with this the elimination half-life of emicizumab is 4 to 5 weeks. The pharmacokinetics of emicizumab do not suggest a mechanism of target-mediated drug disposition.

Elimination

Following intravenous administration of 0.25 mg/kg in healthy subjects, the total clearance of emicizumab was 3.26 mL/kg/day (i.e. 0.228 L/d for a 70 kg adult) and the mean terminal half-life was 26.7 days.

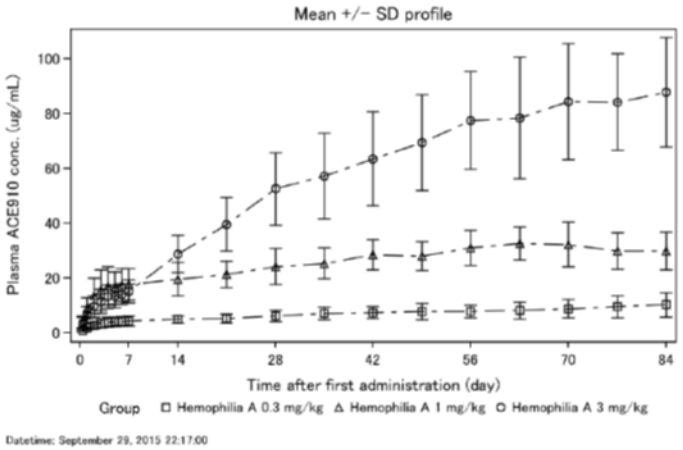
Following single subcutaneous injection in healthy subjects, the elimination half-life was approximately 4 to 5 weeks.

Following multiple subcutaneous injections in haemophilia A patients, the apparent clearance was 0.244 L/day and the elimination apparent half-life was 27.8 days.

Dose proportionality and time dependencies

In study ACE001JP, in patients with a dosing interval of 7 days, the accumulation index (mean ± SD) was estimated to be 5.53 ± 0.716 (n=3). Moreover, the PK properties of emicizumab do not suggest target-mediated drug disposition in agreement with emicizumab's low affinity for FIX and FX.

Figure 7: Mean time course of plasma Hemlibra concentration following multiple subcutaneous administration (Japanese patients with haemophilia A)



Power model analysis indicated that the Cmax and AUCinf of emicizumab was dose proportional over the range 0.01 mg/kg to 1 mg/kg in healthy subjects and was dose-proportional for steady-state trough concentrations increased in proportion to the doses of 0.3, 1 and 3 mg/kg/week in the multiple ascending dose study in patients.

Population PK model

Two population PK models were used to describe the disposition of emicizumab. The applicant has used appropriate software and methods for the population PK analyses and for the non-compartmental analyses.

The final population PK model was a one-compartment model with first-order absorption and elimination processes. There was moderate variability were estimated for apparent clearance (CL/F) (25.0%) and apparent volume of distribution (V/F) (29.1%), there was relatively high variability for the absorption rate constant (KA) (65.1%). The goodness-of-fit plots and VPCs were fit for purpose.

The applicant initially used a body weight exponent of 0.891 on CL/F rather than the standard 0.75. This reflects the known variability therapeutic proteins especially ones targeting coagulation pathways (Mahmood, 2009, Haemophilia, 15: 1109–1117). The population PK model showed that albumin was a significant covariate on CL/F and V/F. With albumin value slightly below the LLN (e.g. 30 g/L), emicizumab trough concentration is predicted to remain above 40 µg/mL. With albumin value almost 3 times lower than the LLN (e.g. 10 g/L), predicted emicizumab trough concentration is predicted to remain above 30 µg/mL.

Special populations

- ***Impaired renal function***

No dedicated studies of the effect of renal impairment on the pharmacokinetics of emicizumab have been conducted.

The safety and efficacy of emicizumab have not been specifically tested in patients with renal impairment. There are limited data available on the use of Hemlibra in patients with mild renal impairment. No data are available on the use of Hemlibra in patients with moderate to severe renal impairment. Mild renal impairment did not affect the pharmacokinetics of emicizumab.

Emicizumab is a monoclonal antibody and is cleared via catabolism rather than renal excretion and a change in dose is not expected to be required for patients with renal impairment.

- ***Impaired hepatic function***

Given the metabolic pathway of antibodies, no dedicated studies on the effect of hepatic impairment on the pharmacokinetics of emicizumab have been conducted. Rather than being cleared by hepatic metabolism, antibodies are thought to be internalised in endothelial cells bound to the neonatal Fc receptor and rescued from metabolism by recycling. They are degraded in the reticulo-endothelial system to small peptides and amino acids, which are then used by the body for protein de-novo synthesis (Tabrizi *et al*. 2006; Roskos *et al.* 2004).

Furthermore, the PK profile of emicizumab does not suggest target-mediated disposition and, thus, reduced hepatic production of factor IX (FIX) and FX, which are the binding targets of emicizumab, should not affect the pharmacokinetics of emicizumab. However, a possible PD effect of reduced concentrations of FIX and FX cannot be excluded, in particular, given the fact that patients with haemophilia have a higher risk of developing liver impairment as a consequence of transfusion-acquired infections.

Most of the patients with haemophilia A in the population pharmacokinetic analysis had normal hepatic function (bilirubin and AST ≤ ULN, n=113) or mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin < 1.0 to 1.5 × ULN and any AST, n=17). Mild hepatic impairment did not affect the pharmacokinetics of emicizumab. The safety and efficacy of emicizumab have not been specifically tested in patients with hepatic impairment. Patients with mild and moderate hepatic impairment were included in clinical trials. No data are available on the use of Hemlibra in patients with severe hepatic impairment.

Emicizumab is a monoclonal antibody and cleared via catabolism rather than hepatic metabolism and a change in dose is not expected to be required for patients with hepatic impairment.

- ***Gender***

No gender effect was investigated in the population PK model as all patients included in Study BH29884, Study BH29992 and Study ACE001JP / ACE002JP were male.

- ***Race***

V/F was substantially affected in Black or African American patients, the maximum change in V/F being estimated to be -36% compared with white/Asian patients. Despite a change in the shape of the concentration-time profile at steady state, no obvious difference in PK concentrations was predicted between Black and white/Asian patients (Population PK and PK/PD Report).

The effect of Black status on apparent volume of distribution only barely modifies the shape of the PK profile at steady state. A reduction of only 2.08% of the Css,trough and an augmentation of only 1.11% of the Css,max is predicted for a Black patient compared to a White or Asian one (assuming typical 22-year patients of 70 kg with 45 g/L of albumin). Furthermore, no obvious difference in PK between Japanese and Caucasian healthy subjects was observed in Study ACE001JP Parts A and B. Across all clinical studies in patients with haemophilia A (Studies ACE001JP Part C/ACE002JP, BH29884, and BH29992), the majority of patients included in the popPK analysis were white (n = 76, 54%), followed by Asian (n = 43, 30.5%), Black or African American (n = 12, 8.5%), and others (n = 10, 7.1%). No obvious difference was observed in the PK across these patient populations.

- **Weight**

As anticipated, strong relationships between body weight and CL/F as well as body weight and V/F were estimated, modifying up to about ± 80% those parameters for extreme body weights.

Negligible body weight impact on the level of PK concentration at steady state is predicted, as is expected with a weight-based dosing.

- ***Elderly***

About 2% of patients with haemophilia A and B surveyed in U.S. comprehensive haemophilia treatment centres were 65 years of age or older (Philipp 2010). Due to the extremely limited population of elderly patients with haemophilia, the applicant did not perform a dedicated study to investigate the pharmacokinetics in elderly patients. Instead, participation to blood sampling for PK assessments was mandatory in the Phase III Study BH29884 (enrolling patients from > 12 years of age), and the influence of age on emicizumab pharmacokinetics was investigated via population PK analysis.

Older patients (> 22 years) had increased CL/F with age and consequently decreased steady state exposure. This, for instance, leads to a predicted exposure (AUCSS,1week) at steady state 25.8% lower in a 75-year old patient compared to a 22-year old patient (assuming typical values for body weight (70 kg), albumin (45 g/L) and White status). Although this age effect was not precisely estimated (RSE = 37.2%) and is unusual for antibodies (Tabrizi *et al*. 2006), it was kept in the model as the estimated probability from posterior distribution showed a 91% risk of clinical importance of this covariate for a typical 75-year patient.

Individual PK profiles observed in Studies BH29884 and BH29992 support the tendency of lower concentrations with age (Population PK and PK/PD Report). However, a consistent and meaningful reduction of ABR in patients < 65 and ≥ 65 years old was observed, indicating that no dose adjustment is required in elderly patients.

Indeed, in the exposure-efficacy database (from Phase III Study BH29884), among the 3 patients above 65 years old 2 of them (75- and 67-years old) were fully controlled (ABRT = 0) and the other one, 68- years old, were well controlled with an ABRT of 1.48.

	Age 65-74 **(Older subjects number /total number)**	**Age 75-84** **(Older subjects number /total number)**	**Age 85+** **(Older subjects number /total number)**
PK Trials	2	1	None

- ***Children***

To date PK data is available for 60 patients with haemophilia < 18 years of age. This includes 10 patients of 2 years and below and 5 that are 1- 2 years old, for whom PK profiles are available for 4 patients. Ongoing studies are investigating patients with haemophilia birth to <12 years of age and patients 12-17 years with body weight <40 kg.

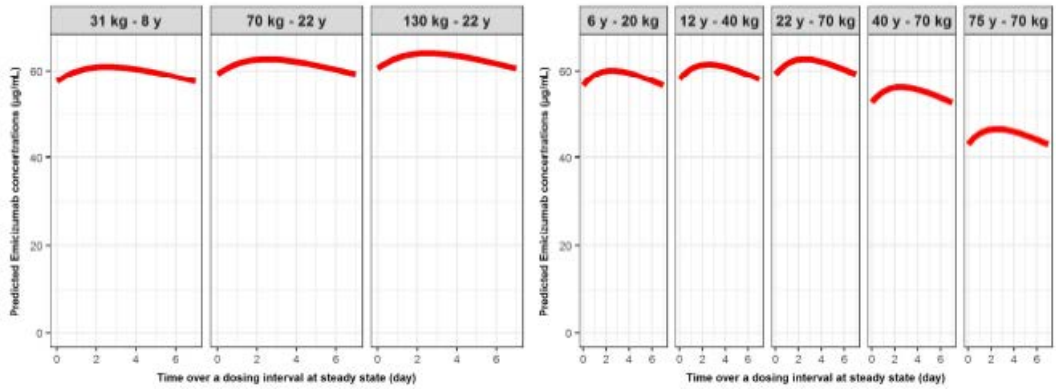
A PBPK model was also developed in SIMCYP to investigate the effects of IgG levels in younger children.

An update to the PopPK model was provided focussing on subjects below one year of age. This included the larger database of patients (a total of 189 vs. initially 141 patients), including 9 patients between 1 and 2 years of age who were dosed with emicizumab. This new model included body weight (exponent 0.75) and a maturation effect on clearance and an effect of changing albumin concentration on the apparent clearance.

The popPK model was agreed to be a better fit to the data with regard to simulation of steady state exposure in patients less than 1 year of age; noting that the one individual patient closest to 1 year of age appeared to have a small underprediction of clearance. The initial model used did not take into account potential variation of albumin with age. In the new model, the variation in albumin concentration with age, and in particular in patients <1 year, was taken into account, and with or without a maturation function. Simulations predicted slightly lower exposures than previous ones performed with a constant value of 45 g/L of albumin and slightly higher exposures are predicted when the maturation of clearance with age is taken into account. Exposure in neonates is predicted to be 23% (with maturation; AUCSS of ~250 µg*day/mL) and 27% (without maturation; AUCSS of ~240 µg*day/mL) lower than that observed for of older patients (1–12 years).

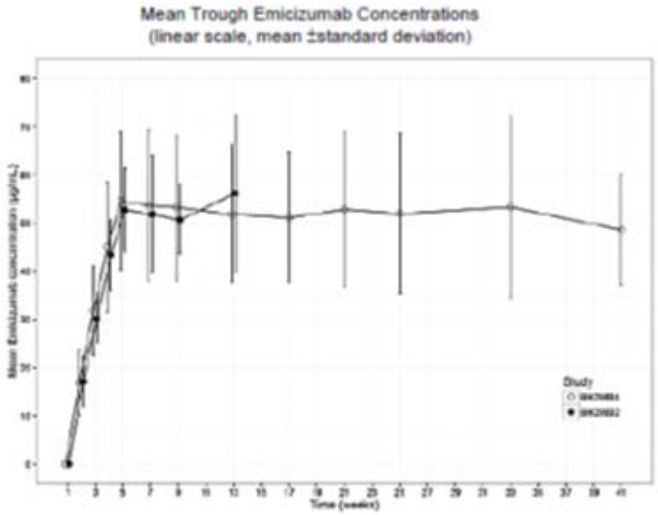
PopPK report

Figure 8: Illustration at Steady State of the Impact of Body Weight, Age, on the Predicted PK Concentration Profile at Steady State Following 3 mg/kg/week subcutaneously for 4 Weeks, Followed by 1.5 mg/kg/week subcutaneously



There was no difference in mean emicizumab PK profiles between patients aged ≤12 years in Study BH29992 and adults/adolescents in Study BH29884 with mean emicizumab concentration-time profiles being superimposed in both categories of patients. Furthermore, no effect of age on emicizumab exposure (trough concentrations) has been identified in patients aged ≤12 years from Study BH29992.

Figure 9: Study BH29884 Mean profile following multiple weekly SC Injections of Emicizumab in Patients ≤12 years Old and Adolescents/Adults with Hemophilia A



Source: BH29884 and BH29992 CSR.

No effect of age on CL/F was found for patients below the age of 22 years (median age of the patients included in the covariate population PK model building) indicating that no dose adjustment by age is required in adolescents (≥ 12 years of age to < 18 years of age) and children (< 12 years of age) patients with haemophilia A.

Pharmacokinetic interaction studies

- ***In vivo***

Drug-drug interaction studies were not conducted as PK drug-drug interactions are not expected given that the metabolic pathways (monoclonal antibodies are neither metabolised via the cytochrome P450 system nor is there conjugation with glucuronic acid, esterases, etc.) and elimination pathways of small molecules do not overlap with metabolism or elimination of antibodies. Moreover, antibodies are not bound to drug transporters such as p-glycoprotein, breast cancer resistance protein, organic cation transporters, or organic anion transporter.

Pharmacokinetics using human biomaterials

Not applicable.

2.4.3. Pharmacodynamics

Mechanism of action

Emicizumab is a recombinant, humanised, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity in the low µM range to the human FIX (hFIX), human FX (hFX), human FIXa (hFIXa), and human activated FX (hFXa) in a concentration-dependent manner. Upon binding, emicizumab enhances the activation of hFX by hFIXa, thereby restoring haemostatic function. Emicizumab thus activates downstream haemostasis at the site of bleeding in haemophilia

A patients, irrespective of the presence of FVIII inhibitors, as it shares no sequence homology with FVIII.

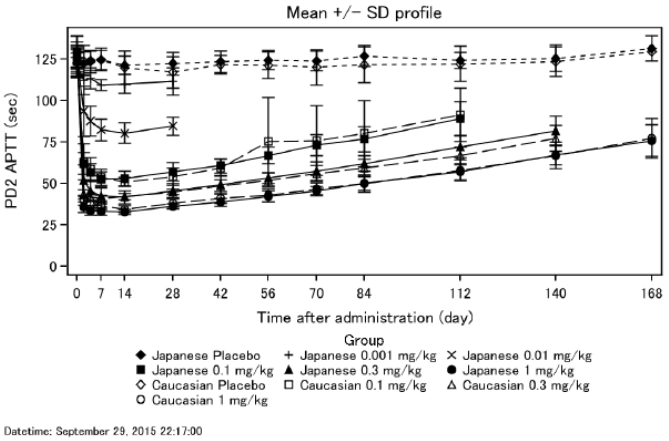
Primary and Secondary pharmacology

Primary pharmacodynamics

- Pharmacodynamic response in healthy volunteers (HVs) (trial ACE001JP)

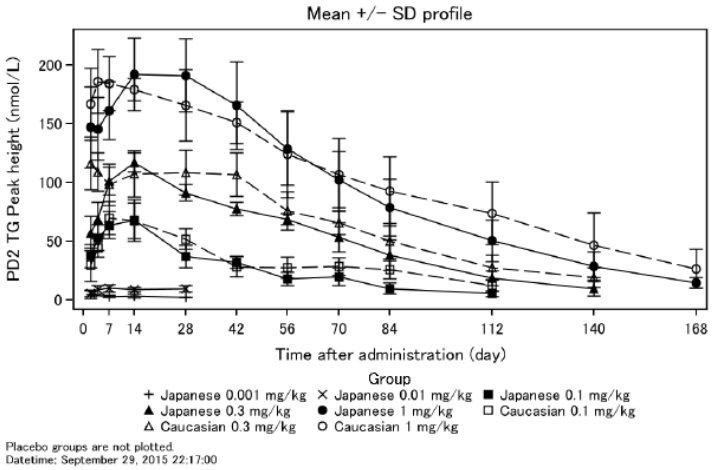
Activated partial Thromboplastin Time (aPPT)

Figure 10: Mean time course of APTT following a single subcutaneous administration (Japanese and Caucasian healthy male adults, pharmacodynamic coagulation test 2)



Thrombin Generation

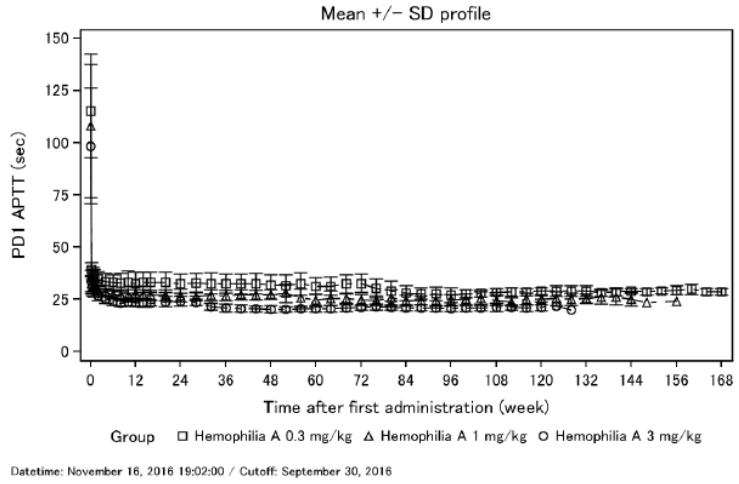
Figure 11: Mean time course of Peak height following a single subcutaneous administration (Japanese and Caucasian healthy male adults, pharmacodynamic coagulation test 2)



- Study ACE001JP (Part C) / ACE002JP (Extension in Patients with Haemophilia A)

aPTT

Figure 12: Mean time course of APTT following multiple subcutaneous administration (pharmacodynamic coagulation test 1)



Thrombin Generation

After the start of emicizumab administration, peak height of TG increased in all dose groups with a slight dose dependency. The mean (±SD) TG peak height at steady state was 261.09 ±78.28 at 12 weeks' post-dose, 273.98 ±29.39 at 12 weeks' post-dose, and 284.96 ±53.27 nmol/L at 24 weeks' post-dose in the 0.3, 1, and 3 mg/kg/week dose groups, respectively.

The maximal effect of ACE910 on thrombin generation was achieved at approximately ≥30 µg/mL for Peak height and over the entire detected concentrations of approximately ≥1 µg/mL for ETP.

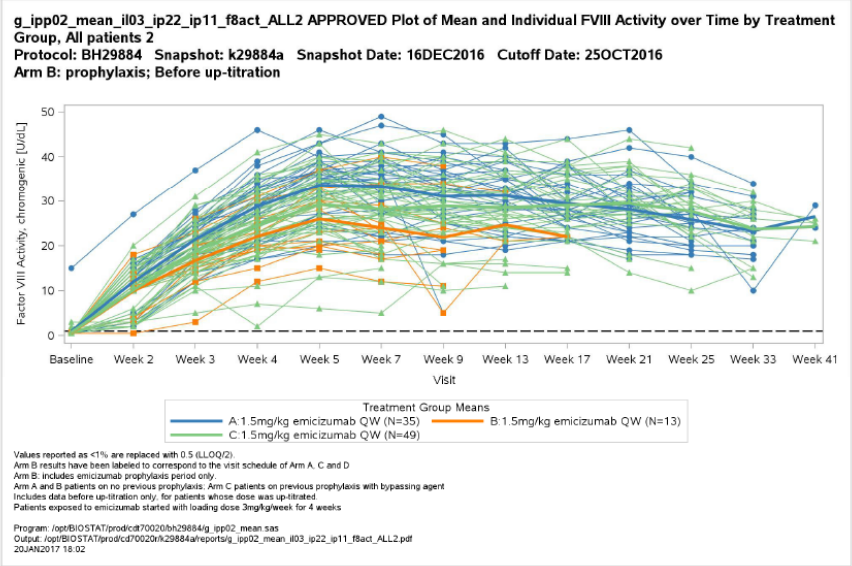
FVIII activity measured in pivotal studies BH29984 and BH29992

FVIII activity was measured with a chromogenic assay (Biophen FVIII:C – for further details see Methods Section 2.1.2 above) containing human FIXa and FX proteins. Reported FVIII activity values provided by this assay should not be viewed as equivalent to FVIII activity data obtained in patients treated with FVIII because the biochemical (enzymatic) properties of emicizumab and FVIII are not identical. Nevertheless, FVIII activity provides a relative indication of the procoagulant activity of emicizumab and thus serves as a PD marker.

Study BH29984

The slight decline over time for Arms A and C from Week 5 to Week 25+, and the lower mean values for Arm B after switch to emicizumab, are both thought to be the result of the same laboratory artefact. All Arm B emicizumab samples were collected and analysed after June 2016, as were the later visit samples for Arms A and C; whereas early time points for Arms A and C patients were generally collected and analysed prior to that date. Thus, the declining %FVIII values over time and the apparent difference between arms are thought by the Applicant to be likely due to signal drift in the central lab assay over time.

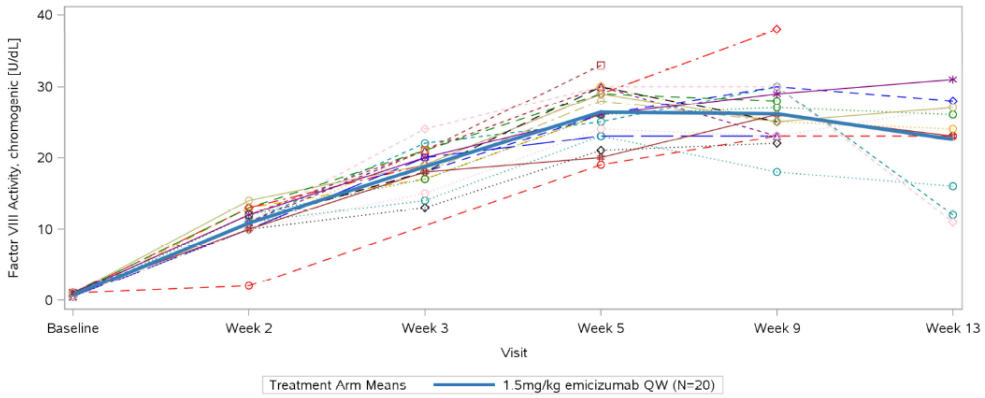
Figure 13: **Time course of Fator VIII activity by treatment arm (All emicizumab treated patients in arm A, arm B(emi) and arm C)**



Study BH29992

Following treatment with emicizumab, increases in reported FVIII activity were observed for all patients recruited so far, reaching levels between 19 and 33 U/dL at Week 5 and sustained at approximately this level during the study period.

Figure 14: **Mean and individual FVIII activity over time (treated patients)**



Secondary pharmacology

No dedicated, thorough QT study was conducted to evaluate the effect of emicizumab on ECG parameters (QTc). But intensive ECG assessments were performed, and the relationship between emicizumab PK and 12-Lead ECG (QTcF) was investigated in patients with haemophilia A in Studies ACE001JP Part C and ACE002JP. In part C of study ACE001JP, there were no obvious plasma ACE910 concentration-dependent prolongation of ΔQTcB and ΔQTcF within the concentration range up to 115 µg/mL in haemophilia A patients. The point estimates [95% CI] of the regression coefficient on plasma ACE910 concentration for ΔQTcB and ΔQTcF were −0.115 [−0.266 to 0.036] and −0.066 [−0.172 to 0.041], respectively. The same holds true for long term exposure based on results from the extension study ACE002JP, also showing no obvious plasma emicizumab concentration-dependent prolongation of ΔQTcF (Absolute change in QTcF interval from baseline; i.e., pre-treatment time-matched baseline) within the tested concentration range up to 144 µg/mL was observed.

Pharmacodynamic interactions with other medicinal products or substances

In conjunction with non-clinical results, an increased thrombotic effect of bypassing agents used in combination with emicizumab is hypothesised, with the effect being more pronounced in combination with aPCC. This is based on 2 confirmed cases of thromboembolic events (TE) and 2 cases of thrombotic microangiopathy (TMA), all observed in Study BH29884.

Bypassing agents (rFVIIa and aPCC) may be administered to emicizumab-treated patients with haemophilia A as episodic treatments for bleeds. The possibility of a PD interaction (hypercoagulability/thrombosis) between emicizumab and aPCC is likely and one between emicizumab and rFVIIa cannot be ruled out. This is further discussed in Section 3.3.8 Clinical Safety.

Relationships between plasma concentration and effect

The Repeated Time-to-Event Model developed from the phase 2 data demonstrated that bleeding frequency was reduced in a plasma emicizumab concentration-dependent manner and that cumulative bleeding events are reduced significantly when plasma emicizumab concentrations are > 45 µg/mL.

The applicant has provided a straightforward graphical analysis for exposure-efficacy, -pharmacodynamic and -safety endpoints. The dose regimen of 3 mg/kg/week SC for 4 weeks followed by 1.5 mg/kg/week SC results in a ABRT reduction that is near maximal at all exposure. Following 24 weeks of exposure, patients with 0 ABRTs had a median Cav of 55.8 ug/mL vs 47.7 and 41.9 µg/mL for patients with 1-10 and >10 ABRTs, respectively. aPTT was normalised (<40 seconds) at a plasma emicizumab concentration ≥ 5 ug/mL; peak height for thrombin generation and Factor VIII activity increased with increasing emicizumab concentration and this was not influenced by Factor XI or Factor X exposure.

There was no apparent relationship between plasma emicizumab concentration and occurrence of injection site reactions, thromboembolic events, or thrombotic microangiopathy. However, this may be due to low number of patients and/or events.

Analytical Methods

Drug concentration in plasma

A validated enzyme-linked immunosorbent assay (ELISA) developed by Chugai Pharmaceutical Co., Ltd. and validated at Chugai, SRL, Inc., and QPS Netherlands B.V. was used to measure emicizumab concentrations in plasma.

Immunogenicity

A panel of assays was used to detect, confirm, and characterise the antibody responses to emicizumab, as follows: screening electrochemiluminescence immunoassay (ECL) or ELISA to detect emicizumab antibodies in samples; followed by confirmatory assays (ECL or ELISA) to assess the specificity of the screenpositive results by competition with excess of emicizumab. Titration assays (ECL or ELISA) were used to determine the antibody titres for confirmed positive samples. A neutralising antibody assay and immunoglobulin E (IgE) assay was developed to characterize the confirmed antibodies to emicizumab (only in clinical studies ACE001JP, ACE002JP, and JP29574).

The assay for the detection of anti-emicizumab IgE antibodies in human plasma was based on the principles of fluorescent-enzyme immunoassay (FEIA), and the anti-emicizumab IgE antibodies were detected by measuring the reaction's fluorescence intensity.

Biomarker assays

Factor VIII activity was measured using a validated CE-marked chromogenic assay containing human FIXa and FX (Hyphen Biomed, Neuville-sur-Oise, France). A Bethesda assay method was used to detect FVIII inhibitors in patients in Study ACE002JP. FVIII inhibitor titre was measured in BH29884 and BH29992 using the Chromogenic Bethesda Assay (CBA) procedure published by the U.S. Centers for Disease Control (CDC). FIX was measured using a validated ELISA based on an AssayMax Human FIX ELISA Kit (Assaypro, Catalog No. EF1009-1). Factor X was measured using a validated ELISA based on an assay kit AssayMax Human X (FX) ELISA Kit (Assaypro, Catalog No. EF1010-1). Thrombin Generation (TG) was measured with a research-grade assay validated as fit-for-purpose. A Calibrated Automated Thrombogram method (Diagnostica Stago, Asnieres sur Seine, France) was modified by using a triggering reagent containing FXIa rather than tissue factor.

The Applicant also highlights the issue of interference of emicizumab with laboratory assays, such as aPTT, the one-stage (clotting) FVIII activity assay utilizing aPTT reagents, and the Bethesda or Nijmegen Bethesda assays for measuring FVIII inhibitor titre, those frequently used in management of patients with Haemophilia A. In these tests, and in all tests based on aPTT, emicizumab interferes with the test results, such that they do not accurately reflect the patient's underlying haemostatic potential.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of emicizumab have been described in healthy subjects and male patients with haemophilia A. There is limited, yet reassuring data in patients less than 2 years of age and no data in those less than 1. An extrapolation approach was required to support dosing in those less than 1 years of age. Modelling and simulations have been performed utilising the updated PopPK model which includes a maturation factor and the effects of changing albumin concentrations. A PBPK model was also developed which investigated the impact of changing IgG levels. It is agreed with the applicant that quantitative knowledge about age related processes is not well established and recognised that only the competition with varying levels of endogenous IgG levels is implemented in the PBPK model therefore this limits its usefulness. However, taken as a whole, the different models provide a range of clearance predictions in those less than 1 year. Typically an increase in clearance may be expected of up to 2 fold in neonates (PBPK model prediction). For the POPPK model, exposure in neonates is predicted to be 23% (with maturation; AUC_{SS} of ~250 µg*day/mL) and 27% (without maturation; AUC_{SS} of ~240 µg*day/mL) lower than that observed for of older patients (1–12 years).
There is limited data in this age range with other similar molecules which could support the extrapolation, the exception being pavlizumab, which has a significant amount of data (this data being the source of the maturation function) and infliximab which has some data in 6 patients less than 1 year of age (these showed similar exposure to older subjects when dosed on a weight based basis). The data shows similar relationships with age for the different drugs and therefore it is agreed that the popPK model, including the effect of body weight and albumin on the apparent clearance with a maturation function appears to be the most appropriate approach to extrapolate exposure for patients aged less than 1 year.
The results of these considerations suggest that the risk, if any, in this patient population will be slight under-exposure, however given the exposure-response analysis, this is unlikely to result in lack of efficacy.
Emicizumab induces a dose-dependent shortening of aPTT, with normalisation of aPTT occurring at low concentrations, at approximately ≥ 5µg/mL. It furthermore induces a dose-dependent promotion of Thrombin Generation, which is maintained over time, indicative of a 'pro-thrombotic

state' the coagulation system maintains while on emicizumab prophylaxis. No obvious changes in plasma FIX and FX concentrations have been observed. Reported FVIII activity levels, although not equivalent to FVIII activity data obtained in patients treated with FVIII, provide a relative indication of the procoagulant activity of emicizumab, thus serving as a PD marker, showing an increase, which plateaus after the 4-week period of loading doses. However, a slight decline can be observed over time likely due to quality control issues of the assay and not due to clinical or biological factors related to emicizumab PK, PD, or immunogenicity. Even if this would not be the only root cause, the consistency of clinical efficacy results observed are supportive of sustained clinical effect beyond the date the assay kit lot changed.

The proposed posology of 3 mg/kg/week s.c. for 4 weeks followed by 1.5 mg/kg/week s.c. is based on graphical analysis for exposure-efficacy, -pharmacodynamic and -safety endpoints, showing that this dose regimen results in a ABRT reduction that is near maximal at all exposure. No apparent relationship between plasma concentration and occurrence of ADRs (i.e. injection site reactions, thromboembolic events, or thrombotic microangiopathy) can be observed.

Drug-drug interaction with concomitant use of bypassing agents (i.e. aPCC, rFVIIa) has been identified and thoroughly investigated. This is discussed in more detail in the Section 2.6. Clinical Safety. Other secondary pharmacology, i.e. such as ECG assessment indicated no drug-related changes.

The validated assays used are generally considered adequate. In earlier clinical studies (ACE001JP/ACE002JP and JP29574), a tiered approach was used for analysis of anti emicizumab antibodies. All samples were analysed using an ECL screening assay, and positive samples were further analysed in a confirmatory assay by competition with excess of emicizumab. Finally, samples were titrated using the ECL assay. In the pivotal studies, a second-generation ELISA was used, which contained an overnight incubation step, allowing detection of free and initially complexed ADAs. With regards to drug tolerance, the applicant confirmed that that ADA can be detected when levels are ~ 40 micrograms/ml (trough concentrations with a maintenance dose of 1.5mg/kg/week), yet the applicant indicates a potential concentration-dependent interference of emicizumab with ADA detection. This conflicting information is noted. Nevertheless, development of clinically relevant ADA will likely affect efficacy and hence be recorded by clinicians by means of continuous monitoring of their patients. A statement has been included in section 5.1 of the SmPC to prompt physicians to consider a change of treatment in case of clinical signs of loss of efficacy.

The neutralising AB assay, in presence of anti-drug antibodies, measures a prolongation of aPTT time, with output of clotting time in seconds, meant as a qualitative assay, not intended for commercial use, with no inter-assay variability applying.

About the biomarker assays, although only used as exploratory endpoints, the applicant clarified that identical volumes in test and calibrator wells were used.

The applicant acknowledged the limitations of the biological tests used in patients with Haemophilia A including inhibitor measurement in the presence of emicizumab and has developed strategies to overcome this, by using the chromogenic assay with the bovine reagent. The inclusion of warnings and educational material for healthcare professionals and caregivers as part of the RMP has addressed this risk.

2.4.5. Conclusions on clinical pharmacology

PK and PD parameters have been characterised. The lack of data in patients aged 0-1 years of age has been reassuringly addressed through modelling and simulation. Limitations and concerns around the clinical use of emicizumab, particularly with regards to the concomitant use of

bypassing agents as well as interference with standard lab tests have been identified. Appropriate measures have been implemented to address these concerns (see Section 2.6 below).

2.5. Clinical efficacy

2.5.1. Dose response studies

Clinical efficacy data to support this current application in patients with FVIII inhibitors are derived primarily from the adult and adolescent pivotal Phase III Study BH29884 in patients ≥12 years of age.

Interim results from the ongoing paediatric pivotal Phase III Study BH29992 in children <12 years of age further support this application and an initial indication that encompasses all age groups.

Supporting data are also provided from the ongoing Phase I/II extension Study ACE002JP, which provides long-term efficacy data of emicizumab prophylaxis following more than 2 years of treatment.

Overall this submission includes efficacy data from 104 adult and adolescent patients (Study BH29884), 19 children aged <12 years and 1 aged 12 years old and less than 40kg (Study BH29992), as well as 18 adult and adolescent Japanese patients (ACE002JP, extension study of Part C of study ACE001JP).

In addition, the Phase III clinical program also includes a non-interventional study (NIS BH29768). NIS BH29768 prospectively collected bleed and haemophilia medication data and provided eligible patients the opportunity to enrol in the Phase III Studies BH29884 and BH29992.

- **Dose-response study ACE001JP**

This was a three-part trial conducted between 17th of August 2012 to 17th of April 2015; Part A and B being a randomised, placebo-controlled, double-blind, inter-individual, subcutaneous single ascending dose study in healthy Japanese adult male volunteers conducted at one site in Japan.

Part C was designed as an open-label, inter-individual, subcutaneous multiple-ascending dose study in Japanese patients with haemophilia A, conducted at 6 sites in Japan.

Study participants

All 64 HV enrolled in Part A and B were dosed, hence no subjects were excluded from safety, pharmacokinetic, or pharmacodynamic analyses. One HV in the placebo group and 1 in the 0.3 mg/kg group in Part B withdrawn for failure to cooperate.

For Part C a total of 18 haemophilia A patients were enrolled and dosed in three groups of 6 patients with only one patient in the 1 mg/kg/week group discontinued study administration due to an adverse event (AE).

One patient each in the 0.3 mg/kg/week group and the 3 mg/kg/week group in Part C transitioned to the observation period, and 5 patients in the 0.3 mg/kg/week group, 5 patients in the 1 mg/kg/week group and 5 patients in the 3 mg/kg/week group transitioned to the ACE002JP study and continued ACE910 administration with no interruptions. One patient in the 0.3 mg/kg/week group transitioned to the ACE002JP study after completing the observation period.

Study conduct & deviations

The applicant amended 6 times the protocol. The amendments are not considered to have any impact on the study outcomes.

Most of the protocol deviations (13) are due to inadequate primary endpoint investigations, mainly deviations from the protocol set timepoints for investigations, or missing data.

For more detailed pharmacokinetic results from Study ACE001JP see above. The extension study of part C, ACE002JP will be discussed under Section Supportive studies in the below.

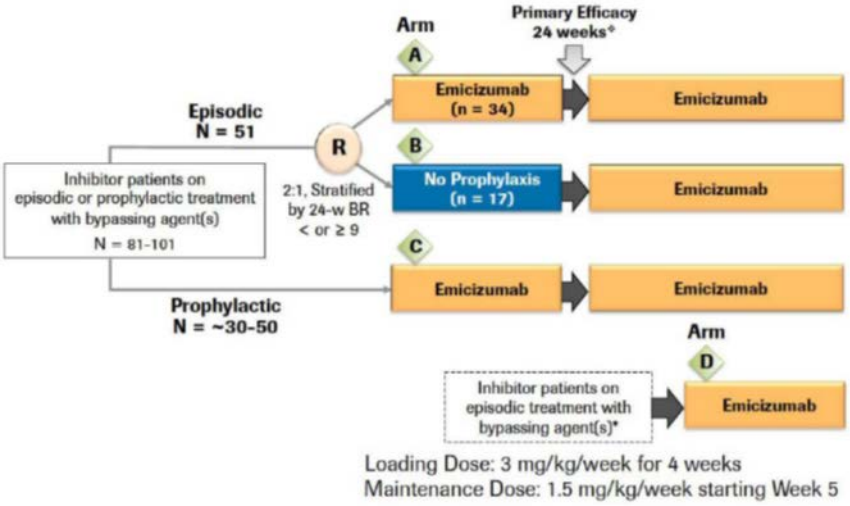
2.5.2. Main studies

Study BH29884: open label, multicentre, global, randomized study, with two additional, separate therapeutic arms

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 15: **Overview of study design – study BH29884**



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

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.

Objectives

The primary 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.

The secondary objectives for this study was to 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).

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

The PK objective for this study was to characterise the exposure (Ctrough) of emicizumab prior to drug administration on Day 1 at the following time points while on emicizumab: Every week during Weeks 1-4; Every 2 weeks during Weeks 5-8; Every 4 weeks during Weeks 9-24; Every 8 weeks during Weeks 25-48; Every 12 weeks thereafter, until the end of the study.

The exploratory biomarker objectives were to assess potential pharmacodynamic (PD) biomarkers of emicizumab.

Outcomes/endpoints

Primary endpoint was number of bleeds over time (i.e., bleed rate), defined as a bleed for which coagulation factors are administered. Bleeds due to surgery/procedure were not included in the primary analysis.

For the purposes of the efficacy analyses, a standardised definition of bleed, adapted from standard criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Haemostasis was used (Blanchette *et al*. 2014).

Secondary endpoints were number of all bleeds (i.e., those treated and not treated with coagulation factors) over time (added in Amendment 1); number of spontaneous bleeds over time (added in Amendment 2); number of joint bleeds over time; number of target joint bleeds over time (defined as a major joint e.g., hip, elbow, wrist, shoulder, knee, and ankle into which repeated bleeds occur (frequency of ≥ 3 bleeds into the same joint over the last 24 weeks prior to study entry); HRQoL of patients according to Haem-A-QoL (aged ≥18) or Haemo-QoL-Short Form (ages 12-17) scores at 24 weeks; health status of patients according to EuroQoL Five-Dimension-

Five Levels Questionnaire (EQ-5D-5L) scores at 24 weeks; number of bleeds over time compared with the patient's historical bleed rate (both for treated bleeds and all bleeds).

Exploratory endpoints were differences in number of days away from school/work and differences in number of days hospitalised.

Assessments

Data on bleeds and medications were collected using an electronic, handheld device using a BMQ developed and validated by the applicant as a patient-reported measure of bleeding episodes (including cause, type, location, day and start time of bleed, and symptoms) and haemophilia-related medication use, completed at least weekly.

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 Bcontrol), 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 who took episodic treatment with bypassing agents prior to study entry were randomised in a 2:1 ratio to receive either emicizumab prophylaxis (Arm A) or to receive no prophylaxis (Arm B control).

A central randomisation procedure was used for all patients who fulfilled the entry criteria at screening, with block-based randomisation stratified by the number of bleeds in the last 24 weeks (< 9 or ≥ 9). The stratification cut-point was chosen to approximate an ABR of 18, which was estimated to be approximately halfway between the minimum ABR to be eligible for this study and median ABR for inhibitor patients receiving episodic bypassing agents.

A total of 114 patients were screened prior to enrolment into this study, with 109 eligible patients enrolled. The countries from which the most patients were enrolled were the United States (33.0%), followed by Japan (11.0%) and Poland (8.3%).

Among the 109 patients, 66 patients (60.6%) had previously participated in NIS BH29768 (24 randomised to Arm A; 11 to Arm B; 24 eligible for Arm C; 7 for Arm D).

Three patients were withdrawn from emicizumab treatment, all in Arm A (2 patients due to an AE – see also Section 3.3.8 Clinical safety below - and 1 patient per physician decision; one patient randomised to Arm A withdrew prior to Study Day 1; patient decision to not participate).

Blinding (masking)

This was an open-label study.

Statistical methods

Formal hypothesis testing was conducted only for the randomised comparison of Arm A versus Arm $B_{control}$, and for the intra-patient comparisons in Arms A and C. The comparison of the number of bleeds over time between the randomised treatment arms was performed using a negative binomial (NB) regression model, which accounted for different follow-up times, with the patient's number of bleeds as a function of randomisation and the time that each patient stays in the study included as an offset in the model. The model also included the number of bleeds (< 9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomisation. This analytic model estimated the rate ratio, lambda t/ lambda c., which quantified the risk of bleeding associated with emicizumab prophylaxis (lambda t) in comparison to no prophylaxis (lambda c). Statistical significance was controlled at the 2-sided, 0.05 alpha level, and the estimated risk ratio was compared with 1, assuming the following statistical hypothesis:

- H0 (null hypothesis): rate ratio=1
  versus
- H1 (alternative hypothesis): rate ratio ≠ 1.

Statistical significance was controlled at a two-sided alpha level of 0.05 based on a Wald testing procedure. Bleed rates for emicizumab prophylaxis and for no prophylaxis, together with the rate ratio including 95% confidence intervals, were described.

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

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

Both NB regression model-based and calculated ABR results are presented.

It was pre-specified in the SAP that the non-parametric Van Elteren test of ABR was to be provided as a sensitivity analysis. If convergence of the NB regression model was not achieved or was questionable, the primary efficacy analysis would then be based on the Van Elteren test of ABR.

The start of the efficacy period for each individual patient was defined as the first day there were data available from the BMQ. For patients who started the study on emicizumab (Arms A, C, and D), this coincided with the Week 1 visit and the day of the first emicizumab dose, and for the patients who did not start the study on emicizumab (i.e., Arm $B_{control}$), this coincided with the Week 1 visit. The second efficacy period for patients in Arm B started when they switched to receive emicizumab prophylaxis (i.e., Arm B_{emi}), on the day of their first emicizumab dose.

For patients in Arms A, C or D the end of the efficacy period was defined as the date of the CCOD or the date of withdrawal from the initial study period (i.e., treatment phase according to eCRF), whichever was earlier.

For patients randomised to Arm $B_{control}$ (no prophylaxis), the end of the first efficacy period was defined as either the day before the first emicizumab dose was administered (for patients who switched to receive emicizumab after 24 weeks) or the date of withdrawal from the initial study period. The second efficacy period ended on the date of the CCOD or the date of withdrawal from emicizumab treatment.

For the intra-patient comparisons the efficacy period in NIS BH29768 comprised total time in NIS BH29768 prior to enrolment in Study BH29884, and the efficacy period during the participation in Study BH29884 was calculated as above for the efficacy periods in Arms A and C.

For patients whose dose was up-titrated, the efficacy period ended the day before the first day on the up-titrated dose. The bleeds on the up-titrated dose were analysed separately. The efficacy

period on a given up-titrated dose started with the first day on this dose and ended on the day of the CCOD or withdrawal.

For a patient who withdrew from the study before reaching the Week 1 visit, the duration of the efficacy period was set to 1 day, starting and ending on the day of randomisation/enrolment.

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 belonged 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). 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.

As per the adapted ISTH definition, 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 (72-hour rule) 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. This was in line with the above definition that bleeds and treatments were considered to be pairs.

Secondary Efficacy Endpoints

For the intra-patient comparisons, only patients who participated in the NIS BH29768 were included as bleed and treatment data were collected with the same level of granularity in both time periods. Of note, for some patients who participated in NIS BH29768, the total time in that study prior to enrolment in Study BH29884 was less than 24 weeks

The pre-specified endpoints on the Haemo-QoL-SF were not tested, due to an insufficient number of adolescent patients randomised to Arm A or B. All analyses of the Haemo-QoL-SF were descriptive only.

Type I error for secondary endpoints was controlled through a hierarchical testing framework. The alpha level was 0.05. The hierarchy was designed both with clinical relevance as well as probability of success in mind. The endpoints were included in the following order:

- A versus B randomised comparison: all bleeds
- A intra-patient: all bleeds
- A intra-patient: treated bleeds
- A versus B randomised comparison: joint bleeds
- C intra-patient: all bleeds
- C intra-patient: treated bleeds
- A versus B randomised comparison: spontaneous bleeds
- A versus B randomised comparison: target joint bleeds
- A versus B randomised comparison: Haem-A-QoL physical health subscale at 24 weeks
- A versus B randomised comparison: Haem-A-QoL Total Score at 24 weeks
- A versus B randomised comparison: EQ-5D-5L VAS at 24 weeks

- A versus B randomised comparison: EQ-5D-5L Index Utility Score at 24 weeks

The analysis methodology for all secondary endpoints was the same as for the primary endpoint, except for the EQ-5D-5L and Haem-A-QoL at 24 weeks, which used analysis of covariance (ANCOVA) with treatment group, baseline score, time and treatment by baseline interaction term as covariates.

Sensitivity Analyses

Pre-specified sensitivity analyses included different methods to define bleeds or eligible bleed data as well as alternative statistical tests to NB regression.

Bleed definitions:

- Analysis including all bleeds recorded by patients in the electronic patient-reported outcomes device (i.e., without the 72-hour rule).
- Analysis including only patients who received at least 12 weeks of emicizumab treatment.
- Analysis based on counting days when treatment for bleeds was administered instead of the bleeds themselves.
- Analysis including only patients who had at least 12 weeks of follow-up in NIS BH29768 (for the intra-patient comparison secondary endpoints only).
- Alternative tests:
- ANCOVA
- Van Elteren (non-parametric stratified test)
- Wilcoxon Rank Sum (non-parametric unstratified test)

Subgroup analyses

The primary endpoint was analysed by the following pre-defined subgroups:

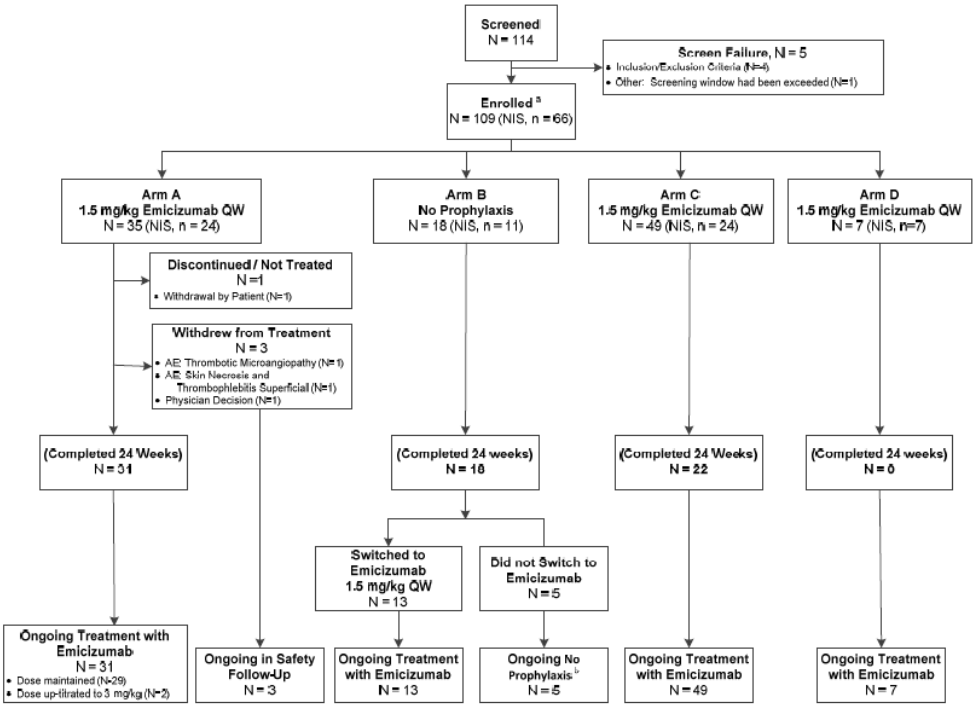
- Age: < 18, ≥ 18
- Age: < 65, ≥ 65
- Race: Asian, Black or African American, White, Other
- Number of bleeds during 24 weeks prior to study entry: ≤ 9, >9
- Number of target joints: no target joint, any target joint

In addition, estimated ABR including 95% confidence interval (CI) were calculated for all treatment arms for each of these subgroups. Due to the small sample size, all subgroup analyses are highly sensitive to variability caused by individual patients and should be interpreted with caution. No p-values were calculated.

Results

Participant flow

Figure 16: Patient disposition–study BH29884



AE = adverse event; N = number of patients from Study BH29884; n = number of patients from NIS BH29768; NIS = non-interventional study; QW = once weekly

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

[b] After completing 24 weeks, these patients remained on No Prophylaxis (Arm $B_{control}$) due to the temporary enrollment halt.

The total observation time for all patients in the study (calculated as the time from 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.

The shorter observation time in Arms C and D is not surprising (completed 24 weeks of treatment Arm C: 44.9% [22 patients]; Arm D: 0), as recruitment was prioritised into Arm A and B triggering the primary analysis.

Most patients in Arm B (13 patients [72.2%]) switched to receive emicizumab (Arm Bemi) after completion of the 24-week evaluation and the remaining patients (5 patients; 27.8%) did not switch. This was due to the temporary enrolment halt following the SAEs of TE and TMA.

Table 6: Total observation Time (all patient) –Cutoff date 25 Oct 2016 –study BH29884

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=7)	Total (N=109)
Observation Time (weeks)					
n	18	35	49	7	109
Mean (SD)	31.14 (5.06)	30.71 (7.76)	22.44 (11.84)	7.59 (3.87)	25.58 (11.19)
Median	31.00	31.00	20.00	6.14	28.14
Min - Max	24.1 - 42.3	0.1 - 49.0	6.9 - 45.3	4.0 - 14.9	0.1 - 49.0
Observation Time (week categories)					
>0 w	18 (100.0%)	35 (100.0%)	49 (100.0%)	7 (100.0%)	109 (100.0%)
>=4 w	18 (100.0%)	34 (97.1%)	49 (100.0%)	7 (100.0%)	108 (99.1%)
>=12 w	18 (100.0%)	34 (97.1%)	37 (75.5%)	1 (14.3%)	90 (82.6%)
>=24 w	18 (100.0%)	34 (97.1%)	22 (44.9%)	0	74 (67.9%)
>=36 w	3 (16.7%)	6 (17.1%)	7 (14.3%)	0	16 (14.7%)
>=48 w	0	1 (2.9%)	0	0	1 (0.9%)

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

Recruitment

The study is conducted in 43 sites across 14 countries.

The study was sponsored by the applicant (F. Hoffmann-La Roche Ltd) and Chugai Pharmaceutical Co. Ltd.

Study period

First patient entered was 18th of November 2015.

Last patient entered was 28th of September 2016.

Last patient randomised was 11th of May 2016.

Data cut-off/ LPLV was 25th of October 2016.

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.

The few cases of non-compliance, where the patients did not fill out a questionnaire via the BMQ, and the site supplemented the information via a site data entry system was balanced between treatment arms. Compliance of providing responses to the quality of life questionnaires was high with no apparent drop over time. The missing data are mostly due to individual patient's low compliance across all time points.

Table 7: 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 8: 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

The number of patients per arm is small, especially in Arms B and D.

Patient demographic characteristics were generally well balanced between Arm A and Arm B, except race.

Table 9: Summary of demographic characteristics

	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=7)	Total (N=109)
Sex					
n	18	35	49	7	109
Male	18 (100.0%)	35 (100.0%)	49 (100.0%)	7 (100.0%)	109 (100.0%)
Age (years)					
n	18	35	49	7	109
Mean	37.2	35.8	25.6	30.3	31.1
SD	13.7	13.9	16.8	10.8	15.8
SEM	3	2	2	4	2
Median	35.5	38.0	17.0	26.0	28.0
Min - Max	13 - 65	12 - 68	12 - 75	19 - 49	12 - 75
Age Category 1					
n	18	35	49	7	109
< 18	2 (11.1%)	4 (11.4%)	26 (53.1%)	0	32 (29.4%)
>= 18	16 (88.9%)	31 (88.6%)	23 (46.9%)	7 (100.0%)	77 (70.6%)
Age Category 2					
n	18	35	49	7	109
< 65	17 (94.4%)	34 (97.1%)	47 (95.9%)	7 (100.0%)	105 (96.3%)
>= 65	1 (5.6%)	1 (2.9%)	2 (4.1%)	0	4 (3.7%)

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

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=7)	Total (N=109)
Weight (kg)					
n	18	35	49	7	109
Mean	81.64	75.86	67.56	66.41	72.47
SD	23.61	18.31	17.92	20.79	19.78
SEM	5.6	3.1	2.6	7.9	1.9
Median	79.45	72.00	65.50	58.00	69.00
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	6	105
Mean	1.96	1.88	1.76	1.80	1.83
SD	0.25	0.23	0.26	0.24	0.26
SEM	0.1	0.0	0.0	0.1	0.0
Median	1.96	1.85	1.79	1.69	1.82
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	6	105
Mean	26.86	26.09	23.78	23.03	24.98
SD	7.99	5.66	4.98	7.91	6.01
SEM	1.9	1.0	0.7	3.2	0.6
Median	25.97	24.35	23.54	20.63	23.81
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

Table 10: Summary of Non Emicizumab haemophilia medication (ITT population) –Cutoff date 25 Oct 2016 –study BH29884

	B: no prophylaxis (N=18)	A:1.5mg/kg emicizumab QW (N=35)
Total number of patients with at least one treatment	17 (94.4%)	17 (48.6%)
Total number of treatments	815	117
Purpose of the medication		
Treatment for bleed	17 (94.4%)	17 (48.6%)
Preventative dose before activity	6 (33.3%)	2 (5.7%)
Preventative dose for procedure/surgery	3 (16.7%)	3 (8.6%)
Prothrombin Complex Concentrate		
Total number of patients with at least one treatment	13 (72.2%)	11 (31.4%)
Total number of treatments	302	70
Purpose of the medication		
Treatment for bleed	13 (72.2%)	11 (31.4%)
Preventative dose before activity	4 (22.2%)	0
Preventative dose for procedure/surgery	2 (11.1%)	1 (2.9%)
Recombinant Factor VIIa		
Total number of patients with at least one treatment	12 (66.7%)	12 (34.3%)
Total number of treatments	511	47
Purpose of the medication		
Treatment for bleed	12 (66.7%)	12 (34.3%)
Preventative dose before activity	5 (27.8%)	2 (5.7%)
Preventative dose for procedure/surgery	3 (16.7%)	2 (5.7%)
Fresh Frozen Plasma/Whole Blood		
Total number of patients with at least one treatment	1 (5.6%)	0
Total number of treatments	2	0
Purpose of the medication		
Preventative dose for procedure/surgery	1 (5.6%)	0

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 11 Hemophilia A History (all patients) – study BH29884

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=7)	Total (N=109)
Hemophilia severity at baseline					
n	18	35	49	7	109
Mild	0	2 (5.7%)	1 (2.0%)	0	3 (2.8%)
Moderate	0	2 (5.7%)	1 (2.0%)	1 (14.3%)	4 (3.7%)
Severe	18 (100.0%)	31 (88.6%)	47 (95.9%)	6 (85.7%)	102 (93.6%)
Time from Factor VIII inhibitor diagnosis date (months)					
n	17	34	49	6	106
Mean (SD)	306.28 (183.83)	276.45 (164.87)	210.88 (122.21)	268.96 (166.19)	250.50 (152.67)
Median	302.52	258.33	177.18	272.77	199.75
Min - Max	49.7 - 578.9	16.3 - 548.2	8.0 - 577.7	62.7 - 500.4	8.0 - 578.9
n	17	34	49	6	106
<24 months	0	3 (8.8%)	3 (6.1%)	0	6 (5.7%)
24-<48 months	0	0	0	0	0
48-<72 months	3 (17.6%)	1 (2.9%)	0	1 (16.7%)	5 (4.7%)
>=72 months	14 (82.4%)	30 (88.2%)	46 (93.9%)	5 (83.3%)	95 (89.6%)
Highest historical inhibitor titer (BU)					
n	16	32	47	6	101
Mean (SD)	706.8 (1450.0)	288.9 (472.8)	815.7 (1148.1)	528.9 (793.4)	614.5 (1037.9)
Median	102.0	84.5	309.0	240.0	180.0
Min - Max	18 - 4500	5 - 1570	11 - 5000	28 - 2125	5 - 5000
n	18	35	49	7	109
<5 BU	0	0	0	0	0
>=5 BU	16 (88.9%)	32 (91.4%)	47 (95.9%)	6 (85.7%)	101 (92.7%)
Unknown	2 (11.1%)	3 (8.6%)	2 (4.1%)	1 (14.3%)	8 (7.3%)
Previously treated with ITI					
n	18	35	49	7	109
Yes	7 (38.9%)	14 (40.0%)	33 (67.3%)	3 (42.9%)	57 (52.3%)
No	11 (61.1%)	21 (60.0%)	16 (32.7%)	4 (57.1%)	52 (47.7%)
Time from most recent ITI date (years)					
n	3	6	28	2	39
Mean (SD)	7.97 (5.09)	9.37 (10.37)	10.41 (5.88)	24.21 (0.19)	10.77 (7.11)
Median	9.01	3.97	11.58	24.21	11.17
Min - Max	2.4 - 12.5	1.2 - 23.1	0.9 - 21.9	24.1 - 24.3	0.9 - 24.3
Time from most recent ITI date					
n	18	35	49	7	109
<2 years	0	2 (5.7%)	2 (4.1%)	0	4 (3.7%)
2-5 years	1 (5.6%)	2 (5.7%)	5 (10.2%)	0	8 (7.3%)
>5 years	2 (11.1%)	2 (5.7%)	21 (42.9%)	2 (28.6%)	27 (24.8%)
Unknown	15 (83.3%)	29 (82.9%)	21 (42.9%)	5 (71.4%)	70 (64.2%)
Number of patients with prior episodic treatment in the last 24 weeks*					
n	18	35	23	7	83
Prothrombin complex concentrate	13 (72.2%)	27 (77.1%)	15 (65.2%)	5 (71.4%)	60 (72.3%)
Recombinant factor VIIa	17 (94.4%)	22 (62.9%)	15 (65.2%)	5 (71.4%)	59 (71.1%)
Factor VIII	0	1 (2.9%)	1 (4.3%)	2 (28.6%)	4 (4.8%)
Other	0	1 (2.9%)	0	1 (14.3%)	2 (2.4%)
Number of patients with prior prophylactic treatment in the last 24 weeks*					
n			49		49
Prothrombin complex concentrate			36 (73.5%)		36 (73.5%)
Recombinant factor VIIa			15 (30.6%)		15 (30.6%)
Factor VIII			1 (2.0%)		1 (2.0%)
Other			1 (2.0%)		1 (2.0%)
Reason for not being on prophylactic treatment regimen*					
n	18	35		7	60
Availability	6 (33.3%)	10 (28.6%)		1 (14.3%)	17 (28.3%)
Price / Reimbursement	6 (33.3%)	9 (25.7%)		0	15 (25.0%)
Tolerability / Side Effects	4 (22.2%)	2 (5.7%)		0	6 (10.0%)
Efficacy	7 (38.9%)	6 (17.1%)		1 (14.3%)	14 (23.3%)
Frequency of Infusion / Half-Life	5 (27.8%)	8 (22.9%)		2 (28.6%)	15 (25.0%)
Subject Request	9 (50.0%)	11 (31.4%)		3 (42.9%)	23 (38.3%)
Venous Access	5 (27.8%)	9 (25.7%)		2 (28.6%)	16 (26.7%)
Other	4 (22.2%)	10 (28.6%)		0	14 (23.3%)

* Multiple answers are possible.
ITI = Immune Tolerance Induction.
n represents the number of patients contributing to summary statistics.
Percentages are based on n.
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

Table 12: Analysis Populations –study BH29884

	B: no prophylaxis	A:1.5mg/kg emicizumab QW	C:1.5mg/kg emicizumab QW	D:1.5mg/kg emicizumab QW	Total
All patients 1	18	35	49	7	109
All patients 2	13	35	49	7	104
Total exclusions	5	0	0	0	5
ITT	18	35	0	0	53
Total exclusions	0	0	49	7	56
SAP 1	18	34	49	7	108
Total exclusions	0	1	0	0	1
SAP 2	13	34	49	7	103
Total exclusions	5	1	0	0	6
NIS patients	11	24	24	7	66
Total exclusions	7	11	25	0	43
Up-titrated patients	0	2	0	0	2
Total exclusions	18	33	49	7	107

Outcomes and estimation

Table 13: Overview of Efficacy (NB Regression model; ITT Population) –Cutoff date 25 Oct 2016 –study BH29884

	B: no prophylaxis (N=18)		A:1.5mg/kg emicizumab QW (N=35)
Number of Patients	18		35
Treated Bleeds			
ABR, model based [95% CI]	23.3 [12.33;43.89]		2.9 [1.69; 5.02]
ABR Ratio		0.13	
95% CI for the ratio between bleeding rates		[0.057;0.277]	
p-Value (Stratified Wald test)		<.0001	
p-Value (Non-Stratified Wald test)		<.0001	
All Bleeds			
ABR, model based [95% CI]	28.3 [16.79;47.76]		5.5 [3.58; 8.60]
ABR Ratio		0.20	
95% CI for the ratio between bleeding rates		[0.102;0.375]	
p-Value (Stratified Wald test)		<.0001	
p-Value (Non-Stratified Wald test)		<.0001	
Treated Spontaneous Bleeds			
ABR, model based [95% CI]	16.8 [9.94;28.30]		1.3 [0.73; 2.19]
ABR Ratio		0.08	
95% CI for the ratio between bleeding rates		[0.037;0.154]	
p-Value (Stratified Wald test)		<.0001	
p-Value (Non-Stratified Wald test)		<.0001	
Treated Joint Bleeds			
ABR, model based [95% CI]	6.7 [1.99;22.42]		0.8 [0.26; 2.20]
ABR Ratio		0.11	
95% CI for the ratio between bleeding rates		[0.025;0.520]	
p-Value (Stratified Wald test)		0.0050	
p-Value (Non-Stratified Wald test)		0.0052	
Treated Target Joint Bleeds			
ABR, model based [95% CI]	3.0 [0.96; 9.13]		0.1 [0.03; 0.58]
ABR Ratio		0.05	
95% CI for the ratio between bleeding rates		[0.009;0.227]	
p-Value (Stratified Wald test)		0.0002	
p-Value (Non-Stratified Wald test)		0.0002	

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

Efficacy observation time for the intra-patient comparison (Arm A and C) based on the NIS BH29768 trial were 8 patients (33.3%) for ≥24 weeks for episodic bypassing agents of the NIS population and 22 patients (91.7%) for Arm A, 16 patients (66.6%) for prophylactic bypassing therapy of the NIS and 15 (62.5%) for patients on Arm C, both for the efficacy period ≥24 weeks.

Two patients in Arm A had their dose up-titrated from 1.5 to 3 mg/kg/week. One patient after week 27 after physicians verified ≥ 2 spontaneous and clinically significant bleeds; one after week 25 again due to verified ≥ 2 spontaneous and clinically significant non-limb-threatening joint bleeds. Preliminary results show improved efficacy. In the intra-patient analysis, Hemlibra prophylaxis resulted in statistically significant (p = 0.0003) and clinically meaningful reduction (79%) in bleed rate for treated bleeds compared with previous bypassing agent prophylaxis collected in the NIS prior to enrolment. See Tables below for overview of intra-patient comparisons in Arm A and C.

Table 14: Overview of Efficacy for intra-patient comparison in Arm A –Cutoff date 25 Oct 2016 –study BH29884

	Episodic bypassing agents (N=24)		A: 1.5mg/kg emicizumab QW (N=24)
Number of Patients	24		24
Treated Bleeds			
ABR, model based [95% CI]	21.6 [15.40;30.22]		1.7 [0.71; 4.06]
ABR Ratio		0.08	
95% CI for the ratio between bleeding rates		[0.031;0.198]	
p-Value (Non-Stratified Wald test)		<.0001	
All Bleeds			
ABR, model based [95% CI]	37.7 [28.40;50.04]		4.1 [2.10; 8.02]
ABR Ratio		0.11	
95% CI for the ratio between bleeding rates		[0.055;0.218]	
p-Value (Non-Stratified Wald test)		<.0001	

Only patients who participated in the NIS BH29768 and in study BH29884 are included.
Includes data before up-titration only, for patients whose dose was up-titrated.
Intra-patient comparator data from non-interventional study BH29768

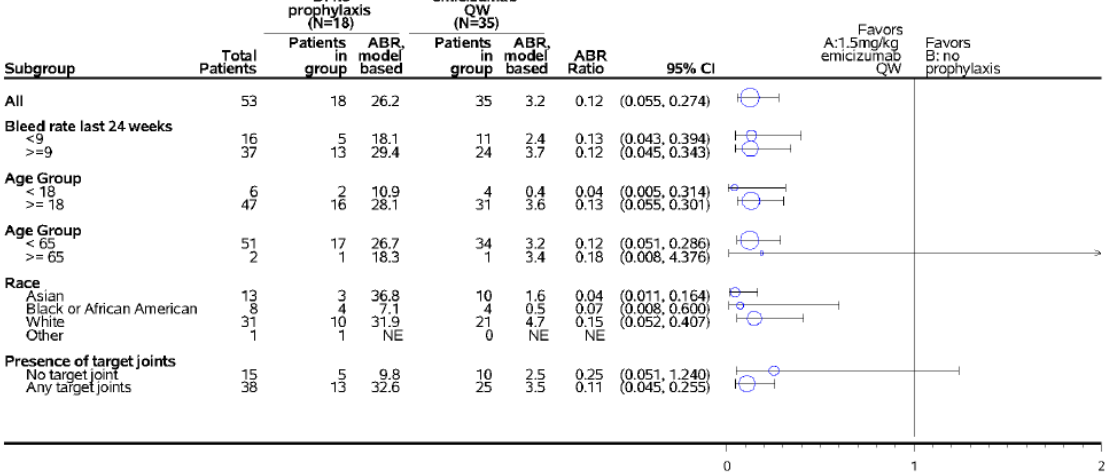
Table 15: Overview of Efficacy for intra-patient comparison in Arm C –Cutoff date 25 Oct 2016 –study BH29884

	Prophylactic bypassing agents (N=24)		C: 1.5mg/kg emicizumab QW (N=24)
Number of Patients	24		24
Treated Bleeds			
ABR, model based [95% CI]	15.7 [11.08;22.29]		3.3 [1.33; 8.08]
ABR Ratio		0.21	
95% CI for the ratio between bleeding rates		[0.089;0.486]	
p-Value (Non-Stratified Wald test)		0.0003	
All Bleeds			
ABR, model based [95% CI]	24.3 [18.11;32.67]		5.5 [2.98;10.26]
ABR Ratio		0.23	
95% CI for the ratio between bleeding rates		[0.119;0.435]	
p-Value (Non-Stratified Wald test)		<.0001	

Only patients who participated in the NIS BH29768 and in study BH29884 are included.
Includes data before up-titration only, for patients whose dose was up-titrated.
Intra-patient comparator data from non-interventional study BH29768

Table 16: Subgroup Analyses for Treated Bleeds (ITT population) - BH29884 study

Subgroup	Total Patients	B: no prophylaxis (N=18) Patients in group	B: no prophylaxis (N=18) ABR, model based	A:1.5mg/kg emicizumab QW (N=35) Patients in group	A:1.5mg/kg emicizumab QW (N=35) ABR, model based	ABR Ratio	95% CI
All	53	18	26.2	35	3.2	0.12	(0.055, 0.274)
Bleed rate last 24 weeks							
<9	16	5	18.1	11	2.4	0.13	(0.043, 0.394)
>=9	37	13	29.4	24	3.7	0.12	(0.045, 0.343)
Age Group							
< 18	6	2	10.9	4	0.4	0.04	(0.005, 0.314)
>= 18	47	16	28.1	31	3.6	0.13	(0.055, 0.301)
Age Group							
< 65	51	17	26.7	34	3.2	0.12	(0.051, 0.286)
>= 65	2	1	18.3	1	3.4	0.18	(0.008, 4.376)
Race							
Asian	13	3	36.8	10	1.6	0.04	(0.011, 0.164)
Black or African American	8	4	7.1	4	0.5	0.07	(0.008, 0.600)
White	31	10	31.9	21	4.7	0.15	(0.052, 0.407)
Other	1	1	NE	0	NE	NE	
Presence of target joints							
No target joint	15	5	9.8	10	2.5	0.25	(0.051, 1.240)
Any target joints	38	13	32.6	25	3.5	0.11	(0.045, 0.255)



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

Health Status and Quality of Life

In Study BH29884, health-related quality of life for patients aged ≥ 18 years was evaluated at Week 25 based on the Haemophilia-specific Quality of Life (Haem-A-QoL) questionnaire for adults. Baseline Total Scores (mean = 41.14 and 44.58, respectively) and Physical Health scale scores (mean = 52.41 and 57.19, respectively) were similar for Hemlibra prophylaxis and no prophylaxis. Table below provides a summary of the comparison between the Hemlibra prophylaxis arm (Arm A) and the no prophylaxis arm (Arm B) on the Haem-A-QoL Total Score and Physical Health scale after 24 weeks of treatment adjusting for baseline. Weekly Hemlibra prophylaxis showed a statistically significant and clinically meaningful improvement compared with the no prophylaxis in the pre specified endpoints of Haem-A-QoL Total Score and Physical Health Scale score at the Week 25 assessment. All the secondary endpoints for the Haem A-QoL and EQ-5D-5L were met.

Table 17: Overview of Health Status and Quality of Life Efficacy Endpoints ITT population –study BH29884

	B: no prophylaxis (N=18)		A:1.5mg/kg emicizumab QW (N=35)
Haem-A-QoL physical health subscale at week 25			
n	14		25
Adjusted Mean	54.17		32.61
Difference in Adjusted Means		21.55	
p-Value		0.0029	
Haem-A-QoL total score at week 25			
n	14		25
Adjusted Mean	43.21		29.20
Difference in Adjusted Means		14.01	
p-Value		0.0019	
EQ-5D-5L VAS at week 25			
n	16		29
Adjusted Mean	74.36		84.08
Difference in Adjusted Means		-9.72	
p-Value		0.0171	
EQ-5D-5L index utility score at week 25			
n	16		29
Adjusted Mean	0.65		0.81
Difference in Adjusted Means		-0.16	
p-Value		0.0014	

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 18: Study BH29884: Haem-A-QoL Scores in patients ≥ 18 years after 24 weeks

Haem-A-QoL scores after 24 weeks	Arm B: no prophylaxis (n=14)	Arm A: 1.5 mg/kg Hemlibra weekly (n=25)
Total score		
Adjusted mean	43.21	29.2
Difference in adjusted means (95% CI)	14.01 (5.56, 22.45)	
p-value	0.0019	
Physical health		
Adjusted mean	54.17	32.61
Difference in adjusted means (95% CI)	21.55 (7.89, 35.22)	
p-value	0.0029	

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 a loading dose of 3 mg/kg/week for 4 weeks.
Haem-A_QoL scales range from 0 to 100; lower scores are reflective of better HRQoL.
Clinically meaningful difference: Total score: 7 points; Physical Health: 10 points.

In Study BH29884, patients' health status was assessed according to the EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L). Table below provides a summary of the comparison between the Hemlibra prophylaxis arm (Arm A) and the no prophylaxis arm (Arm B) on the EQ-5D-5L index utility scale and visual analog scale after 24 weeks of treatment adjusting for baseline. Weekly Hemlibra showed a statistically significant and clinically meaningful improvement compared with no prophylaxis in the pre specified endpoints of EQ-5D-5L index utility scale and visual analogue scale at the Week 25 assessment.

Table 19: Study BH29884: EQ-5D-5L scores in patients ≥ 12 years after 24 weeks

EQ-5D-5L scores after 24 weeks	Arm B: no prophylaxis (n=16)	Arm A: 1.5 mg/kg Hemlibra weekly (n=29)
Visual Analogue Scale		
Adjusted mean	74.36	84.08
Difference in adjusted means (95% CI)	-9.72 (-17.62, -1.82)	
p-value	0.0171	
Index Utility Score		
Adjusted mean	0.65	0.81
Difference in adjusted means (95% CI)	-0.16 (-0.25, -0.07)	
p-value	0.0014	

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 a loading dose of 3 mg/kg/week for 4 weeks.
Higher scores indicate better quality of life.

Clinically meaningful difference: VAS: 7 points, Index Utility Score: 0.07 points

Ancillary analyses

Exploratory endpoints (ITT population) showed that most treated bleeds reported during the study in both study arms occurred in joints (Arm B 70.9% and Arm A 80.8%; predominantly in elbows, knees, and ankles). Analysis of treated bleeds by cause of bleed indicates that over two-thirds of the treated bleeds in Arm B (68.6%) and almost half of the treated bleeds in Arm A (46.2%) were spontaneous, with the remaining bleeds resulting from trauma (Arm A 28 [53.8%] vs Arm B 69 [31.4%]). The summary of all bleeds (without 72-hour rule) by cause of bleed during the randomised period indicates that 69.0% of all bleeds in Arm B and 38.2% of all bleeds in Arm A were spontaneous. Only a small number of bleeds in both treatment arms was due to a surgery or procedure (Arm B 5 bleeds [1.8%]; Arm A 7 bleeds [6.4%])

Summary of main study

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

Table 20: Summary of Efficacy for trial BH29884

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		
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 intra-patient comparison with data from NIS29768); Arm D including patients unable to be enrolled in Arms A, B or C		
	Duration of main phase:		First patient entered: 18 Nov 2015 Last Patient Randomised: 11 May 2016
Hypothesis	Formal hypothesis testing for superiority only for the randomized comparison of Arm A versus Arm B, and for the intra-patient comparisons in Arms A and C		
Treatments groups	Arm A		Emcizumab prophylaxis for 24 weeks in 25 patients (4 discontinuations/ withdrawals)
	Arm B		No prophylaxis (episodic bypassing agents) for 24 weeks in 18 patients
	Arm C		Emicizumab prophylaxis – ongoing in 49 patients
Endpoints and definitions	Primary endpoint	ABR/ treated bleeds	number of bleeds over time (excl. bleeds due to surgery/ procedures)
	Secondary endpoints	- number of all bleeds (treated and not treated) - number of joint bleeds - number of target joint bleeds - HRQoL; Haem-A-QoL (aged ≥18) or Haemo-QoL-Short Form (ages 12-17) - health status (EQ-5D-5L) - number of bleeds over time compared with the patient's historical bleed rate (both for treated bleeds and all bleeds)	
	Other secondary endpoint	- number of spontaneous bleeds over time	Added in amendment 2 after the database lock
Database lock	25th of October 2016		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat at 24 weeks		
Descriptive statistics and estimate variability	Treatment group	Arm A Emicizumab prophylaxis	Arm B No prophylaxis
	Number of subject	35	18
	ABR Treated bleeds (model based)	2.9	23.3
	95% CI	1.69;5.02	12.33;43.89

	ABR All bleeds (model based)	5.5	28.3
	95% CI	3.58;8.60	16.79;47.76
	ABR Treated Joint bleeds (model based) 95% CI	0.8 0.26;2.20	6.7 1.99;22.42
	ABR Treated Target Joint bleeds (model based) 95% CI ABR treated spontaneous bleeds (model based) 95% CI	0.1 0.03;0.58 1.3 0.73; 2.19	3.0 0.96;9.13 16.8 9.94; 28.3
	Treatment group	All patients from Arm C on Bypassing prophylaxis NIS BH29768	Arm C Emicizumab prophylaxis BH29884
	Number of subjects	24	24
	Intra-patient comparison – treated bleeds (model based)	15.7	3.3
	95% CI	11.08;22.29	1.33;8.08
	ABR All bleeds (model based)	24.3	5.5
	95% CI	18.11;32.67	2.98;10.26

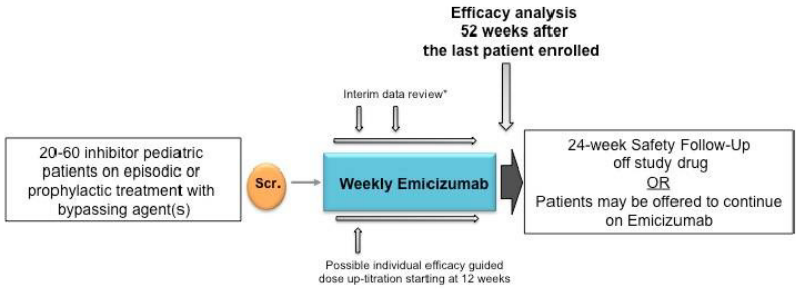
Effect estimate per comparison	Primary endpoint	Comparison groups	ABR Treated Bleeds
		ABR ratio	0.13
		95% CI for the ratio between bleeding rates	0.057;0.277
		P-value (stratified and non-stratified Wald test)	<0.0001
	Secondary endpoints	Comparison groups	ABR All bleeds
		ABR ratio	0.20
		95% CI for the ratio between bleeding rates	0.102;0.375
		P-value (stratified and non-stratified Wald test)	<0.0001
		Comparison groups	Treated Joint Bleeds
		ABR ratio	0.11

		95% CI for the ratio between bleeding rates	0.025;0.520
		P-value (stratified and non-stratified Wald test)	0.005; 0.0052
		Comparison groups	Treated Target Joint Bleeds
		ABR ratio	0.05
		95% CI for the ratio between bleeding rates	0.009;0.227
		P-value (stratified and non-stratified Wald test)	0.0002
		Comparison groups	Treated Spontaneous bleeds
		ABR ratio	0.08
		95% CI for the ratio between bleeding rates	0.037;0.154
		P-value (stratified and non-stratified Wald test)	<0.0001
	Intra-patient comparison Arm C	Comparison groups	Treated Bleeds
		ABR ratio	0.21
		95% CI for the ratio between bleeding rates	0.089;0.486
		P-value (non-stratified Wald test)	0.0003
		Comparison groups	All Bleeds
		ABR ratio	0.23
		95% CI for the ratio between bleeding rates	0.119;32.67
		P-value (non-stratified Wald test)	<0.0001
	All secondary endpoints for the Haem A-QoL and EQ-5D-5L were met.		

Study BH29992 paediatric phase III study

This is an ongoing single-arm, multicentre, open-label, Phase III clinical study enrolling children with haemophilia A with FVIII inhibitors, recruiting patients younger than 12 years of age or between 12 -17 years who weigh <40 kg at the time of informed consent.

Figure 17: Study scheme BH29992



JMC = Joint Monitoring Committee; Scr = screening.

* Two interim data reviews were planned for this study. The first interim data review was planned to assess the starting maintenance dose after the first 3 – 5 patients (≥ 2 to < 12 years of age) had been dosed for a minimum of 12 weeks. A JMC planned to review all cumulative data (e.g., safety, efficacy, and PK) to provide recommendations on increasing the starting maintenance dose. A second interim data review was planned to occur when at least 10 patients (≥ 2 to < 12 years of age) had been dosed for a minimum of 12 weeks, at which time all available cumulative data (e.g., safety, efficacy, and pharmacokinetics) would be evaluated to provide recommendations for the enrollment of children < 2 years of age, as well as on the maintenance dose.

Study participant (BH29992 study)

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.

Treatment (BH29992 study)

Treatment is similar to study BH29884, with emicizumab administered at 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).

Following an interim data review of all available data up to the clinical cut-off date of 28 October 2016 (e.g., safety, efficacy, PK and PD), the independent data monitoring committee recommended that the selected maintenance dose of 1.5 mg/kg/week should be continued in all enrolled and new patients.

Similar to study BH29884, individual patients were able to have their dose up-titrated if they experienced suboptimal bleeding control on emicizumab during the 52-week treatment period. This is on the basis of three predefined maintenance doses (1.5, 2.25, and 3.0 mg/kg/week).

Objectives (BH29992 study)

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.

Assessments were similar to study BH29884.

Outcomes/endpoints

The following analyses were conducted:

- Treated bleeds – if the bleed was treated with coagulation factors.
- All bleeds – irrespective of treatment with coagulation factors.

- Treated spontaneous bleeds – if the bleed was treated with coagulation factors.
- Treated joint bleeds – if the bleed was treated with coagulation factors.
- Treated target joint bleeds – if the bleed was treated with coagulation factors.

Efficacy and safety endpoints are the same as the study BH 29884.

Table 21: ***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 (BH29992 study)

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

The primary analysis of bleed rate is to be performed 52 weeks after the last patient in the primary cohort has been enrolled or withdrawn prematurely, whichever occurs first. For the interim analysis presented in this CSR the number of bleeds, types, and locations of bleeds are summarised for all patients and listed for each patient individually.

Several exploratory analyses were conducted to characterise the type, location, frequency, and pattern of bleeds.

Negative Binomial Regression Model

At the time of the primary analysis, the number of bleeds over time (bleed rate) will be calculated using a negative binomial (NB) regression model, which accounts for different follow-up times, with time that each patient stayed in the study (efficacy period) included as an offset in the model.

Calculated Annualised Bleeding Rate

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

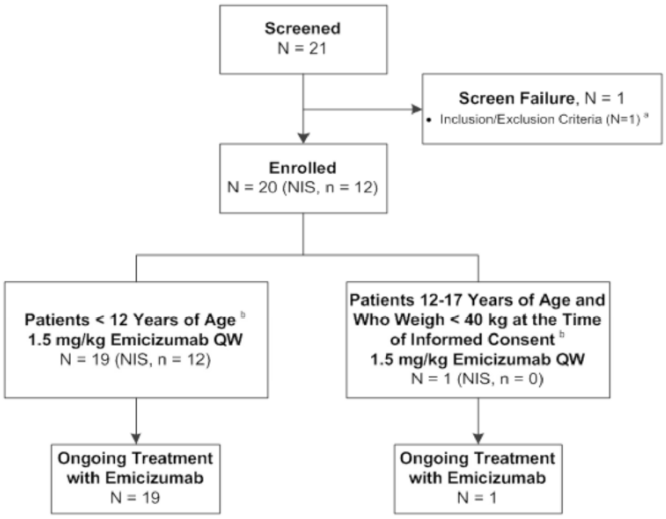
ABR = (Number of bleeds/number of days during the efficacy period) x 365.25. For this interim CSR, the population ABR may not be robust as it might be driven by only a few extreme observations because of the short follow-up time. Therefore, the bleed rate was characterised on an individual patient basis. In addition, with such a short follow up period, the NB model might not converge or the results might be unreliable. For all patients, the number of bleeds was described with use of descriptive statistics. The individual ABR was calculated for patients who were on the study for at least 12 weeks at the same dose (including the loading doses) using the above formula.

Intra-Patient Comparison

In order to increase the robustness of the intra-patient comparison, only patients who participated in NIS BH29768 were included. This is because it is only possible to apply the detailed definition if the data are collected with the same granularity for both time periods. For the primary analysis a NB regression model will be used. This model estimates the rate ratio, lambda t/lambda c., which quantifies the risk of bleeding associated with prophylactic emicizumab (lambda t) in comparison to the historical bleeding events (lambda c). For this interim CSR, only individual patient's ABRs are provided, in a descriptive manner, including the reduction in ABR comparing before (i.e. during NIS BH29768) and after entering into Study BH29992. The intra-patient comparison was performed on patients who were enrolled at least 12 weeks before the cut-off date of the interim CSR for Study BH29992

Results

Participant flow *study (BH29992 study)*



N = number of patients from Study BH29992; n = number of patients from NIS; NIS = non-interventional study; QW = once weekly

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

[b] Patients exposed to emicizumab started with loading dose 3 mg/kg/week for 4 weeks

The interim analysis of efficacy and safety data, as of 28 October 2016, present a total of 20 patients, with 19 less than 12 years of age and one ≥12 years but with a weight <40 kg. A total of 11 (55%) patients had completed at least 12 weeks of treatment. No patient withdrew from treatment yet.

Recruitment

This is an ongoing Phase III clinical study conducted at 12 sites in 6 countries. First patient entered 22nd of July 2016.

The study is conducted at 12 sites in 6 countries.

The study is also sponsored by the applicant (F. Hoffmann-La Roche Ltd) and Chugai Pharmaceutical Co. Ltd.

Study period

First patient entered study: 22nd of July 2016

Final clinical data cut-off for all data considered for this application: 08 May 2017 for all patients, with an additional unplanned interim analysis for patients ≤2 years of age of 29th of September 2017.

Conduct of the study

There were two protocol amendments, with Amendment 1 approved on 12th of July 16 and Amendment 2 in December 2016, which are not considered to impact the efficacy analyses. Amendment 1 contained changes to up-titration criteria, additional efficacy objectives (treated, non-treated bleeds) and to increase the maximum number of patients from 40 to 60 based on the rapid enrolment. It was also decided to leave enrolment open for patients <2 years if no patients

are included in the primary cohort, to enrol up to 5 such patients. Amendment 2 was in line with study BH29884, addressing the safety concerns of concomitant use of bypassing agents.

Protocol deviations

A total of 11 major protocol deviations occurred in 7 of 20 patients in the All Patients population (6 patients [30.0%] with 9 procedural deviations, and 2 patients [10.0%] with 2 deviations relating to medication, which are not considered to have any impact. However, there appear to be some clusters around certain sites; e.g. site 291660.

BMQ compliance was high (97.5%). Only 16 of the 19 (84.2%) expected Adapted Inhib-QoL questionnaires were completed at baseline, with all (n=10; 100%) expected questionnaires completed at week 13. Haemo-QoL-SF was completed only by patients aged ≥8 years at study entry. At baseline, 7 of the 10 (70.0%) expected questionnaires were completed, with all (n = 6; 100%) of the expected questionnaires were completed at week 13.

Table 22: Major protocol Deviations (all patients) –Study BH29992 as of 28 October 2016

Category Protocol Deviation Term	1.5mg/kg emicizumab QW (N=20)
Total number of patients with at least one major protocol deviation	7 (35.0%)
Total number of major protocol deviations	11
Procedural	
Total patients	6 (30.0%)
Total protocol deviations	9
Any HRQoL questionnaires not completed	5 (25.0%)
Missing hematology or blood chemistry per SoA	2 (10.0%)
>2 consecutive PK missed in 1st 12wks of given emi	1 (5.0%)
Medication	
Total patients	2 (10.0%)
Total protocol deviations	2
Incorrect medication or emi dose/sched. deviation	1 (5.0%)
Received prohibited therapy	1 (5.0%)

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

Baseline characteristics of patients in study BH29992 are described in the tables below.

Four patients (20.0%) were age 2 to < 6 years. Of these, 3 patients were 3 years of age.

All but one patient (n = 19, 95.0%) had severe haemophilia. The mean time from FVIII inhibitor diagnosis was 78.06 months, with the majority (n = 12, 60.0%) of patients diagnosed = 72 months prior to study entry. Patients with a documented history of high inhibitor titre were enrolled in this study, however the titre was unknown for 2 patients. For the knowns, no patients had Factor VIII inhibitor < 5 BU. Overall, 17 patients (85.0%) had previously been treated with ITI. The majority (n = 18, 90.0%) of patients were treated with a prophylactic regimen prior to enrolment, with 2 patients (10.0%) previously on episodic treatment. The median number of bleeds in the last 24 weeks prior to study entry was 6.0 bleeds (range: 0 - 35). Five patients (25.0%) had at least one target joint, with a total of 8 target joints.

Table 23: Baseline characteristics - study BH29992 as of 28 October 2016

	1.5mg/kg emicizumab QW (N=20)
Sex	
n	20
Male	20 (100.0%)
Age (years)	
n	20
Mean	7.8
SD	2.9
SEM	1
Median	8.5
Min - Max	3 - 12
Age group (years)	
n	20
0 - <2	0
2 - <6	4 (20.0%)
6 - <12	15 (75.0%)
>=12	1 (5.0%)
Race	
n	20
American Indian or Alaska Native	0
Asian	5 (25.0%)
Black or African American	1 (5.0%)
Multiple	1 (5.0%)
Native Hawaiian or other Pacific Islander	0
White	10 (50.0%)
Unknown	3 (15.0%)
Ethnicity	
n	20
Hispanic or Latino	2 (10.0%)
Not Hispanic or Latino	18 (90.0%)
Height (cm)	
n	18
Mean	129.47
SD	20.00
SEM	4.7
Median	128.00
Min - Max	97.3 - 164.0

Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks
n represents the number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).

Numbers analysed

Table 24: Analysis population - study BH29992

Analysis Populations	1.5mg/kg emicizumab QW (N=20)
Enrolled Patients (Assigned Treatment)	20
All Patients	20
Total Exclusions	0
Treated Patients	20
Total Exclusions	0
NIS Patients	12
Total Exclusions	8
Patients >=12 years and <40kg Body Weight	1
Total Exclusions	19
Individual Up-Titration Patients	0
Total Exclusions	20
ABR Patients	11
Total Exclusions	9

Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks

At the time of the interim analysis submitted with the data cut-off of May 2017, the clinical study had enrolled 60 male patients. Two patients aged < 2 years old, 17 patients aged 2 to < 6 years, 38 patients aged 6 to < 12 years and 3 patients aged ≥ 12 years, resulting in 57 patients that were < 12 years old and evaluable for efficacy.

The annualized bleed rate and percent of patients with zero bleeds were calculated for 23 patients <12 years old who received weekly Hemlibra prophylaxis for at least 12 weeks (see Table below). The median observation time for these patients was 38.1 weeks (range: 12.7 to 41.6 weeks).

Table 27: Annualized Bleed Rate Overview (Treated Patients Aged<12 Years, ABR Population)

	1.5mg/kg emicizumab QW (N=23)
Number of Patients	23
Treated Bleed	
ABR, model based (95% CI)	0.2 [0.06; 0.62]
Mean ABR, Calculated (95% CI)	0.2 [0.00; 4.04]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-1.37]
All Bleed	
ABR, model based (95% CI)	2.9 [1.75; 4.94]
Mean ABR, Calculated (95% CI)	3.2 [0.72; 9.12]
Median ABR, Calculated (IQR)	1.5 [0.00; 4.53]
Min-Max, Calculated ABR	[0.00-16.42]
Treated Spontaneous Bleed	
ABR, model based (95% CI)	0.1 [0.01; 0.47]
Mean ABR, Calculated (95% CI)	0.1 [0.00; 3.81]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-1.30]
Treated Joint Bleed	
ABR, model based (95% CI)	0.1 [0.01; 0.47]
Mean ABR, Calculated (95% CI)	0.1 [0.00; 3.81]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-1.37]
Treated Target Joint Bleed	
ABR, model based (95% CI)	Not Estimable
Mean ABR, Calculated (95% CI)	0.0 [NA ; 3.69]
Median ABR, Calculated (IQR)	0.0 [0.00; 0.00]
Min-Max, Calculated ABR	[0.00-0.00]

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.

Program: /opt/BIOSTAT/prod/cdt30082/t_ueft_ovabr_bm.sas
Output: /opt/BIOSTAT/prod/cdt30082/i29992i7reports/t_ueft_ovabr_bm_mde_ABR_TRT1.out
05JUL2017 15:48 Page 1 of 1

Outcomes and estimation- Study BH29992

Bleed related endpoint

The interim analysis efficacy results for Study BH29992 are summarised below. In total 20 of 23 (87%) patients had zero treated bleeds and 8 of 23 (34.8%) did not have any bleeds while receiving Hemlibra prophylaxis.

Table 25: Categorised Number of Bleeds and ABR (treated bleeds, Treated Patients Aged <12 Years) -Study BH29992

Endpoint	ABR (95% CI) N = 23	Median ABR (IQR) N = 23	% Zero Bleeds (95% CI) N = 23
Treated bleeds	0.2 (0.06; 0.62)	0 (0; 0)	87 (66.4; 97.2)
All bleeds	2.9 (1.75; 4.94)	1.5 (0; 4.53)	34.8 (16.4; 57.3)
Treated spontaneous bleeds	0.1 (0.01; 0.47)	0 (0; 0)	95.7 (78.1; 99.9)
Treated joint bleeds	0.1 (0.01; 0.47)	0 (0; 0)	95.7 (78.1; 99.9)
Treated target joint bleeds	Not Estimable*	0 (0; 0)	100 (85.2; 100)

*No treated target joint bleeds reported
ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

Intra-patient comparison

Table 26: Study BH29992: Annualised Bleed Rate for Hemlibra prophylaxis intra-patient comparison in paediatric patients < 12 years of age (interim analysis) – treated bleeds (NIS patients)

Endpoint	Previous bypassing agent treatment* (N = 13)	Hemlibra prophylaxis (N = 13)
Treated bleeds		
ABR (95% CI)	17.2 (12.38; 23.76)	0.2 (0.06; 0.76)
% reduction RR (95% CI)	99% 0.01 (0.004; 0.044)	
% patients with zero bleeds (95% CI)	7.7 (0.2; 36)	84.6 (54.6; 98.1)
Median ABR (IQR)	14.3 (11.02; 24.35)	0 (0; 0)

ABR = annualized bleed rate; CI = confidence interval; RR = rate ratio

* Previous prophylactic treatment for 12 patients; previous episodic (on-demand) treatment for 1 subject

Treated bleeds

At the time of the clinical cut-off date of September 2017 for Study BH29992, none of the 8 patients had experienced any type of treated bleed, appreciating that one patient had an ABR of 0 in the NIS and in Study BH29992.

Treated spontaneous bleeds

At the clinical cut-off date of September 2017 for Study BH29992, no patients had experienced a treated spontaneous bleed, appreciating that one patient had an ABR of 0 in the NIS and in Study BH29992.

Treated joint bleeds

At the clinical cut-off date of September 2017 for Study BH29992, no patients had experienced a treated joint bleed, appreciating that two patients had an ABR of 0 in the NIS and in Study BH29992.

Health-Related Quality of Life Results

At the clinical cut-off date of 7 of 19 caregivers had completed Adapted Inhib-QoL questionnaires at both baseline and Week 13.

1. Proxy report of child's HRQoL scales: Treatment (mean change from baseline = - 33.93; IQR = −37.50 – −12.50); Physical Health (mean change from baseline = - 37.76; IQR - −53.57 – −17.86).

2. Caregiver scales: Family Life (mean change from baseline = - 33.93; IQR = −50.00 – −12.50); Deal with Inhibitor (mean change from baseline = - 27.38; IQR = −41.67 – −12.50); Perceive Treatment (mean change from baseline = - 22.45; IQR = −39.29 – 3.57); Contact with Others (mean change from baseline = - 21.43; IQR = −37.50 – 0.00); Siblings (mean change from baseline = - 15.00; IQR = −25.00 – 0.00); Perceive Condition (mean change from baseline = - 10.71; IQR = −31.25 – 0.00).

3. Total score: mean change from baseline = - 27.04; IQR = −39.39 – −9.38.

At clinical cut-off 3 of 10 patients aged ≥ 8 years had completed Haemo-QoL-SF questionnaires at baseline and Week 13. For the 3 patients with available results at baseline and Week 13, improvements (change from baseline) were observed across several of the domains of the Haemo-QoL-SF.

Supportive studies

- **Non-interventional study (NIS) BH29768**

This non-interventional study (NIS) prospectively collected bleed, treatment patterns, health-related quality of life (HRQoL), health status, and safety information in patients with haemophilia A in routine clinical practice. 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.

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.

It included three cohorts (Cohort A – patients age ≥ 12 years; B – age 0-11 years both with inhibitors; C -patients age ≥12 years without inhibitors). Inclusion/ exclusion criteria were like the ones set out in the pivotal studies, however patients age ≥2 to < 12 years needed to have a higher previous reported bleeding history (minimum of 4 bleeds in last 6 months) compared to the pivotal paediatric study BH29992. Relevant results are presented as part of the intra-patient comparisons in the results section for the pivotal studies above.

- **Extension trial ACE002JP**

This was an extension of the Phase I trial ACE001JP as outlined above, conducted in 6 sites in Japan, including patients with and without inhibitors. Primary objective was to investigate the safety and efficacy of emicizumab on bleeding during long-term treatment. The study is still ongoing at the data cut-off date of 30th of September 2016.

Patients were assigned to one of three emicizumab dosing groups: 0.3, 1 or 3 mg/kg/week. Study ACE002JP calculated individual patient ABRs but did not estimate population rates based on the NB regression model. ABRs were calculated by annualising the number of bleeding episodes that required treatment with coagulation factor products (‘treated bleed’).

Results

Study results presented herein are for all 18 patients who participated in Part C of Study ACE001JP. A total of 16 patients were enrolled in the extension Study ACE002JP and remained on treatment at the interim analysis.

All patients were male with a median age at baseline of 32, 30, and 33 years in the 0.3, 1, and 3 mg/kg/week groups, respectively (3 patients were adolescents 12 – 17 years of age, and 15 patients were ≥18 and < 60 years of age).

At study entry, 11 patients had inhibitors and 7 patients did not have inhibitors. All but 3 patients had a prior history of inhibitors and 8 patients overall had a prior history of ITI treatment. Ten patients were on prophylactic treatment prior to study entry: 7 patients without inhibitors were on FVIII prophylaxis, and 3 patients with FVIII inhibitors were on bypassing agent prophylaxis. The median numbers of bleeding episodes in the 6 months prior to first emicizumab administration

varied by dose group: 16.0 (range: 4 - 38), 9.0 (range: 5 - 19), and 7.5 (range: 0 - 16) in the 0.3, 1, and 3 mg/kg/week groups, respectively.

Overall, 4 patients had had their doses up-titrated in Study ACE002JP, and 3, 5, and 8 patients were receiving maintenance doses of 0.3, 1, and 3 mg/kg/week, respectively at the time of the interim analysis.

The median efficacy period was 134.1 weeks (range: 12.3 - 177.3 weeks) for the 0.3 mg/kg/week group (n=6), 81.0 weeks (range 4.1 - 156.3 weeks) for the 1 mg/kg/week group (n=9), and 121.1 weeks (range: 12.1 - 130.6 weeks) for the 3 mg/kg/week group (n=9). Note that these values also account for those patients who up-titrated to a higher dose.

The ABR of all patients decreased from the pre-dose period (6 months before study enrolment) following emicizumab administration regardless of the presence of inhibitors and/or prior use of prophylactic treatment. One patient had an ABR of 0 in the pre-dose period which did not change during treatment with emicizumab. Eight patients (1, 3, and 4 patients in the 0.3, 1, and 3 mg/kg/week groups, respectively) experienced zero bleeding episodes on emicizumab prophylaxis. Of these, 6 patients had inhibitors (including 4 patients treated with prior prophylactic bypassing agents), and 2 patients did not have inhibitors. Three patients originally in the 0.3 mg/kg/week group had their dose up-titrated to 1 mg/kg/week, of which 2 patients underwent further dose increase to 3 mg/kg/week, and 1 patient originally in the 1 mg/kg/week group also had his dose up-titrated to 3 mg/kg/week. ABR for these 4 patients decreased with each up-titration step.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Two pivotal studies have been submitted. One randomised, open label, Phase III trial in patients aged 12 years or older with haemophilia A who have inhibitors against FVIII (BH29884) and one ongoing, single-arm, open-label Phase III trial in children < 12 years (study BH29992). Emicizumab was administered s.c. at in both studies a loading dose of 3 mg/kg/week for 4 weeks, followed by 1.5 mg/kg/week thereafter. Dose-up titration was an option in both trials after at least 24 weeks.

Both trials were designed and monitored in accordance with ICH-GCP and carried out in keeping with local legal requirements and meeting the ethical requirements of Directive 2001/20/EC.

Both studies had two protocol amendments of similar content, not expected to have any impact on the efficacy results. The total number of major protocol deviations in both studies, are not considered to have major impact on the primary analyses. Compliance of providing response to the QoL questionnaires was high with no apparent drop over time.

Study BH29884 enables comparison of current standard of care (episodic use of bypassing agents when needed – Arm B), as the control arm, with prophylactic use of emicizumab (Arm A); but also, intra-patient comparison of emicizumab prophylaxis (Arm C) compared to historical prophylactic use of bypassing agents utilising data from the non-interventional study NIS29768 of the same patients. Open label comparison of prophylactic use against on demand treatment is not ideal and raises concerns, particularly in view of observation bias regarding the secondary QoL endpoints. The consistency in maintaining the improvements in QoL however are reassuring in that any potential for bias can be considered overcome by the observed treatment effect. The chosen endpoints of bleeding rates, with the primary endpoint of reduction of treated bleeds (excluding bleeds due to procedures/ surgery) are endorsed, being patient relevant measures. The primary

endpoint was measured at 24 weeks, which is considered adequate in context of results from the Phase I extension study, evidence suggesting an association between longer duration of prophylactic therapy with maintenance of ARB reduction, as well as evidence of no seasonal variation in bleeding. The QoL questionnaires used are validated, including cross cultural validity ensured. In case of the possibility of a patient/caregiver having missed the completion of a full questionnaire, or in case of a technical error in the device, the questionnaires were imputed and considered missing at random.

Inclusion/ exclusion criteria are considered acceptable. The inclusion of adolescents (≥12 years) is endorsed based on disease similarity. Overall, patients included represent a population of high unmet need; haemophilia A patients with a documented history of high-titre inhibitors and high numbers of bleeds experienced while on episodic, or prophylactic bypassing treatment respectively. The latter highlights the importance to evaluate the potential benefit of emicizumab therapy on an individual basis, taking into account all clinically relevant disease history. Ongoing, or plan to receive ITI during the study was excluded, which is supported. Nonetheless this raises the question to where appropriately position emicizumab in context of the existing treatment guideline for patients with inhibitors, recommending immune tolerance as first line choice.

The statistical methodology applied is considered adequate.

Study BH29992 with its single arm design is endorsed. Inclusion/ exclusion criteria were similar, apart from less stringent requirements regarding previous bleeding history in patients aged ≥2 to < 12 years, understood as a measure to increase feasibility. The fact that patients participating in study BH29992 reported higher median ABRs in the run-up prior to enrolment than the minimum inclusion criteria for the NIS study, suggests that these patients were not considerably better controlled compared with those who had enrolled on the NIS study. The differences in inclusion criteria are not considered to have any clinically meaningful impact on the results, nor any impact on the ability to extrapolate efficacy based on consistent PK.

There is inconsistency regarding the exclusion criteria of ITI between the two pivotal trials, with patients allowed to be recruited in case of awaiting ITI initiation and after a 72 hrs wash-out after failure of ITI in the paediatric trial (BH29992), in contrast to these patients excluded in study BH29884. The applicant acknowledges that no formal study evaluating the safety and efficacy of emicizumab in relation to ITI was performed, which has been added to section 4.2 of the SmPC.

Patients scheduled to undergo major elective surgery were excluded in both trials. Whilst the restriction is understood from a risk mitigation perspective, emicizumab is intended for long term prophylactic administration. This is hence important data missing, particularly regarding efficacy and safety during major surgeries in emergency situations. This has consequently been included in the RMP as missing information. Adequate wording has been added to section 4.2 of the SmPC to indicate that safety and efficacy has not formally been evaluated in the surgical setting, with reference made to the dosing guidance on the use of bypassing agents in section 4.4 of the SmPC.

The long-term extension study ACE002JP, conducted in Japan, enrolled patients with and without inhibitors using a different maintenance dosing regimen (0.3, 1, and 3 mg/kg/week). It calculated individual patient ABRs but did not estimate population rates based on the NB regression model. Nonetheless it provides long term efficacy data.

The non-interventional study NIS BH29768, set up to collect bleed, treatment patterns, health-related quality of life, health status, and safety information in patients with haemophilia A in routine clinical practice used inclusion/ exclusion criteria like the ones set out in the pivotal trials. It included three cohorts. It was set up to allow intra-patient comparison, with patients enrolled into the NIS given priority for enrolment into the pivotal trials.

Efficacy data and additional analyses

The data cut-off for study BH29884 (25th of Oct 2016) was triggered by the primary analysis (randomised comparison), with the interim analysis for BH29992 conducted around the same time to prepare the dossier for MAA (data cut-off 28th of Oct 2016). This means that follow-up data on patients beyond 6 months from study BH29884 are limited (74 patients with observation time ≥ 6 months; 1 patient ≥ 1 year). For the paediatric study BH29992, only interim results on ABR are presented for 10 patients who completed 12 weeks of treatment. Long term efficacy is based on a total of 16 Japanese patients on study ACE002JP exposed for > 1 year.

Study BH29884 screened 114 patients of which 109 were eligible for enrollment (total of 32 [29.4%] under age 18); 35 enrolled into Arm A and 18 into Arm B (with 4, respectively 2 patients under the age of 18 years). A total of 4 patients withdrew from the trial, one prior dosing due to personal reasons and 3 from treatment (2 due to AEs; 1 due to physician's decision based on mental illness), all in the prophylaxis arm. The small number of withdrawals due to AEs (1.8%) although both related to the safety concern around concomitant use of bypassing agents (see Safety section below), is reassuring as regards to any potential tolerability concerns. Following the initial data cut-off, additional 4 patients were included in Arm D and 4 switching to Arm Bemi. The additional data from these patients do not change the overall effect size observed and are therefore not discussed any further.

Overall, baseline demographics, disease characteristics and past medical and medication history are as expected, representing the target population; patients with long standing history of mainly severe haemophilia A and inhibitors, with half of them having had previous ITI; a majority with target joints and more than 9 bleeds in the past 24 weeks. Patients on Arm C have been on prophylactic bypassing treatment. Comparing use of bypassing agents (aPCC, rFVIIa) during prophylactic treatment with emicizumab with the non-haemophilia medication history, it appears that there is a trend for increasing use of rFVIIa for treatment of bleeds while on emicizumab prophylaxis, most apparent for those on previous aPCC prophylaxis, is likely due to the fact that patients were no longer using aPCC for prophylaxis and on-demand treatment with rFVIIa is far more convenient with a shorter preparation and infusion time.

Using the NB regression model to analyse the bleed rate for treated bleeds for the randomised population, there was a statistically significant 87% reduction in bleed rate with emicizumab prophylaxis compared with no prophylaxis (Arm B ABR = 23.3; Arm A = 2.9; ABR ratio 0.13 [95% CI: 0.057; 0.277]; p < 0.0001 for stratified Wald test. A total of 22 of 35 patients (62.9%) in Arm A had no treated bleeds at all. The robustness was confirmed through additional sensitivity analyses. Subgroup analyses confirmed the primary endpoint, with a wide CI noted for those patients without the presence of a target joints. Although likely to contribute, this observation is not merely due to the small sample size. Calculating the individual ABRs of patients with no target joints at baseline it can be considered that the wide confidence interval associated with the risk ratio for treated bleeds are not reflective of a more heterogeneous patient population, but rather as a result of individual outliers in each arm.

The results of the secondary bleed endpoints are consistent with the primary endpoint, with all bleeds, treated joint bleeds and target joint bleeds, all showing similar rates of reduction of around 80-90%. With the caveated of no direct comparison of different prophylactic treatments, the consistency of results is considered reassuring. The intra-patient comparison of bleed rates in Arm A and C showed a statistically significant reduction of ABR (Arm A NB analysis for patients with at least 12 weeks of treatment (Arm A NIS ABR = 21.9; Arm A ABR = 1.8; ABR ratio = 0.08 [95% CI: 0.033;0.209], p < 0.0001; Arm C NB analysis for patients with at least 12 weeks of treatment (Arm C NIS ABR = 17.0; Arm C ABR = 3.6; ABR ratio = 0.21 [0.090;0.488], p < 0.0003),

confirmed by sensitivity analyses. When adjusting for lack of compliance, the ABR ratio in the adjusted intra-patient analysis was similar to that from the non-adjusted analysis (ABR Ratio=0.34 for both), showing that the effect of emicizumab is consistent even after adjusting for compliance.

The quality of life measures evaluated as secondary endpoints confirm the overall benefit observed with treatment of emicizumab up to week 24. When comparing QoL responses at time of bleeds (i.e. unscheduled visits), indeed on a patient level the health status is lower at the time of patient experiencing a bleed, which would be considered expected. Yet when looking at the group level, the average score for the Emicizumab arm as higher in excess of the clinically meaningful improvement of 0.07 points on the IUS versus no prophylactic patients (i.e., emicizumab mean IUS=0.56; no prophylaxis mean IUS=0.38), which was similar on the VAS as well. The latter is reassuring in view of a clinically meaningful improvement, shown even in case of a bleed.

Most treated bleeds occurred in joints. Around 2/3 and almost half of treated bleeds in Arm B and A respectively were spontaneous. The summary of all bleeds (without 72 hrs rule) indicated a reduction in spontaneous bleeds (Arm B 69.0% vs Arm A 38.2%). Whilst the number of patients with trauma was lower in the emicizumab arm (Arm A 45.7% vs Arm B 77.8%), there were more numbers of traumatic bleeds in the emicizumab arm (Arm A 55.5% vs Arm B 29.2%), which could well be due to the open label design, with patients feeling more protected on emicizumab prophylaxis. The median time of all bleeds (without 72 hrs rule) was similar, with the mode at week 4 and 24 (~70% vs 76% for Arms A and B). Appreciating the small numbers, there is some concern around the higher numbers of treated bleeds and all bleeds following minor surgery/ procedures on the emicizumab arm (treated Arm A 53.8% vs Arm B 31.4%]; all bleeds 6.4% Arm A vs 1.8% Arm B). Again, this might well be due to the open label design, with physicians feeling the 'prophylactic' patient being better protected, which would be consistent with the results of traumatic bleeds as described above. But it could equally be a sign of investigators' apprehension to proactively and early on, intervene with the use of bypassing agents due to concerns around drug-drug interactions. Additional summary data of bleeding events following minor procedures/ surgery are however not available, mainly due to the fact that management was based on the physicians discretion, hence the lack of detailed data collection. Appreciating that the use of emicizumab in the surgical setting has not formally been evaluated, no clear conclusions are able to be drawn from the descriptive individual evidence available on this issue. Hence, the proposed inclusion in section 4.2 of the SmPC of the statement that safety and efficacy in the surgical setting has not been evaluated which reflects the lack of these data and is endorsed to adequately inform physicians.

Study BH29992 enrolled 20 patients up to the time of the initial data cut-off, aged between 3-11 years. No patient withdrew from treatment so far. One patient included age 12 years was enrolled because of weight (<40kg), but was not included in the primary efficacy population.

In the 19 patients observed the number of patients without treated bleeds, treated spontaneous bleeds or treated joint and target joint bleeds ranged between 95% and 100%. Annualised bleed rate was calculated only for patients who had been on study treatment for at least 12 weeks. Nine of ten patients (90.0%) had an ABR of 0, while 1 patient (10.0%) had an ABR of 4.1 due to the 1 treated spontaneous bleed. Appreciating disease similarity between adults/ adolescents (≥ 12 years) and children as currently included in the analysis (3- < 12years), the observed ABR for all bleeds appear similar to the model based ABR described for Arm A in study BH29884 (5.5 [95% CI (2.58; 8.6)].

During the procedure, updated data from the pivotal Study BH29992 with a clinical cut-off date of 08 May 2017 were presented by the applicant, including data from a total of 60 patients of whom 7 patients are ≤2 years of age (including 2 patients < 2 years of age), 50 patients aged > 2 and ≤12

years, and 3 patients are ≥12 years of age (weight < 40 kg). This gives an additional approximately 6 months of follow-up, with a median observation period of 9 weeks (range. 1.6 - 41.6 weeks). The ABR for treated (treated bleeds) patients aged < 12 years and on the same dose for at least 12 weeks in the 'ABR Patients population' (n=23) was shown to be 0.2 (95% CI: 0.06; 0.62). For all bleeds the ABR was 2.9 (95% CI:1.75; 4.94). For both treated spontaneous bleeds and treated joint bleeds the ABR was 0.1 (95% CI: 0.01; 0.47). For treated target joint bleeds the ABR was not estimable by the NB regression model as no treated target joint bleeds were reported. The calculated ABRs were consistent with the ABRs estimated using the NB regression model. The median ABR was 0 for all endpoints except all bleeds. Overall the results were consistent with results from the BH29884 trial.

Additional data for children ≤2 years of age have been provided with a clinical cut-off date of 29 September 2017. The efficacy and safety data include a total of 10 patients ≤2 years of age (including 5 patients <2 years of age; ranging from 14.7 months to 34.2 months) with a median observation period of 23 weeks (range: 7.4 to 28.7 weeks), with 9 patients (90%) having had an efficacy period ≥12 weeks, and 4 patients (40%) ≥ 24 weeks. No intra-patient comparison has been included as none of these patients had participated in the NIS. Overall, no bleeds were reported in 8 of 10 patients; in 2 of 10 patients, traumatic bleeds were reported (2 bleeds in each patient); all were categorised as "other" (non-joint, non-muscle), and none of these bleeds were treated. The results are again considered generally supportive of efficacy, yet to be seen in context of being interim results. The efforts to recruit 10 patients ≤ 2 years needs to be appreciated and seen in context of the rarity of the population.

The applicant's intention to including paediatric patients from birth onwards in the proposed label is based on full extrapolation for patients 0-<1 years of age and partial extrapolation for patients age ≥1-<2 years. The applicant provided literature data showing that the coagulation system matures over time, while maintaining full function, with different levels of FIX and FX reaching maturity, i.e. adult levels, during the adolescent age, yet no difference in efficacy and safety of Emicizumab could be seen between these age groups compared to adults based on the additional data submitted. Literature data on the use of FVIII replacement therapies in pre-term and term neonates, those patients with the lowest levels of FIX and FX, indicate similar efficacy compared to older children, implying the levels of FIX and FX are sufficient to mediate FVIII activity. Given current knowledge it is considered sufficiently justified that that the age-dependent variations of FIX and FX in newborns and infants should have no clinically meaningful impact on response, assuming similar exposure.

In context of the proposed dose being located at the flat part of the dose-response curve, with an overall large effect size observed, the additional modelled data on PK extrapolation have provided sufficient reassurance of similar exposure, with a potential risk of under-exposure, which is, if existing, considered unlikely to result in a clinically meaningful response differences (see Section 2.4.2. above).

Based on the additional study results, modelled data as well as relevant literature data provided by the applicant and discussed in the context of its limitations and strengths, it can be concluded that the exposure-response relationship between the source population (i.e. patients age 1 years and above) and the target population (i.e. 0-1 years of age) is assumed to be similar, with any potential exposure differences not translating into clinically relevant differences.

Overall, this allows agreeing on an extrapolation approach for all patients to be included in the label. The lack of data in this age group has been added to Section 4.2 and 4.4 of the SmPC, as well as missing information in the RMP. .

The applicant commits to continue enrolment of patients < 2 years of age until the protocol defined end for patients ≥2 years of age, expected to be in April-May 2018. This will allow additional patients in the youngest age group to be recruited, increasing the robustness of the data-set in this age group. As study BH29992 is a PIP study, full compliance will need to be shown for which completion is required. In addition to the full compliance check, it is agreed that the results from this paediatric study will then be subject to an obligatory Art. 46 procedure and therefore be assessed by CHMP. It is hence ensured that all available data will be subject to CHMP scrutiny to allow further confirmation of the extrapolation assumptions made, utilising all data available from the relevant clinical study.

2.5.4. Conclusions on the clinical efficacy

Prophylactic use of emicizumab in inhibitor patients age ≥1 years and above with and without previous ITI experience indicates clinically meaningful reduction of bleeds in the range of around 80-90% compared to standard of care of 'on-demand' use of bypassing agents. This is consistent for all bleed related endpoints, including the intra-patient comparison for those patients on previous prophylactic use of bypassing agents. This coherently translates into improvements in QoL. The inclusion of patients <1 year of age based on full extrapolation is considered acceptable.

2.6. Clinical safety

Patient exposure

As of the updated data of 21st of April 2017 (BH29884) and 08th of May 2017 (BH29992), 189 patients had received at least one dose of emicizumab, with an overall exposure of 157.8 patient-years, providing safety data from 48 additional patients with haemophilia A and inhibitors treated with emicizumab compared to the initial submitted data package. The duration of exposure to emicizumab and number of patients exposed varied between arms and studies. See Table below for summary.

Table 27: Summary of Study Drug exposure (Safety population) - studies BH29884; BH29992, ACE002JP

	BH29884					BH29992
	A:1.5mg (N=34)	B:1.5mg (N=17)	C:1.5mg (N=49)	D:1.5mg (N=11)	Total (N=111)	1.5mg (N=60)
Duration of exposure (weeks)						
n	34	17	49	11	111	60
Mean (SD)	52.30 (15.28)	27.74 (12.35)	46.85 (11.90)	22.83 (13.87)	43.21 (16.78)	16.07 (16.10)
Median	56.02	32.47	43.15	29.99	42.18	8.00
Min - Max	3.3 - 74.2	4.0 - 42.0	31.9 - 70.0	5.0 - 40.0	3.3 - 74.2	0.8 - 41.0
Total Patient Years	34.2	9.1	44.1	4.8	92.2	18.5
Duration of exposure (weeks)						
n	34	17	49	11	111	60
0 - 4	1 (2.9%)	1 (5.9%)	0	0	2 (1.8%)	21 (35.0%)
5 - 12	1 (2.9%)	3 (17.6%)	0	4 (36.4%)	8 (7.2%)	17 (28.3%)
13 - 24	1 (2.9%)	0	0	0	1 (0.9%)	2 (3.3%)
25 - 36	1 (2.9%)	10 (58.8%)	13 (26.5%)	6 (54.5%)	30 (27.0%)	6 (10.0%)
37 - 52	7 (20.6%)	3 (17.6%)	17 (34.7%)	1 (9.1%)	28 (25.2%)	14 (23.3%)
>52	23 (67.6%)	0	19 (38.8%)	0	42 (37.8%)	0
Number of doses						
n	34	17	49	11	111	60
Mean (SD)	52.8 (15.2)	28.6 (12.3)	47.2 (12.1)	23.8 (13.9)	43.7 (16.7)	17.1 (16.1)
Median	56.0	33.0	44.0	31.0	43.0	9.0
Min - Max	4 - 75	5 - 43	28 - 71	6 - 41	4 - 75	2 - 42
Total cumulative dose (mg)						
n	34	17	49	11	111	60
Mean (SD)	6726.62 (2458.92)	3845.29 (1485.60)	5309.02 (1610.48)	3004.23 (1768.10)	5290.66 (2243.66)	950.51 (1044.20)
Median	6431.25	3763.50	5088.00	3288.00	5041.50	399.00
Min - Max	838.5 - 11596.5	1026.0 - 6151.5	2395.5 - 10812.0	1036.5 - 6909.0	838.5 - 11596.5	57.9 - 4560.0

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
A dose is a day with injection of emicizumab. A dose can be given with 1 or more injections.
Includes also data after up-titration, for patients who were up-titrated.

	ACE002JP				
	0.3mg (N=6)	1.0mg (N=6)	3.0mg (N=6)	Total (N=18)	All Patients (N=189)
Duration of exposure (weeks)					
n	6	6	6	18	189
Mean (SD)	174.22 (2.18)	126.41 (60.52)	106.56 (47.00)	135.73 (50.82)	43.41 (39.17)
Median	174.06	149.63	124.75	149.63	38.00
Min - Max	172.0 - 177.2	3.0 - 155.9	10.9 - 130.3	3.0 - 177.2	0.8 - 177.2
Total Patient Years	20.1	14.6	12.3	47.0	157.8
Duration of exposure (weeks)					
n	6	6	6	18	189
0 - 4	0	1 (16.7%)	0	1 (5.6%)	24 (12.7%)
5 - 12	0	0	1 (16.7%)	1 (5.6%)	26 (13.8%)
13 - 24	0	0	0	0	3 (1.6%)
25 - 36	0	0	0	0	36 (19.0%)
37 - 52	0	0	0	0	42 (22.2%)
>52	6 (100.0%)	5 (83.3%)	5 (83.3%)	16 (88.9%)	58 (30.7%)
Number of doses					
n	6	6	6	18	189
Mean (SD)	169.5 (13.6)	126.2 (60.0)	107.3 (46.8)	134.3 (49.8)	43.9 (38.5)
Median	173.5	149.5	125.5	146.5	39.0
Min - Max	142 - 178	4 - 157	12 - 131	4 - 178	2 - 178
Total cumulative dose (mg)					
n	6	6	6	18	189
Mean (SD)	9613.05 (8672.79)	9288.43 (5136.35)	20784.32 (9811.75)	13228.60 (9404.21)	4668.83 (4789.65)
Median	6175.47	10543.75	23103.90	12055.80	3988.50
Min - Max	2193.2 - 21015.1	313.6 - 14941.9	2384.0 - 29132.6	313.6 - 29132.6	57.9 - 29132.6

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
A dose is a day with injection of emicizumab. A dose can be given with 1 or more injections.
Includes also data after up-titration, for patients who were up-titrated.

There was good compliance with the emicizumab treatment regimen across the studies, 13.2% of patients missed one emicizumab dose, and 5.3% missed more than one dose.

Adverse events

Table 28: Overview of adverse events – safety population- studies BH29884, BH29992, ACE002JP

	BH29884					BH29992	ACE002JP			
	A:1.5mg (N=34)	B:1.5mg (N=17)	C:1.5mg (N=49)	D:1.5mg (N=11)	Total (N=111)	1.5mg (N=60)	0.3mg (N=6)	1.0mg (N=6)	3.0mg (N=6)	Total (N=18)
Total number of patients with at least one AE	32 (94.1%)	10 (58.8%)	43 (87.8%)	7 (63.6%)	92 (82.9%)	40 (66.7%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	18 (100.0%)
Total number of AEs	137	43	168	16	364	201	121	63	62	246
Total number of patients with at least one										
AE with fatal outcome	0	0	1 (2.0%)	0	1 (0.9%)	0	0	0	0	0
Serious AE	7 (20.6%)	2 (11.8%)	7 (14.3%)	0	16 (14.4%)	6 (10.0%)	1 (16.7%)	3 (50.0%)	1 (16.7%)	5 (27.8%)
AE leading to withdrawal from treatment	2 (5.9%)	0	1 (2.0%)	0	3 (2.7%)	0	0	1 (16.7%)	0	1 (5.6%)
AE leading to dose modification/interruption	1 (2.9%)	0	5 (10.2%)	0	6 (5.4%)	0	0	1 (16.7%)	0	1 (5.6%)
Related AE	14 (41.2%)	3 (17.6%)	13 (26.5%)	3 (27.3%)	33 (29.7%)	10 (16.7%)	2 (33.3%)	2 (33.3%)	4 (66.7%)	8 (44.4%)
Selected AEs										
Local injection site reaction	8 (23.5%)	2 (11.8%)	6 (12.2%)	1 (9.1%)	17 (15.3%)	10 (16.7%)	1 (16.7%)	3 (50.0%)	4 (66.7%)	8 (44.4%)
Systemic hypersensitivity/ anaphylactic/anaphylactoid reaction	1 (2.9%)	0	0	0	1 (0.9%)	0	0	0	0	0
Thrombotic microangiopathy	1 (2.9%)	0	2 (4.1%)	0	3 (2.7%)	0	0	0	0	0
Thromboembolic event	1 (2.9%)	1 (5.9%)	1 (2.0%)	0	3 (2.7%)	0	0	0	0	0

Investigator text for AEs encoded using MedDRA version 20.0. Percentages are based on N in the column headings.
Multiple occurences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurences 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.
For studies BH29884 and BH29992, Thrombotic microangiopathy are identified by a tick box on the study eCRF and by a thromboembolic events SMQ search. For ACE002JP, they are identified only from the SMQ search.

	All Patients (N=189)
Total number of patients with at least one AE	150 (79.4%)
Total number of AEs	811
Total number of patients with at least one	
AE with fatal outcome	1 (0.5%)
Serious AE	27 (14.3%)
AE leading to withdrawal from treatment	4 (2.1%)
AE leading to dose modification/interruption	7 (3.7%)
Related AE	51 (27.0%)
Selected AEs	
Local injection site reaction	35 (18.5%)
Systemic hypersensitivity/ anaphylactic/anaphylactoid reaction	1 (0.5%)
Thrombotic microangiopathy	3 (1.6%)
Thromboembolic event	3 (1.6%)

Investigator text for AEs encoded using MedDRA version 20.0. Percentages are based on N in the column headings.
Multiple occurences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurences 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.
For studies BH29884 and BH29992, Thrombotic microangiopathy are identified by a tick box on the study eCRF and by a thromboembolic events SMQ search. For ACE002JP, they are identified only from the SMQ search.

Table 29: Overall Safety Profile: Emicizumab Prophylaxis versus No Prophylaxis (Safety Population 1) study BH29884

	B: no prophylaxis (N=18)	A:1.5mg/kg emicizumab QW (N=34)
Total number of patients with at least one AE	9 (50.0%)	29 (85.3%)
Total number of AEs	27	85
Total number of patients with at least one		
AE with fatal outcome	0	0
Serious AE	4 (22.2%)	4 (11.8%)
AE leading to withdrawal from treatment	0	2 (5.9%)
AE leading to dose modification/interruption	0	0
Grade >=3 AE	4 (22.2%)	3 (8.8%)
Related AE	0	13 (38.2%)
Local injection site reaction	0	8 (23.5%)
Thrombotic microangiopathy	0	1 (2.9%)
Adverse events of special interest		
Elevated AST/ALT with elevated bilirubin or clinical jaundice	0	0
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	0	1 (2.9%)
Thromboembolic event	1 (5.6%)	1 (2.9%)
Suspected transmission of an infectious agent by the study drug	0	0

The numbers for systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the Sampson Criteria include all patients that experienced indicative symptoms.
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.
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 30: Summary of All Adverse Events with an Incidence at least ≥ 5% (Safety Population) studies BH29884; BH29992, ACE002JP

	BH29884					BH29992	ACE002JP				
MedDRA Preferred Term*	A:1.5mg (N=34)	B:1.5mg (N=17)	C:1.5mg (N=49)	D:1.5mg (N=11)	Total (N=111)	1.5mg (N=60)	0.3mg (N=6)	1.0mg (N=6)	3.0mg (N=6)	Total (N=18)	All Patients (N=189)
VIRAL UPPER RESPIRATORY TRACT INFECTION	6 (17.6%)	6 (35.3%)	10 (20.4%)	1 (9.1%)	23 (20.7%)	10 (16.7%)	5 (83.3%)	3 (50.0%)	1 (16.7%)	9 (50.0%)	42 (22.2%)
INJECTION SITE REACTIONS	8 (23.5%)	2 (11.8%)	6 (12.2%)	1 (9.1%)	17 (15.3%)	9 (15.0%)	1 (16.7%)	3 (50.0%)	4 (66.7%)	8 (44.4%)	34 (18.0%)
HEADACHE	4 (11.8%)	2 (11.8%)	11 (22.4%)	2 (18.2%)	19 (17.1%)	4 (6.7%)	4 (66.7%)	0	1 (16.7%)	5 (27.8%)	28 (14.8%)
UPPER RESPIRATORY TRACT INFECTION	8 (23.5%)	0	2 (4.1%)	2 (18.2%)	12 (10.8%)	7 (11.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	3 (16.7%)	22 (11.6%)
ARTHRALGIA	4 (11.8%)	2 (11.8%)	7 (14.3%)	0	13 (11.7%)	4 (6.7%)	0	1 (16.7%)	0	1 (5.6%)	18 (9.5%)
CONTUSION	2 (5.9%)	0	1 (2.0%)	0	3 (2.7%)	5 (8.3%)	4 (66.7%)	2 (33.3%)	3 (50.0%)	9 (50.0%)	17 (9.0%)
INFLUENZA	1 (2.9%)	0	6 (12.2%)	0	7 (6.3%)	4 (6.7%)	0	1 (16.7%)	1 (16.7%)	2 (11.1%)	13 (6.9%)
PYREXIA	1 (2.9%)	2 (11.8%)	4 (8.2%)	0	7 (6.3%)	5 (8.3%)	0	1 (16.7%)	0	1 (5.6%)	13 (6.9%)
DIARRHOEA	2 (5.9%)	1 (5.9%)	3 (6.1%)	0	6 (5.4%)	3 (5.0%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	3 (16.7%)	12 (6.3%)
DENTAL CARIES	2 (5.9%)	0	1 (2.0%)	0	3 (2.7%)	2 (3.3%)	3 (50.0%)	2 (33.3%)	1 (16.7%)	6 (33.3%)	11 (5.8%)
COUGH	2 (5.9%)	0	1 (2.0%)	0	3 (2.7%)	7 (11.7%)	0	0	0	0	10 (5.3%)

Investigator text for AEs encoded using MedDRA version 20.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurences of the same AE in an individual are counted only once.
*Injection site reactions are reported by high level term.
AEs with Incidence >=5% are selected on the "All Patients" column.

In total, 4 patients (2.1%) had AEs leading to discontinuation from study treatment.
The additional safety data for patients age ≤2 years of age (study BH29992) based on the data cut-off of September 2017 showed a similar picture with no AEs with fatal outcome, serious

adverse events (SAEs), Grade ≥3 AEs, adverse events of special interest (AESIs), or AEs that led to withdrawal from treatment, dose modification, or interruption, were reported.

The additional safety data for patients age ≤2 years of age (study BH29992) based on the data cut-off of September 2017 showed a similar picture (see table below), with no AEs with fatal outcome, serious adverse events (SAEs), Grade ≥3 AEs, adverse events of special interest (AESIs), or AEs that led to withdrawal from treatment, dose modification, or interruption, were reported.

Table 31: Adverse events, treated patients aged ≤ 2 years

MedDRA System Organ Class MedDRA Preferred Term	1.5mg/kg emicizumab QW (N=10)
Total number of patients with at least one AE	6 (60.0%)
Overall total number of events	16
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Total number of patients with at least one AE	3 (30.0%)
Total number of events	4
INJECTION SITE REACTION	1 (10.0%)
PYREXIA	1 (10.0%)
VACCINATION SITE ERYTHEMA	1 (10.0%)
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	2 (20.0%)
Total number of events	2
VIRAL INFECTION	1 (10.0%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (10.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	2 (20.0%)
Total number of events	5
CONTUSION	2 (20.0%)
SKIN ABRASION	1 (10.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (10.0%)
Total number of events	1
IRON DEFICIENCY ANAEMIA	1 (10.0%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one AE	1 (10.0%)
Total number of events	1
VOMITING	1 (10.0%)
METABOLISM AND NUTRITION DISORDERS	
Total number of patients with at least one AE	1 (10.0%)
Total number of events	1
IRON DEFICIENCY	1 (10.0%)
RENAL AND URINARY DISORDERS	
Total number of patients with at least one AE	1 (10.0%)
Total number of events	1
OLIGURIA	1 (10.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one AE	1 (10.0%)
Total number of events	1
RHINORRHOEA	1 (10.0%)

Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks
Investigator text for AEs encoded using MedDRA version 20.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Adverse drug reactions

Table 32: Adverse Drug Reaction related to study treatment – study BH29884

MedDRA System Organ Class MedDRA Preferred Term	A:1.5mg/kg emicizumab QW (N=34)	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=103)
Total number of patients with at least one AE	13 (38.2%)	1 (7.7%)	9 (18.4%)	0	23 (22.3%)
Overall total number of events	25	1	16	0	42
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
Total number of patients with at least one AE	8 (23.5%)	1 (7.7%)	4 (8.2%)	0	13 (12.6%)
Total number of events	16	1	10	0	27
INJECTION SITE REACTION	7 (20.6%)	1 (7.7%)	3 (6.1%)	0	11 (10.7%)
FATIGUE	2 (5.9%)	0	0	0	2 (1.9%)
GENERAL PHYSICAL HEALTH DETERIORATION	0	0	1 (2.0%)	0	1 (1.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
Total number of patients with at least one AE	4 (11.8%)	0	2 (4.1%)	0	6 (5.8%)
Total number of events	4	0	2	0	6
HAIR GROWTH ABNORMAL	3 (8.8%)	0	0	0	3 (2.9%)
PETECHIAE	0	0	1 (2.0%)	0	1 (1.0%)
SKIN LESION	0	0	1 (2.0%)	0	1 (1.0%)
SKIN NECROSIS	1 (2.9%)	0	0	0	1 (1.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS					
Total number of patients with at least one AE	1 (2.9%)	0	1 (2.0%)	0	2 (1.9%)
Total number of events	1	0	1	0	2
THROMBOTIC MICROANGIOPATHY	1 (2.9%)	0	1 (2.0%)	0	2 (1.9%)
GASTROINTESTINAL DISORDERS					
Total number of patients with at least one AE	0	0	1 (2.0%)	0	1 (1.0%)
Total number of events	0	0	2	0	2
ABDOMINAL PAIN	0	0	1 (2.0%)	0	1 (1.0%)
NAUSEA	0	0	1 (2.0%)	0	1 (1.0%)
INFECTIONS AND INFESTATIONS					
Total number of patients with at least one AE	0	0	1 (2.0%)	0	1 (1.0%)
Total number of events	0	0	1	0	1
CAVERNOUS SINUS THROMBOSIS	0	0	1 (2.0%)	0	1 (1.0%)
METABOLISM AND NUTRITION DISORDERS					
Total number of patients with at least one AE	1 (2.9%)	0	0	0	1 (1.0%)
Total number of events	2	0	0	0	2
DECREASED APPETITE	1 (2.9%)	0	0	0	1 (1.0%)
DEHYDRATION	1 (2.9%)	0	0	0	1 (1.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
Total number of patients with at least one AE	1 (2.9%)	0	0	0	1 (1.0%)
Total number of events	1	0	0	0	1
THROAT IRRITATION	1 (2.9%)	0	0	0	1 (1.0%)
VASCULAR DISORDERS					
Total number of patients with at least one AE	1 (2.9%)	0	0	0	1 (1.0%)
Total number of events	1	0	0	0	1
THROMBOPHLEBITIS SUPERFICIAL	1 (2.9%)	0	0	0	1 (1.0%)

Investigator text for AEs encoded using MedDRA v19.1. 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 events" rows, multiple occurrences of the same AE in an individual are counted separately.
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

Study BH29992

Based on the initial data cut-off date, three patients (15.0%) reported a total of 9 AEs that were related to emicizumab treatment. All of these related AEs were ISRs. None of the ISRs required treatment, and all resolved within 1-2 days without dose modification or interruption. Three patients (15%) reported 3 SAEs in total: catheter site infection, mouth haemorrhage, and

appendicitis during the treatment period. Each of the SAEs was associated with a surgery or procedure.

The additional safety data for patients age ≤2 years of age (study BH29992) based on the data cut-off of September 2017 showed a similar picture (see table below), with no AEs with fatal outcome.

Table 33: Summary of Adverse Drug Reactions in Patients treated with Emicizumab

System Organ Class ADR (preferred term, MedDRA)	Number of patients (n=189)	Percentage of patients	Frequency
General disorders and administration site conditions			
Injection site reactions	35	19%	Very common
Pyrexia	13	7%	Common
Nervous system disorders			
Headache	28	15%	Very common
Gastrointestinal disorders			
Diarrhea	12	6%	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	18	10%	Very common
Myalgia	9	5%	Common
Blood and Lymphatic system disorders			
Thrombotic microangiopathy	3	2%	Common
Infections and Infestations			
Cavernous sinus thrombosis	1	<1%	Uncommon
Skin and subcutaneous tissue disorders			
Skin necrosis	1	<1%	Uncommon
Vascular Disorders			
Thrombophlebitis superficial	1	<1%	Uncommon

MedDRA=Medical Dictionary for Regulatory Activities.

Serious adverse event / deaths / other significant events

Table 34: Summary of Serious Adverse Events, Safety Population- studies BH29884; BH29992; ACE002JP

Summary of Serious Adverse Events, Safety Population
Protocols: BH29884, BH29992, ACE002JP
Cutoff Date: BH29884 - 25OCT2016; BH29992 - 28OCT2016; ACE002JP - 30SEP2016
Snapshot Date: BH29884 - 16DEC2016; BH29992 - 14DEC2016; ACE002JP - 11NOV2016
Safety Population

	BH29884					BH29992	ACE002JP				
MedDRA System Organ Class MedDRA Preferred Term*	A:1.5mg (N=34)	B:1.5mg (N=13)	C:1.5mg (N=49)	D:1.5mg (N=7)	Total (N=103)	1.5mg (N=20)	0.3mg (N=6)	1.0mg (N=6)	3.0mg (N=6)	Total (N=18)	All Patients (N=141)
Total number of patients with at least one AE	4 (11.8%)	1 (7.7%)	4 (8.2%)	0	9 (8.7%)	3 (15.0%)	1 (16.7%)	3 (50.0%)	1 (16.7%)	5 (27.8%)	17 (12.1%)
Total number of AEs	5	1	6	0	12	3	1	3	1	5	20
INFECTIONS AND INFESTATIONS											
Total number of patients with at least one AE	0	0	2 (4.1%)	0	2 (1.9%)	2 (10.0%)	0	1 (16.7%)	0	1 (5.6%)	5 (3.5%)
Total number of AEs	0	0	2	0	2	2	0	1	0	1	5
APPENDICITIS	0	0	0	0	0	1 (5.0%)	0	1 (16.7%)	0	1 (5.6%)	2 (1.4%)
CATHETER SITE INFECTION	0	0	0	0	0	1 (5.0%)	0	0	0	0	1 (0.7%)
CAVERNOUS SINUS THROMBOSIS	0	0	1 (2.0%)	0	1 (1.0%)	0	0	0	0	0	1 (0.7%)
SEPSIS	0	0	1 (2.0%)	0	1 (1.0%)	0	0	0	0	0	1 (0.7%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS											
Total number of patients with at least one AE	2 (5.9%)	0	1 (2.0%)	0	3 (2.9%)	0	0	0	0	0	3 (2.1%)
Total number of AEs	2	0	1	0	3	0	0	0	0	0	3
THROMBOTIC MICROANGIOPATHY	1 (2.9%)	0	1 (2.0%)	0	2 (1.9%)	0	0	0	0	0	2 (1.4%)
IRON DEFICIENCY ANAEMIA	1 (2.9%)	0	0	0	1 (1.0%)	0	0	0	0	0	1 (0.7%)
GASTROINTESTINAL DISORDERS											
Total number of patients with at least one AE	0	0	1 (2.0%)	0	1 (1.0%)	1 (5.0%)	0	1 (16.7%)	0	1 (5.6%)	3 (2.1%)
Total number of AEs	0	0	1	0	1	1	0	1	0	1	3
GASTRIC ULCER HAEMORRHAGE	0	0	1 (2.0%)	0	1 (1.0%)	0	0	0	0	0	1 (0.7%)
MESENTERIC HAEMATOMA	0	0	0	0	0	0	0	1 (16.7%)	0	1 (5.6%)	1 (0.7%)
MOUTH HAEMORRHAGE	0	0	0	0	0	1 (5.0%)	0	0	0	0	1 (0.7%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS											
Total number of patients with at least one AE	0	0	0	0	0	0	1 (16.7%)	1 (16.7%)	0	2 (11.1%)	2 (1.4%)
Total number of AEs	0	0	0	0	0	0	1	1	0	2	2
HAEMOPHILIA	0	0	0	0	0	0	1 (16.7%)	1 (16.7%)	0	2 (11.1%)	2 (1.4%)

	BH29884					BH29992	ACE002JP				
MedDRA System Organ Class MedDRA Preferred Term*	A:1.5mg (N=34)	B:1.5mg (N=13)	C:1.5mg (N=49)	D:1.5mg (N=7)	Total (N=103)	1.5mg (N=20)	0.3mg (N=6)	1.0mg (N=6)	3.0mg (N=6)	Total (N=18)	All Patients (N=141)
VASCULAR DISORDERS											
Total number of patients with at least one AE	1 (2.9%)	0	0	0	1 (1.0%)	0	0	0	0	0	1 (0.7%)
Total number of AEs	1	0	0	0	1	0	0	0	0	0	1
THROMBOPHLEBITIS SUPERFICIAL	1 (2.9%)	0	0	0	1 (1.0%)	0	0	0	0	0	1 (0.7%)

Investigator text for AEs encoded using MedDRA version 19.1. Percentages are based on N in the column headings.
Multiple occurences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurences of the same AE are counted separately.
*Injection site reactions are reported by high level term.

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Updated safety information regarding SAEs based on the April 2017 data-cut off showed similar results to the ones presented as part of the initial submission. Across all studies, 27 patients (14.3%) had a total of 35 SAEs. System organ classes with the highest incidence of SAEs were infections and infestations (9 patients, 4.8%), musculoskeletal and connective tissue disorders (5 patients, 2.6%), blood and lymphatic system disorders (4 patients, 2.1%), and gastrointestinal disorders (4 patients, 2.1%). The following SAEs occurred in more than 1 patient: device-related infection (3 patients), appendicitis (2 patients), muscle haemorrhage (3 patients), thrombotic microangiopathy (3 patients), and haemophilia (2 patients).

Study BH29992

As per data cut off May 2017, six patients (10%) reported SAEs: catheter site infection (2x), mouth haemorrhage, and appendicitis, muscle haemorrhage (2x), eye pain during the treatment period. All of the SAEs resolved and were mainly associated with a surgery or procedure.

No SAEs were reported in treated patients aged ≤2 years (data cut-off September 2017).

Deaths

Although there were no deaths in any of the emicizumab clinical studies at the time of data cut-off date, one patient in Arm C in study BH29884 died due to an SAE of rectal haemorrhage after the initial data cut-off date for the primary analysis This patient also experienced thrombotic microangiopathy.

There was also one death reported in a compassionate use program.

The narratives are provided below:

1. Patient

This was a 41-year-old white male with haemophilia A and history of high-titre inhibitor. The patient was initially diagnosed with severe haemophilia A and developed a Factor VIII inhibitor in 1981. The patient underwent previous immune tolerance induction in March 2014. Prior prophylactic treatment included aPCC. At study entry, the patient had 22 bleeds in the last 24 weeks, with no target joints.

Patient's surgical history includes ileostomy placement due to perforated bowel secondary to high-dose opiate use in 2007. His baseline conditions were hepatitis C, hypertension, haemophilic arthropathy, and pain. The patient received the first of his four-weekly loading dose of emicizumab 3 mg/kg/week on 8 June 2016. From the study start to the time of the two SAEs described herein, he reported 13 bleeds but had not used bypassing agents to treat any of them. At the patient's week 33 visit on 18 January 2017 (Study Day 225), the patient's haemoglobin was 144 g/L, platelet count was 181 x 10^9/L, lactate dehydrogenase (LDH) and serum creatinine within normal range.

On 30th of January 2017 (study Day 238), the patient presented to the hospital complaining of rectal bleeding, postural dizziness, and exertional dyspnoea. Of note, the patient did not have any bleeding from the ileostomy site and declined receipt of blood and blood products throughout his entire hospital course despite experiencing an SAE of rectal haemorrhage. He received 11 doses of rFVIIa over 3 consecutive days and underwent multiple interventions (haemostatic powder application, absorbable haemostat packing, and embolisation of rectal arteries) in attempts to control the bleeding. Despite these, the patient continued to have rectal haemorrhage. On Study Day 240, the patient's bypassing agent treatment was changed to aPCC, with temporary cessation of bleeding. On Study Day 243 (05 Feb 2017; 4 days following the start of aPCC), the patient was diagnosed with thrombotic microangiopathy after being found to have microangiopathic haemolytic anaemia, thrombocytopenia, and acute renal failure. aPCC was discontinued, and the patient underwent 2 sessions of total plasma exchange with albumin as the replacement fluid. On Study Day 246, the patient had recurrent rectal haemorrhage, for which additional arterial embolisation and surgery were deemed not to be feasible. At the time of the patient's last laboratory assessment (3 days after discontinuing aPCC), the patient's platelet count and LDH were improving, and the investigator assessed the patient's thrombotic microangiopathy to be recovering/resolving. The patient continued to decline receipt of blood and blood products and was placed on comfort care before passing away the same day.

The patient's most recent trough emicizumab concentration prior to the rectal haemorrhage was 37.2 µg/mL (range while receiving maintenance dose of 1.5 mg/kg/week: 33.7-48.9 µg/mL).

2. Case narrative for patient on compassionate use program

This was a 38-year-old male patient with a past medical history of Haemophilia A, who experienced a fatal intracranial bleed and fatal disseminated methicillin-susceptible Staphylococcus Aureus

(MSSA) infection. In August 2014, he developed Factor VIII inhibitors and was reportedly having multiple bleeding episodes, some of which were life-threatening.

The patient attempted multiple alternative therapies (Porcine FVIII and aPCC), but developed allergic reactions to them. The patient also tried multiple unsuccessful immune tolerance therapies involving the use of immune suppressive agents. The patient started emicizumab in September 2015.

On 17 February 2016, the patient presented to the emergency room complaining of chest pain with worsening leg pain and swelling. His initial evaluation included a lower extremity ultrasound that did not reveal a deep vein thrombosis, a chest computed tomography (CT) scan that was consistent with a pulmonary infarct and blood cultures that grew Staphylococcus Aureus. The patient was admitted to the intensive care unit for monitoring and started on treatment with broad-spectrum antibiotics for treatment of sepsis and septic emboli. According to the treating physician, anti-coagulation was not started. Over the next several days, the patient's neurologic condition began to deteriorate. He initially complained of weakness, which progressed to altered mental status. Initial CT scans showed no evidence of intracranial pathology, but on 21 February 2016, an MRI of his brain showed that he had an intracranial haemorrhage. The patient was treated with rFVIIa when a ventriculostomy catheter was placed. Despite this, his condition continued to deteriorate, and he died on 24 February 2016.

The treating physician assessed that the cause of death was due to intracranial haemorrhage and disseminated MSSA infection. An autopsy was performed and early preliminary information from the pathologist showed evidence of extensive infection throughout the body (i.e., purulent material). The final autopsy report showed there were abscesses throughout the body involving multiple organs (lungs, heart and kidney). There was extensive involvement of the heart including the left ventricle. There was no evidence of a deep vein thrombus from the lower extremity that migrated to the pulmonary vessels, instead they were septic emboli. The treating physician and the sponsor assessed the fatal intracranial haemorrhage and fatal disseminated MSSA infection as not related to emicizumab.

Immunological events

Injection Site Reactions (ISR)

Following the data cut-off April/May 2017, the incidence of local ISRs was similar in all three age groups: 17.5% in children, 18.4% in adolescents, and 19.1% in adults. In addition, in studies BH29884 and BH29992, there were no ISRs leading to discontinuation, as part form one patient in study ACE002JP presented as part of the initial data package.

Anti-drug antibodies (ADA)

Patients (trial ACE002JP, BH29884 & BH29992)

The incidence of anti-emicizumab antibodies was low (4 patients, 2.8%). All 4 patients received treatment with emicizumab in Study ACE002JP (3 patients in the 0.3 mg/kg cohort and 1 patient in the 1.0 mg/kg cohort).

Three patients tested negative prior to administration and positive after treatment start (treatment-induced response), while 1 patient tested positive prior to administration and had post-baseline samples with a titre at least 4- fold greater compared with the baseline sample (treatment-boosted response). In one of the four patients, the ADA detected at two occasions was IgE based, with ISR observed. The other patients no IgE AB were detected.

No patients had neutralising anti-emicizumab antibodies, and there was no clinical significance associated with these anti-emicizumab antibodies.

No anti-emicizumab antibodies were detected in Studies BH29884 or BH29992. Two patients however had pharmacokinetic profiles potentially indicative of the generation of anti-emicizumab antibodies. Patient #1002 had emicizumab plasma concentrations that consistently declined between week 13 and 33 with decreasing PD markers over time (thrombin generation and chromogenic FVIII activity). However, no bleeds were experienced while participating in this study. The second patient (#1121) had a similar decline in emicizumab plasma concentrations over time (between week 5, to week 25). This patient qualified for up-titration to 3 mg/kg/week but his emicizumab plasma concentration after up-titration at week 33 was, however, lower than anticipated. The patient experienced one additional bleed (spontaneous left ankle hem arthrosis) 14 days after up-titration but no additional bleeds thereafter.

Healthy subjects (trial ACE001JP Part A & B, JP29574)

After a single SC dose of emicizumab, 2 of 48 Japanese and Caucasian healthy subjects in study ACE001JP tested positive for ADAs. Both subjects (1 Japanese and 1 Caucasian) received the 0.1 mg/kg emicizumab dose. One of the 2 subjects tested positive for treatment-induced anti-emicizumab antibodies (negative at pre-dose and positive at two post-dose occasions). In this subject (Caucasian HV), emicizumab was eliminated earlier than in subjects who tested negative, and the shortening of aPTT and promotion of thrombin generation dissipated earlier than in subjects who tested negative. The anti-emicizumab antibodies detected in the plasma of both healthy subjects were not IgE. No adverse events were observed in subjects with detected antibodies.

In study JP29574 anti-drug antibodies were detected in four subjects. Of these subjects, the subjects in whom ADAs were newly detected were 2/36 (treatment induced 5.6%) receiving subcutaneous injections of the new preparation in Groups B through D (one in each group, with one 1 of 12 subjects (8.3%) in the IV Group E). In these 3 subjects, plasma emicizumab was eliminated earlier than in subjects who tested negative. PD responses (shortening of aPTT and promotion of thrombin generation in FVIII-neutralised plasma) dissipated earlier than in the subjects who tested negative. No obvious effect on plasma FIX and FX concentrations was observed in these subjects. The anti-emicizumab antibodies detected in plasma were non-IgE. No adverse events were observed in subjects with detected antibodies.

Updated safety data

No new anti-drug antibodies were detected in patients between the first and the second data cut-off.

Laboratory findings

Overall, there were no changes of clinical significance in haematology or chemistry laboratory parameters in the emicizumab clinical studies.

Safety in special populations

Overall, no appreciable differences were observed in the AE profile of emicizumab as a function of age, based on the current available data (only 3 patients ≥ 65 years).

Safety related to drug-drug interactions and other interactions

The incidence of thromboembolic and thrombotic microangiopathy events in the emicizumab clinical development program was 1.4% for each type of event (i.e. 2 of 141 patients with thromboembolic events and 2 of 141 patients with thrombotic microangiopathy). All cases were observed in Study BH29884, and all 4 patients had recent exposure to aPCC concurrently with emicizumab. Overall, these cases were associated with a cumulative dose of aPCC that was higher than the majority of those received in the study. Evidence of thrombotic microangiopathy resolution was seen within 1 week following discontinuation of aPCC. Patients who experienced thromboembolic, with emicizumab treatment stopped, were reported as recovering in the presence of emicizumab given its long half-life. The TE of skin necrosis was also confirmed to be resolved at the time of the second data cut-off (with the onset date of 28 September 2016, not until 29 March 2017), but still taking longer than the other TE events.

No thromboembolic or thrombotic microangiopathy events were reported in patients receiving rFVIIa alone concurrently with emicizumab. An interaction between aPCC and emicizumab treatment resulting in these events was therefore initially suspected, and detailed investigations were performed.

As a first step, the applicant conducted an aggregate analysis at the level of individual administrations of aPCC ('treatment events'). The analysis focused on Study BH29884 only. 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. The aim was to examine whether the cumulative dose of aPCC per treatment event was linked to the occurrence of these AEs. Based on this analysis, there were 18 patients who experienced a total of 65 treatment events of the use of aPCC. All 4 cases of thromboembolic and thrombotic microangiopathy events were linked to high cumulative doses of aPCC (i.e., > 200 U/kg). Note that 2 of the patients who experienced thromboembolic or thrombotic microangiopathy events each had an earlier treatment event, or events, with cumulative doses of aPCC <100 U/kg that were not associated with thromboembolic or thrombotic microangiopathy events.

To further support that thrombotic microangiopathy or thromboembolic events were associated with aPCC use, rather than patient characteristics, the applicant also reviewed baseline demographics and disease characteristics (haemophilia history, medical history, and bleeding events in the last 24 weeks prior to study entry), with no obvious differences in these baseline characteristics observed.

Categorical analyses looked at the average exposure to aPCC over 24 hours and the total duration of the aPCC treatment events, as well as the distribution of cumulative doses of treatment events and compared those consisting of a single dose of aPCC with those consisting of multiple doses. Of the 65 aPCC treatment events, 7 consisted of an average 24-hour aPCC dose ≥100 U/kg and lasted over multiple 24-hour periods. Four of these 7 events were associated with thromboembolic and thrombotic microangiopathy events. All of the treatment events associated with thromboembolic or thrombotic microangiopathy events consisted of multiple aPCC doses.

In a next step the cumulative dose of aPCC within a 24-hour period was looked at (24-hour interval started at each aPCC dose and included all treatments administered within the next 24 hours; a treatment could belong to more than one 24-hour interval). All thromboembolic and thrombotic microangiopathy events were associated with at least one instance of the cumulative aPCC dose being >100 U/kg within a 24-hour interval during the contemporaneous treatment event.

Similar analyses were performed for treatment events with rFVIIa, which showed that zero treatment events where rFVIIa was administered alone were associated with thromboembolic or thrombotic microangiopathy events. Note that 1 patient had 1 treatment event with rFVIIa prior to diagnosis of thrombotic microangiopathy and 3 additional treatment events with rFVIIa while the AE was ongoing. The thrombotic microangiopathy AE resolved while the patient received factor rFVII.

In summary, 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 received aPCC doses > 100 U/kg over 24 hours, and no patients receiving concomitant aPCC ≤100 U/kg over 24 hours or rFVIIa alone at any dose or duration developed thromboembolic or thrombotic microangiopathy events.

After the initial data cut-off in 2016, an additional patient experienced a thrombotic microangiopathy event (see Section SAE/ Deaths above). This patient received cumulative aPCC doses > 100 U/kg over 24 hours, similar to the other patients who developed thromboembolic or thrombotic microangiopathy events. While this patient also had a rFVIIa treatment event preceding the thrombotic microangiopathy, the aPCC treatment event started after the rFVIIa treatment event 3 days prior to and immediately preceded the diagnosis of the thrombotic microangiopathy event. Overall, the information from this additional case further supports the conclusions of these aggregate analyses.

Updated safety data

No additional patients experienced an AE of TMA following the second amendment and the DIL, which implemented the risk mitigation measures to address the potential risk related to the DDI as discussed above.

One additional even of TE was however reported: a device occlusion. This event occurred in a patient in Arm Bemi who also had experienced deep vein thrombosis prior to switching to emicizumab. The patient was not receiving treatment with aPCC or other bypassing agents when he had the device occlusion. The AE of device occlusion was Grade 1, not serious, and assessed by the investigator as not related to emicizumab. This AE resolved without sequelae.

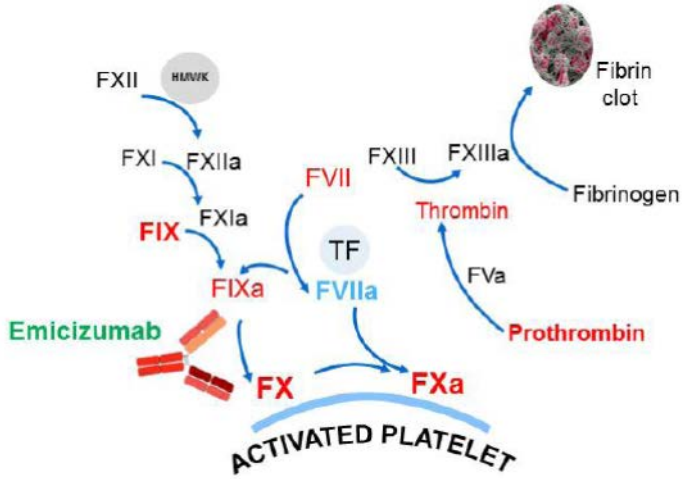
Proposed Mechanism of Action for Drug-Drug Interaction between Emicizumab and aPCC

The pathophysiological mechanism(s) by which the posited drug-drug interaction between emicizumab and aPCC results in thrombotic microangiopathy events has not yet been fully elucidated.

The applicant's key hypothesis is that both thromboembolic and thrombotic microangiopathy events have been mediated by temporarily increased FIXa-emicizumab-activated factor X (FXa) ternary complex formation on the surface of a phospholipid bilayer and excessive thrombin generation, with localisation to certain microvascular beds.

Emicizumab likely has a unique interaction with aPCC, due to the inclusion of emicizumab's substrates within aPCC, as well as other coagulation factors with long half-lives (e.g., prothrombin) that accumulate with repeated dosing (Sørensen *et al.* 2011) Figure 18.

Figure 18: Proposed interaction between emicizumab and aPCC



FXII=factor XII; FXIIa=activated factor XII; FIX=factor IX; FIXa=activated factor IX; FVII=factor VII; FVIIa= activated factor VII; TF= tissue factor; FXa= activated factor X; FVIIIa= activated factro VIII; FX= factor X; FVa= activated factor V; FXIII= factor XIII; FXIIIa= activated factor XIII; HMWK= high-molecular-weight kininogen

It is conceivable that, in addition to the independent, procoagulant effects of aPCC, the presence of FIX, FIXa, FX, and FXa (included at low levels in aPCC, which primarily contains prothrombin complex zymogens) may increase the frequency and concentration of enzyme (FIXa)-cofactor (emicizumab)-substrate (FX) complex formation in a dose-dependent manner, resulting in an increase in emicizumab's cofactor activity and capacity to generate thrombin. In contrast, rFVIIa does not directly impact emicizumab's potential to form the intrinsic tenase complex, which is in agreement with clinical results showing that TE and TME events were associated with high cumulative doses of concomitant aPCC treatment but not rFVIIa treatment.

This hypothesised coagulation-mediated mechanism of action is further supported by *in vitro* and *in vivo* studies (see also non-clinical discussion).

The clinical course of the thromboembolic and thrombotic microangiopathy events in Study BH29884 is not consistent with that of typical thromboembolism (e.g., deep vein thrombosis/pulmonary embolism) and thrombotic microangiopathy events: the thromboembolic events did not require treatment with anticoagulation and the thrombotic microangiopathy events started to resolve within 1 week following discontinuation of aPCC. The latter finding argues against mechanistic processes that involve autoantibodies against von Willebrand factor cleaving proteases (i.e., thrombotic thrombocytopenic purpura) or dysregulation of the alternative complement pathway (i.e., atypical haemolytic uremic syndrome), both of which are generally associated with prolonged, systemic therapeutic interventions before remission can be achieved.

Other potential mechanisms of action of thrombotic microangiopathy associated with the use of aPCC and emicizumab cannot be completely ruled out as an explanation for the interaction between emicizumab with aPCC now.

Discontinuation due to adverse events

Table 35: Adverse Events leading to discontinuation from Treatment, Safety Population - studies BH29884; BH29992; ACE002JP

Adverse Events Leading to Discontinuation from Treatment, Safety Population
Protocols: BH29884, BH29992, ACE002JP
Cutoff Date: BH29884 - 21APR2017; BH29992 - 08MAY2017; ACE002JP - 30SEP2016
Snapshot Date: BH29884 - 22JUN2017; BH29992 - 28JUN2017; ACE002JP - 11NOV2016
Safety Population

	BH29884					BH29992	ACE002JP				
MedDRA System Organ Class MedDRA Preferred Term*	A:1.5mg (N=34)	B:1.5mg (N=17)	C:1.5mg (N=49)	D:1.5mg (N=11)	Total (N=111)	1.5mg (N=60)	0.3mg (N=6)	1.0mg (N=6)	3.0mg (N=6)	Total (N=18)	All Patients (N=189)
Total number of patients with at least one AE	2 (5.9%)	0	1 (2.0%)	0	3 (2.7%)	0	0	1 (16.7%)	0	1 (5.6%)	4 (2.1%)
Total number of AEs	3	0	1	0	4	0	0	2	0	2	6
BLOOD AND LYMPHATIC SYSTEM DISORDERS											
Total number of patients with at least one AE	1 (2.9%)	0	0	0	1 (0.9%)	0	0	0	0	0	1 (0.5%)
Total number of AEs	1	0	0	0	1	0	0	0	0	0	1
THROMBOTIC MICROANGIOPATHY	1 (2.9%)	0	0	0	1 (0.9%)	0	0	0	0	0	1 (0.5%)
GASTROINTESTINAL DISORDERS											
Total number of patients with at least one AE	0	0	1 (2.0%)	0	1 (0.9%)	0	0	0	0	0	1 (0.5%)
Total number of AEs	0	0	1	0	1	0	0	0	0	0	1
RECTAL HAEMORRHAGE	0	0	1 (2.0%)	0	1 (0.9%)	0	0	0	0	0	1 (0.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS											
Total number of patients with at least one AE	0	0	0	0	0	0	0	1 (16.7%)	0	1 (5.6%)	1 (0.5%)
Total number of AEs	0	0	0	0	0	0	0	2	0	2	2
INJECTION SITE REACTIONS	0	0	0	0	0	0	0	1 (16.7%)	0	1 (5.6%)	1 (0.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS											
Total number of patients with at least one AE	1 (2.9%)	0	0	0	1 (0.9%)	0	0	0	0	0	1 (0.5%)
Total number of AEs	1	0	0	0	1	0	0	0	0	0	1
SKIN NECROSIS	1 (2.9%)	0	0	0	1 (0.9%)	0	0	0	0	0	1 (0.5%)
VASCULAR DISORDERS											
Total number of patients with at least one AE	1 (2.9%)	0	0	0	1 (0.9%)	0	0	0	0	0	1 (0.5%)
Total number of AEs	1	0	0	0	1	0	0	0	0	0	1
THROMBOPHLEBITIS SUPERFICIAL	1 (2.9%)	0	0	0	1 (0.9%)	0	0	0	0	0	1 (0.5%)

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

A total of 189 patients have received at least one dose of emicizumab at the time of the second clinical data cut-off (21st of April 2017 (BH29884) and 08th of May 2017 (BH29992)), with an overall exposure of 157.8 patient-years, providing safety data from 48 additional patients with haemophilia A and inhibitors. Long term exposure data (i.e. > 1 year) is based on Japanese patients from study ACE002JP.

The overall safety profile of emicizumab appears to be tolerable. A total of 4 patients (2.1%) had AEs leading to discontinuation from study treatment, of which 2 patients were in Study BH29884 (one due to TMA; one due to TA) and 1 patient in Study ACE002JP due to ISR. AEs leading to dose modifications/ interruptions was observed in 5.4% (6/189).

The most common AEs related to nervous system disorders (19.0%, mainly headache), general disorders and administration site conditions (34.9%, mainly ISRs), thrombotic microangiopathy (1.4%), gastrointestinal disorders (21.7%), musculoskeletal and connective tissue disorders (19.6%, mainly arthralgia).

There were no clinically significant changes in haematology or chemistry laboratory parameters in the emicizumab clinical studies.

No appreciable safety differences were observed in special populations. However, due to the limited data currently available (e.g. no patient <1 years; 3 ≥65 years), section 4.2 of the SmPC mentions that there are no data in patients less than 1 year of age and that there are no data in patients over 75 years old. In addition, “use in neonate and infants” and “use in elderly” have been added as missing information in the RMP. Additional safety data in patients < 2 years of age as part of the ongoing study BH29992 (PIP study) will be provided. Please see section below.

No dose adjustments are recommended in patients with mild renal or mild and moderate hepatic impairment (see section 5.2 of the SmPC). Emicizumab has not been studied in patients with moderate or severe renal impairment or severe hepatic impairment.

Treatment with bypassing agents should be discontinued the day before starting Hemlibra therapy.

Physicians should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required while receiving Hemlibra prophylaxis.

Hemlibra increases the patient's coagulation potential. The bypassing agent dose required may therefore be lower than that used without Hemlibra prophylaxis. The dose and duration of treatment with bypassing agents will depend on the location and extent of bleeding, and the patient's clinical condition. Use of aPCC should be avoided unless no other treatment options/alternatives are available. If aPCC is indicated in a patient receiving Hemlibra prophylaxis, the initial dose should not exceed 50 U/kg and laboratory monitoring is recommended (including but not restricted to renal monitoring, platelet testing, and evaluation of thrombosis). If bleeding is not controlled with the initial dose of aPCC up to 50 U/kg, additional aPCC doses should be administered under medical guidance or supervision with consideration made to laboratory monitoring for the diagnosis of TMA or thromboembolism and verification of bleeds prior to repeated dosing. The total aPCC dose should not exceed 100 U/kg in the first 24-hours of treatment. Treating physicians must carefully weigh the risk of TMA and thromboembolism against the risk of bleeding when considering aPCC treatment beyond a maximum of 100 U/kg in the first 24-hours.

In clinical trials, no cases of TMA or thrombotic events were observed with use of activated recombinant human FVII (rFVIIa) alone in patients receiving Hemlibra prophylaxis.

Bypassing agent dosing guidance should be followed for at least 6 months following discontinuation of Hemlibra prophylaxis (SmPC section 4.4). The safety and efficacy of emicizumab in patients receiving ongoing immune tolerance induction have not yet been established. No data are available.

There are two cases of death, although one not as part of the submitted trials, but on the compassionate use program. The cause of death of the patient on trial BH29884 was essentially due to recurrent rectal haemorrhage which occurred due to lack of efficacy while on emicizumab prophylaxis. The special circumstances of the patient not having consented to receive blood products are appreciated and acknowledged to have been a contributory factor. The death of the patient on the compassionate use program due to disseminated MSSA infection followed by an intracranial haemorrhage was most likely triggered by the septic event. It is acknowledged that death due to sepsis is one of the most common causes in patients with haemophilia.

Thrombin generation data from the three studies ACE001JP, ACE002JP, BH29884, indicated a continuous potential for thrombin generation for the duration of treatment, not a continuous presence of activated thrombin. In addition, D-Dimer and prothrombin fragment 1+2 data show a coagulation system not globally activated. Whilst this is not direct evidence of adequate thrombin degradation, indeed it shows a sustained potential for thrombin generation in a coagulation system not globally activated, indicating a balance which is not considered of direct concern.

What remains unknown at present, is the issue of long term use, as reflected in the RMP particularly regarding the impact on the balance of the known bi-directional relationship between coagulation and inflammation (local and systemic). However, as emicizumab is not pro–thrombotic and does not, itself, activate coagulation, it can only accelerate the tenase reaction after FIX is activated by normal physiological processes. Therefore, it is unlikely to cause high or exaggerated levels of coagulation proteases leading to induction of pro-inflammatory processes. In addition,

there is no correlation between increase in infection and infestation AEs and increased exposure to Emicizumab. Whilst no definite conclusion can be drawn, it is agreed to be unlikely that Emicizumab impacts on patients' inflammatory processes or innate immune responses over time.

Generally, haemostatic efficacy requires not only effective initial haemostasis, but also a maintained state of haemostasis with fibrin plugs resistant to premature lysis. Appreciating the clinical course of these events in view of its unusual short and uncomplicated period of resolution, in comparison to other TMA events it needs to be appreciated that the pathophysiology underlying the DDI related TMA remains to be fully elucidated. The 'clean' mechanism of action by which rFVIIa interferes in the coagulation cascade in this patient population could explain that it does not seem to directly impact emicizumab's potential to form the intrinsic tenase complex to increasingly generate thrombin. This proposed hypothesis is supported by the clinical observation which did not reveal any events of TE/TMA following use of rFVIIa, even in case of its use after these events. Although rFVIIa might not directly impact on the emicizumab's triggered generation of thrombin, concomitant use of rFVIIa in a coagulation system maintained in a prothrombotic state while, in the event of acute bleeding, experiencing signal activation through endothelial damage, necessitating the need for additional use of rVFIIa still raises the concern of an increased risk of thromboembolic events. This has been extensively reflected in section 4.4 as well as in section 4.8 of the SmPC. In addition, educational materials for Healthcare Professionals, a patient alert card and a patient/Carer Guide have been developed as a risk minimisation measure. Finally, the concomitant use of rFVIIa is being followed through specific questionnaires as part of routine pharmacovigilance activities.

Hence, the main safety concern is around the development of thromboembolic events (TEs) or thromboembolic microangiopathy (TMA), with 4 patients in study BH29884 who develop such AE (2 patients each). It was considered to be related to concomitant use of bypassing agents (particularly aPCC). This is in addition to a further patient who experienced a SAE of TMA after the initial data cut-off. The applicant conducted a comprehensive review around the ADRs of TE and TMA and concluded that there is sufficient evidence to support a drug-drug interaction. Doses of aPCC ≥100 U/kg over 24 hours were associated with an increased risk for developing TE and TMA, which was not observed with the use of rFVIIa only. The potential mechanism of action for the observed DDI is hypothesised to be mediated by a dose dependant increase in FIXa-emicizumab-FXa complex formations and excessive thrombin generation due to the inclusion of emicizumab's substrates (e.g. FIX, FIXa, FX, and FXa) within aPCC. This is acknowledged. Risk mitigation measures were added as part of amendment 2 (i.e. after data-cut-off). No new events of TMA occurred following these risk mitigation measures, apart from one patient with an event of device occlusion (Grade 1), without receiving treatment with a bypassing agent, and not considered to be related to treatment, showing that there is an intrinsic risk for TE in patients with devices (e.g. catheters) in-situ. The fact that overall no new events of TMA or TE in conjunction with the use of bypassing agents, particularly aPCC, occurred is reassuring.

Since implementation of the risk mitigation measures, no patients in study BH29884 received single infusions of aPCC doses ≥100 U/kg, which means all patients adhered to the SmPC posology recommendation of single doses. A substantial reduction in the number of infusions between 90-270 µg/kg for rFVIIa after the risk mitigation measures were put in place (from 75.7% to 33.9% of all infusions) was observed. Importantly a more focused use of aPCC did not lead to an increase in proportion of patients reporting SAEs or serious haemorrhages. No additional AEs leading to withdrawal from treatment occurred after the clinical cut-off date for the primary analysis.

Regarding the exclusion criteria of 'patients at high risk of TMA' the CHMP considered that a) at the time of adding this as an exclusion criterion, there was limited understanding of these TMA events, which are now considered to be most likely related to a DDI, with adequate risk mitigation

measures in place; with no patient having been excluded due to a high risk for TMA; b) based on current knowledge, patients with a previous medical history of TMA or those with hereditary predispositions to TMA, such as ADAMTS13 deficiency or complement pathway mutation, would not be expected to have increased susceptibility to TMA, as it is considered to be mediated by the drug-drug interaction between emicizumab and aPCC; c) patients would be precluded from resuming emicizumab treatment following complete resolution of a TMA event, even if a positive benefit-risk is still considered based on the prescribers judgment, bearing in mind that emicizumab will be administered by experienced haemophilia physicians. It was agreed to add a warning to Section 4.4 instead as indeed there is currently only paucity of evidence to support a contraindication. The need for a contraindication however should be regularly revisited through the PSUR updates.

The incidence of detected ADAs in the patient population was low (4/189), with no apparent impact on efficacy and safety. The described incidence is based on Japanese patients with positive ADA from the extension study ACE002JP only. Updated immunogenicity data shows that no patient in the pivotal studies tested (i.e. at least one post-baseline assessment) were positive. The concerns around the appropriateness of the assays have overall been adequately addressed. A pragmatic approach is taken in light of the fact that development of clinically relevant ADA will likely effect efficacy and hence be recorded by clinicians by means of continuous monitoring of their patients. The statement proposed for Section 5.1 of the SmPC to consider immunogenicity in cases of loss of efficacy raises awareness around this issue and is considered sufficient to address a remaining uncertainty particularly around drug tolerance. Immunogenicity is also reflected in the RMP and recognised as important potential risk.

Injection site reactions (ISRs) were reported very commonly from clinical trials. All ISRs observed in the Hemlibra clinical trials were reported as being non serious and generally mild to moderate in intensity. Most ISRs resolved without treatment. The most commonly reported ISR symptoms were injection site erythema (7.4 %), injection site pruritus (5.3%) and injection site pain (5.3%) (SmPC section 4.8).

Safety data below patients age 1 are not available. In order to address the question to which extent the quantitatively different haemostatic system in neonates and infants may influence the haemostatic balance, consequently response to emicizumab as well as potentially impacting safety, e.g. increasing the risk for thromboembolic events (TE), the applicant described that haemostatic balance is maintained in an 'equilibrium' through concurrent reduction in levels of anti-coagulant proteins (Hanmod *et al* 2016). That the healthy newborn exists in a 'haemostatic equilibrium', neither prone to bleeding nor to clotting, supported by the observation that healthy infants typically do not suffer haemorrhagic or thrombotic complications spontaneously or in the presence of minor challenges. The imbalance of higher incidences of pro-thrombotic events (e.g. venous thromboembolism - VTE) described in the literature in this age group is thus not due to a 'natural' pro-thrombotic tendency, but considered to be associated with a higher risk of acquired predisposing maternal, neonatal and central venous catheter (CVC) related risk factors leading to the development of thrombotic events, of which many are unique to the perinatal period, such as pre-eclampsia, emergency C-section or perinatal asphyxia (Amankwah *et al.* 2014; Klaassen *et al.* 2015; Haley 2017). If one looks at the complication of TE in the target population of neonates and infants with haemophilia and central venous access devices, it is generally a rare event (1%) (Kulkarni et al. 2009). But if occurring in context of the different risk factors described, TEs are in more than 90% considered CVC-related (van Ommen *et al,* 2001, van Ommen and Nowak-Goettl, 2017). Overall, if it is agreed that a 'haemostatic equilibrium' possibly exists, the deficiencies of anticoagulant proteins in neonates and infants may still, potentially, predispose this group to a higher risk of thrombosis. It looks like this is however largely driven by different risk factors and

prompted by an increased use of invasive procedures and catheter placement in small calibre vessels in such patients (Hanmod *et al* 2016). In context of emicizumab, the question then is to which extent do the potential predispositions influence a balanced response to emicizumab, i.e. emicizumab amplifying the risk for thromboembolic events. In this context, it is important to note that emicizumab is not pro–thrombotic and does not, itself, activate coagulation. It only accelerates the tenase reaction after FIX is activated by normal physiological or indeed pathophysiological processes; with the latter potentially triggering a TE event. Overall, a potential safety concern for this age group is, as for all age groups indeed the risk of thromboembolic events. The question to whether we have to assume an incidence difference in TEs in neonates and infants as compared to our source population is speculation and not part of the extrapolation exercise. Overall, it emphasises that the potential risks for this age group needs to be appreciated, but seen in context of the anticipated benefits (see Section 3 below). In order to inform prescribers regarding the absence of data in patients 0-1 year of age, and to mitigate any risks associated with it, the lack of (safety) data is now adequately reflected in Section 4.2 and data in neonates and infants are considered missing in the RMP. In addition, adequate warnings have been introduced in Section 4.4 regarding the uncertainty around the deficiencies of anticoagulant proteins in neonates and infants which may, potentially, predispose this group to a higher risk of thrombosis in case of a CVC in situ, which should be appreciated when concluding on a patient's individual benefit-risk. Additional safety data in patients < 2 years of age as part of the ongoing study BH29992 (PIP study) will be provided.

To conclude, the additional safety data submitted after the data cut-off have shown no new safety concerns, with a safety profile considered to be tolerable down to the age of 1 year. The applicant showed that following the risk mitigations put in place addressing the potential for drug-drug interaction with aPCC, no new events of TMA and TE occurred. At the same time, no increases in SAEs or serious haemorrhages were seen. This is overall considered supportive of the risk mitigation measures proposed. The data are however limited and this risk remains, with adequate pharmacovigilance measures in place to follow this concern up in the post marketing setting i.e. through specific guided questionnaires which will be assessed as part of routine PSUR reporting as well as through a PASS based on the EUHASS registry. This is in addition to appropriate guidance being included into the SmPC regarding concomitant use of aPCC and warnings regarding patients with potential risk factors for development of TMA.

2.6.2. Conclusions on the clinical safety

The safety data submitted after the data cut-off have shown no new safety concerns, with a safety profile considered to be tolerable down to the age of 1 year. The most common AEs related to nervous system disorders (19.0%, mainly headache), general disorders and administration site conditions (34.9%, mainly ISRs), thrombotic microangiopathy (1.4%), gastrointestinal disorders (21.7%), musculoskeletal and connective tissue disorders (19.6%, mainly arthralgia).

The drug-drug interaction with bypassing agents, particularly aPCC leading to the ADRs of TE and TMA was a concern as part of the assessment. The applicant recognised and investigated the root cause for the DDI and implemented risk mitigation measures as part of the second amendment. Updated safety data show no new cases being observed with clinicians following the aPCC dosing recommendations. Extensive warnings have been included in section 4.4 and 4.8 of the SmPC. Additional risk minimisation measure include educational materials for health care professionals, patient alert card as well as patient/carer educational guide. The proposed pharmacovigilance measures will follow up on this issue, particularly with regards to adherence to dosing recommendation when using concomitant bypassing agents, as well as concerning the lack of data in neonates and infants. Additional data will come through specific guided questionnaires which will

be assessed as part of routine PSUR reporting as well as through a PASS based on the EUHASS registry. Additional safety data in patients < 2 years of age as part of the ongoing study BH29992 (PIP study) will be provided.

2.7. Risk Management Plan

Table 36: Summary table of pharmacovigilance and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Thromboembolic events (associated with emicizumab and aPCC)	Routine risk minimisation measures: • Wording in sections 4.4, 4.5, 4.8 of the SmPC and in sections 2 and 4 of the package leaflet • Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders Additional risk minimisation measures: • Guide for Healthcare Professionals • Patient Alert Card • Patient/Carer Guide	Routine pharmacovigilance activities: • Specific guided questionnaires • PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • HCP and patient/carer survey

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Thrombotic microangiopathy (associated with emicizumab and aPCC)	Routine risk minimisation measures: • Wording in sections 4.4, 4.5, 4.8 of the SmPC and sections 2 and 4 of the package leaflet • Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders Additional risk minimisation 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
Important potential risks		
Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab	Routine risk minimisation measures: • Wording in sections 4.4, 4.5 of the SmPC and section 2 of the package leaflet • Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders Additional risk minimisation 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	Routine risk minimisation measures: • Wording in section 4.3 of	Routine pharmacovigilance activities: • PSUR/PBRER reporting

Safety concern	Risk minimisation measures	Pharmacovigilance activities
reactions	the SmPC and section 2 of the package leaflet No additional measures	Additional pharmacovigilance activities: • PASS based on the EUHASS registry
Immunogenicity	Routine risk minimisation measures: • Wording in section 5.1 of the SmPC No additional measures	Routine pharmacovigilance activities: • PSUR/PBRER reporting
Missing Information		
Use in female patients, pregnancy and lactation	Routine risk minimisation measures: • Wording in section 4.6 of the SmPC and section 2 of the package leaflet No additional measures	Routine pharmacovigilance activities: • PSUR/PBRER reporting
Use in neonates and infants	Routine risk minimisation measures: • Wording in section 4.2 of the SmPC No additional measures	
Use in elderly patients	Routine risk minimisation measures: Wording in section 4.2 of the SmPC No additional measures	
Long term use of emicizumab	No routine or additional measures	
Peri-operative management of patients on emicizumab	Routine risk minimisation measures: Wording in section 5.1 of the SmPC No additional measures	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
The safety of emicizumab in patients receiving ITI	Routine risk minimisation measures: • Wording in section 4.5 of the SmPC No additional measures	

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The IBD is 16.11.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that emicizumab has not been previously authorised in a medicinal product in the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Hemlibra (emicizumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

The applicant has applied for emicizumab to be indicated for prophylaxis to prevent bleeding in patients with haemophilia A with factor VIII inhibitors, in patients of all age.

3.1.2. Available therapies and unmet medical need

The current standard of care for treatment of bleeds in haemophilia A patients with inhibitors is treatment with bypassing agents (BPA). 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.

BPAs are short-acting and may need to be administered often, with long IV infusion times and/or require frequent administration for prophylaxis. This is considered time-consuming and burdensome for patients with haemophilia A and their caregivers. Overall, there is an unmet medical need for new, more convenient, and efficacious treatment options for patients with haemophilia A with inhibitors.

3.1.3. Main clinical studies

Efficacy is based on one randomised control open label trial in patients age ≥12, with a total of 113 patients enrolled, assigned to 4 different treatment arms based on prior treatment regimens with bypassing agents, allowing to compare bleed rates at 24 weeks between patients on episodic use of bypassing agents and those on emicizumab prophylaxis (53 patients randomised 1:2 - ITT population), as well as intra-patient comparison of patients previously treated with prophylactic bypassing regimens.

This is supported by descriptive interim data of 60 patients from an ongoing single-arm, open label trial in children age <12 (data cut-off 08 May 2017). This is addition to 10 patients ≤2 years of age based on a separate later data cut-off (September 2017).

Long term efficacy data are presented from 16 Japanese patients recruited into the Phase I extension trial ACE002JP.

3.2. Favourable effects

Using the NB regression model to analyse the bleed rate for treated bleeds for the randomised population, there was a statistically significant 87% reduction in bleed rate with emicizumab

prophylaxis compared with no prophylaxis (Arm B ABR = 23.3; Arm A = 2.9; ABR ratio 0.13 [95% CI: 0.057; 0.277]; p < 0.0001 for stratified Wald test, confirmed by sensitivity analyses.

The NB regression model analysis of all bleeds showed a statistically significant reduction (Arm B ABR = 28.3; Arm A = 0.8; ABR ratio = 5.5 [95% CI: 0.102;0.375]; p <0.0001 for stratified Wald test), confirmed by sensitivity analyses.

The NB regression model analysis of treated joint bleeds showed a statistically significant 89% reduction in the bleed rate (treated bleeds) (Arm B ABR = 6.7; Arm A = 0.8; ABR ratio = 0.11 [95% CI: 0.025; 0.520]; p <0.0050 for stratified Wald test).

The NB analysis of treated target joint bleeds showed a statistically significant 95% reduction in the bleed rate (Arm B ABR = 3.0, Arm A ABR = 0.1; ABR ratio = 0.05 [95% CI: 0.009; 0.227]; p < 0.0002 for stratified Wald test).

The NB regression analysis of treated spontaneous bleeds showed a statistically significant 92% reduction in the bleed rate (Arm B ABR = 16.8, Arm A ABR = 1.3; ABR ratio = 0.08 [95% CI: 0.037; 0.154]; p < 0.0001 for stratified Wald test).

The intra-patient comparison of bleed rates in Arm A and C showed a statistically significant reduction of ABR (Arm A NB analysis for patients with at least 12 weeks of treatment (Arm A NIS BR = 21.9; Arm A ABR = 1.8; ABR ratio = 0.08 [95% CI: 0.033;0.209], p < 0.0001; Arm C NB analysis for patients with at least 12 weeks of treatment (Arm C NIS ABR = 17.0; Arm C ABR = 3.6; ABR ratio = 0.21 [0.090;0.488], p < 0.0003), confirmed by sensitivity analyses.

The updated intra-patient comparison of bleeds rates in Arm C confirmed the above (ABR ratio treated bleeds 0.13; 95% CI: 0.059; 0.301; P-value (non-stratified Wald test) <0.0001; all bleeds ABR ratio 0.15; 95% CI: 0.078;0.299; P-value (non-stratified Wald test) <0.0001).

All QoL measures indicated a statistically significant and clinically meaningful improvement.

3.3. Uncertainties and limitations about favourable effects

There were no patient <1 years treated with Hemlibra (section 4.2 of the SmPC). The “use in neonate and infants” has been added as missing information in the RMP. The model used for PK extrapolation in children less than 1 year is not reflecting the most optimum fit. This is however considered acceptable as additional safety data in patients < 2 years of age will be provided as part of the ongoing study BH29992 (PIP study).

Efficacy data in situations of major surgery are missing; this has been appropriately reflected in section 4.2 of the SmPC.

Long term data were provided with the extension study ACE002JP, conducted in Japan which enrolled patients with and without inhibitors using a different maintenance dosing regimen (0.3, 1, and 3 mg/kg/week). It calculated individual patient ABRs but did not estimate population rates based on the NB regression model.

3.4. Unfavourable effects

The most common AEs related to nervous system disorders (19.0%, mainly headache), general disorders and administration site conditions (34.9%, mainly ISRs), thrombotic microangiopathy (1.4%), gastrointestinal disorders (21.7%), musculoskeletal and connective tissue disorders (19.6%, mainly arthralgia).

The main safety risks relate to thromboembolic events and thrombotic microangiopathy revealed by two cases of thromboembolic events and three of thrombotic microangiopathy while on emicizumab, related to concomitant use of bypassing agents, particularly aPCC which is considered to be a drug-drug interaction. The applicant recognised and investigated the root cause for the drug-drug interactions and implemented risk mitigation measures as part of the second amendment of the clinical trial protocol. Updated safety data show no new cases being observed with clinicians following the aPCC dosing recommendations. Extensive warnings have been included in section 4.4 and 4.8 of the SmPC. Additional risk minimisation measure include educational materials for health care professionals, patient alert card as well as patient/carer educational guide. In addition, the proposed pharmacovigilance measures will follow up on this issue, particularly with regards to the adherence to dosing recommendation when using concomitant bypassing agents, as well as concerning the lack of data in neonates and infants. Additional data will come through specific guided questionnaires which will be assessed as part of routine PSUR reporting as well as through a PASS based on the EUHASS registry. Additional safety data in patients < 2 years of age as part of the ongoing study BH29992 (PIP study) will be provided.

Injection site reactions in 18.5% of all patients, although as stated in section in 4.8 of the SmPC, most of the injection site reactions resolved without treatment.

3.5. Uncertainties and limitations about unfavourable effects

It is not sure that the long term effectiveness of the risk minimisation measures implemented to address issue of drug-drug interaction with concomitant use of bypassing agents will be successful. A PASS based on the HCP and patient/carer survey will be performed to address this issue as part of the RMP.

The pathophysiology behind thrombotic microangiopathy is considered to be potentially related to concomitant use of aPCC but this has not been fully elucidated.

3.6. Effects Table

Table 37: Effects Table for emicizumab (data cut-off: 25th of October 2016 for BH29884 for the ITT population).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects (ITT population study BH29884 at 24 weeks)					
ABR All treated bleeds (excl. bleeds due to surgery/ procedures)	ABR ratio 0.13 95% CI: 0.057;0.277 P-value (stratified and non-stratified Wald test) <0.0001	Model based Bleeds per year/ Diff. 20.4	2.9 95% CI: 1.69;5.02	23.3 95% CI: 12.33;43.89	• Only patients included with history of bleeds • Efficacy data during major surgery missing • No efficacy data in children age ≤1 years • Longer term follow-up data lacking
ABR Treated Joint bleeds	ABR ratio 0.11 95% CI: 0.025;0.520 P-value (stratified and non-stratified Wald test) 0.005; 0.0052	Model based Bleeds per year/ Diff. 5.9	0.8 95% CI: 0.26;2.20	6.7 95% CI: 1.99;22.42	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
ABR Treated Target Joint bleeds	ABR ratio 0.05 95% CI: 0.009;0.227 P-value (stratified and non-stratified Wald test) 0.0002	Model based Bleeds per year/ Diff. 2.9	0.1 95% CI: 0.03;0.58	3.0 95% CI: 0.96;9.13	• Robustness confirmed by sensitivity analysis • Efficacy data consistent for all types of bleeding endpoints collected • Large effect size
ABR treated spontaneous bleeds	ABR ratio 0.08 95% CI: 0.037;0.154 P-value (stratified and non-stratified Wald test) <0.0001	Model based Bleeds per year/ Diff. 15.5	1.3 95% CI: 0.73; 2.19	16.8 95% CI: 9.94; 28.3	
QoL measures	- Haem-A-QoL Physical Health Score - Haem-A-QoL Total Score - EQ-5D-5L VAS score - EQ-5D-5L Index Utility Score	adjusted mean difference	- 21.55 [95% CI: 7.89, 35.22]; p < 0.0029) - 14.01 [95% CI: 5.56, 22.45]; p < 0.0019 - -9.72 [95% CI: -17.62, -1.82; p-value = 0.0171 - -0.16 [95% CI: -0.25, -0.07]; p = 0.0014		• Intra-patient comparison unknown • Haemo-QoL SF data for children not fully know yet, as study ongoing • All QoL measures consistent with efficacy endpoints • All considered clinically meaningful
Favourable Effects (Intra-patient comparison – data cut-off April 2017) All patients Arm C vs all patients from Arm C on bypassing prophylaxis based on NIS data)					
ABR – treated bleeds	ABR ratio 0.13 95% CI: 0.059;0.301 P-value (non-stratified Wald test) <0.0001	Model based Bleeds per year/ Diff. 13.7	2.1 95% CI: 0.87; 5.13	15.8 95% CI: 11.24;22.22	• ABR from NIS higher compared to published data • Results consistent with ITT data
ABR - all bleeds	ABR ratio 0.15 95% CI: 0.078;0.299 P-value (non-stratified Wald test) <0.0001	Mode based Bleeds per year/ Diff. 20.8	3.8 95% CI: 1.98; 7.16	24.6 95% CI: 18.42;32.88	
Favourable Effects – study BH29992 (12-weeks; 23 patients – data cut off May 2017)					

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Zero bleeds	- Treated bleeds - All bleeds - Treated spontaneous bleeds - Treated joint - Treated target joint bleeds	% patients with 0 bleeds	- 87 - 34.8 - 95.7 - 95.7 - 100	N/A	• Only preliminary data • No data in patients ≤ 1years • Results consistent with BH29884
Favourable Effects – study BH29992 (patients ≤ 2 years; 10 patients, 9 with 12-week efficacy period – data cut -off September 2017)					
Zero bleeds	- Bleed related endpoints	% patients with 0 bleeds	- 80	N/A	• Only preliminary data • No data in patients ≤ 1years • Results consistent with BH2992 overall results and BH29884
Unfavourable Effects (all safety population – data cut off April/May 2017; *ITT population BH29884 in case of comparison – data cut off Oct 2016*)					
Discontinuation due to AEs		% (N)	2.1 (4)	-	• High level of tolerability
ISR			19 (35/189)	-	
ADA/NDA			2.1 (4)	-	• Assay concerns • Unclear if NDA measured in patients with ADA
SAEs - TE - TMA			*11.8 (4)* - 1.9 (2) - 1.9 (2)	*22.6 (4)* - -	• 3rd patient with TMA post data cut-off

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Drug interaction with concomitant use of bypassing agents, particularly aPCC					• Long term effectiveness of risk mitigations measures unclear • It was shown that following implementation of the measures (~6 months post) no new event of TMA occurred (one event of TE, without concomitant use of bypassing agents, considered not related); this can be considered reassuring

Abbreviations: ISR – Injection site reactions; ADA – Anti-drug antibodies; NDA – neutralising drug antibodies; TMA - thromboembolic microangiopathy; TE - thromboembolic events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Treatment of bleeds in patients with haemophilia A who developed inhibitors are limited and confined to the use of bypassing agents.

Overall the observed effect size is consistent, showing reduction of all bleed related endpoints, including joint bleeds, hence reducing any potential subsequent clinical damage. This together with the QoL measures can be considered clinically meaningful.

Inclusion of patients 0-1 years of age based on full extrapolation is considered acceptable, with a positive benefit-risk assumed.

The safety profile of emicizumab is considered tolerable, mainly consisting of injection site reactions, pyrexia and headache. The updated safety data submitted were in line with these observations and did not indicate any additional new safety concerns.

3.7.2. Balance of benefits and risks

Overall efficacy has been shown in patients ≥ 1 year of age, with the lack of data in patients 0-1 year of age addressed through an extrapolation exercise. The safety profile of emicizumab, mainly consisting of injection site reactions, pyrexia and headache is considered as tolerable. The

identified risks of thrombotic microangiopathy and thromboembolic event are adequately addressed by means of the SmPC and within the RMP.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit-risk of Hemlibra is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Hemlibra is favourable in the following indication:

Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors.

Hemlibra can be used in all age groups.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the

agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Hemlibra in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing communication and medical and patient education around the important identified risks of thromboembolic events and thrombotic microangiopathy associated with the concomitant use of emicizumab and activated prothrombin complex concentrate (aPCC), and the important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests (unreliable in patients treated with emicizumab) and provide information on how to manage them.

The MAH shall ensure that in each Member State where Hemlibra is marketed, all healthcare professionals, patients/carers who are expected to prescribe, dispense or use Hemlibra, and laboratory professionals, have access to/are provided with the following educational package:

- Physician educational material
- Patient/Carer educational material
- Laboratory professionals educational material

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient alert card

- **The guide for healthcare professionals** shall contain the following key elements:
  - Brief introduction to emicizumab (chemical class, mode of action, pharmacodynamics and indication)
  - Relevant information (e.g. seriousness, severity, frequency, time to onset, reversibility as applicable) of the following safety concerns associated with the use of Hemlibra:
    - thromboembolic events associated with the concomitant use of emicizumab and activated prothrombin complex concentrate (aPCC),
    - thrombotic microangiopathy associated with the concomitant use of emicizumab and aPCC

        - life-threatening bleeding due to misinterpretation of the standard coagulation tests (unreliable in patients treated with emicizumab)
    - Guidance on the use of bypassing agents concomitantly with emicizumab, including the following information:
        - Treatment with prophylactic bypassing agents should be discontinued the day before starting emicizumab therapy;
        - Physicians should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required while receiving emicizumab prophylaxis;
        - Emicizumab increases the patient's coagulation potential and the dose and duration of treatment with bypassing agents may require adjustment depending on the location and extent of bleeding and on the patient's clinical conditions;
        - For all coagulation agents (aPCC, rFVIIa, FVIII, etc.), consideration should be given to verifying bleeds prior to repeated dosing;
        - Use of aPCC should be avoided unless no other treatment options/alternatives are available and aPCC dosing recommendations in case aPCC is the only option.
        - Treating physicians must carefully weigh the risk of TMA and thromboembolism against the risk of bleeding when considering aPCC treatment.
    - Information on emicizumab's interference with certain laboratory coagulation tests which will affect their reliability in the emicizumab setting and warning that these tests should not be used to monitor for emicizumab activity, determine need for factor replacement dosing, or measure FVIII inhibitors.
    - Information on assays and methods not affected by emicizumab that may be used to monitor coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays;
    - Listing of laboratory tests unaffected by emicizumab;
    - Reminder that all patients receiving treatment with emicizumab should be given a Patient Alert Card and reminded to carry it at all times and show it to any healthcare professionals who may treat them and to laboratory professionals that will perform their coagulation testing;
    - Reminder to report any adverse events associated with the use of emicizumab.
- **The patient alert card** shall contain the following key messages:
    - Instructions for patients to carry the card at any time, including in conditions of emergency and to present the card at visits to doctors, hospital clinics, carers, laboratory professionals or pharmacists to inform on emicizumab treatment and risks;
    - Information on serious, life-threatening thromboembolic events or thrombotic microangiopathy events that have been observed with the concomitant use of

emicizumab with activated prothrombin complex concentrate (aPCC) in patients on emicizumab prophylaxis;

- Guidance on the use of bypassing agents concomitantly with emicizumab and on the dosing recommendations for patients requiring treatment with bypassing agents in the perioperative setting;
- Warning on emicizumab's interference with certain laboratory coagulation tests which will affect their reliability and information that single-factor assays utilising chromogenic or immuno-based methods are not affected by emicizumab and may be used to monitor coagulation parameters during treatment, with specific consideration for factor VIII chromogenic activity assays;
- Contact details of the patient's emicizumab prescriber.

The patient/carer educational material should contain:

- The package leaflet
- Guide for patients/carers

- **The guide for patients/carers** shall contain the following key messages:
  - What is emicizumab, how emicizumab has been tested, and how to use emicizumab;
  - Warning on the risks associated with the concomitant use of bypassing agents and Hemlibra and to discuss with their doctor if they are receiving activated prothrombin complex concentrate (aPCC) when being prescribed or while receiving Hemlibra;
  - Description of the signs and symptoms of the following safety concerns and reminder of the importance of immediately stopping using Hemlibra and aPCC and notifying their treating physician if symptoms occur :
    - Destruction of red blood cells (thrombotic microangiopathy)
    - Blood clots (thromboembolism)
  - Information that they should be given a Patient Alert Card and reminder to carry it at all times and to show it to any healthcare professionals who may treat them;
  - Information on emicizumab's interference with certain laboratory coagulation tests which will affect their reliability and on the importance to show the patient alert card to any healthcare professionals who may treat them and to laboratory professionals that will perform their coagulation testing;
  - Reminder to report any adverse events to their treating doctor.

The laboratory professional educational material should contain:

- The Summary of Product Characteristics
- Guide for Laboratory Professionals

- **The guide for laboratory professionals** shall contain the following key messages:
  - Chemical class, mode of action, pharmacodynamics and indication for emicizumab

- Information on emicizumab's interference with certain laboratory coagulation tests which will affect their reliability and not accurately reflect the patient's underlying haemostatic status during emicizumab prophylaxis. Warning that these tests should not be used to monitor for emicizumab activity, determine need for factor replacement dosing, or measure FVIII inhibitors;
- Information on assays and methods not affected by emicizumab and that may be used to monitor coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays;
- Listing of laboratory tests unaffected by emicizumab;
- Recommendation that the laboratory director contact the patient's treating physician to discuss any abnormal test results.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that emicizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

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