

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761083Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

BLA Multi-disciplinary Review and Evaluation

BLA 761083, Hemlibra®, emicizumab-kxwh

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Original BLA
Application Number	BLA 761083
Priority or Standard	Priority
Submit Dates	May 31, 2017: Quality, Non-clinical June 23, 2017: Clinical
Received Dates	June 23, 2017
PDUFA Goal Date	February 23, 2018 (Expedited date of November 16, 2017)
Division/Office	Division of Hematology Products Office of Hematology and Oncology Products
Review Completion Date	November 14, 2017
Established Name	Emicizumab-kxwh
Proposed Trade Name	Hemlibra®
Pharmacologic Class	Bispecific factor IXa- and factor X-directed antibody
Code name	RO5534262, CH5534262, ACE910, hBS910
Applicant	Genentech
Formulations	(b) (4) vials for subcutaneous injection: <ul style="list-style-type: none">• (b) (4) (30 mg/mL)• 60 mg/0.4 mL (150 mg/mL)• 105 mg/0.7 mL (150 mg/mL)• (b) (4) (150 mg/mL)
Dosing Regimen	3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly
Applicant Proposed Indication/Population	For routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

COA = Clinical Outcomes Assessment

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DMPP=Division of Medical Policy Programs

DRISK=Division of Risk Management

DHP DDS=Division of Hematology Products Deputy Director for Safety

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Glossary

ABR	annualized bleeding rate
ADA	anti-drug antibodies
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
BLA	biologics license application
BTD	breakthrough therapy designation
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
DHOT	Division of Hematology Oncology Toxicology
DHP	Division of Hematology Products
DIL	dear investigator letter
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDP	fibrin and fibrinogen degradation products
GCP	good clinical practice
GLP	good laboratory practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ITI	immune tolerance induction
ITT	intent to treat
IV	intravenous
K _D	disassociation constant
MAED	MedDRA Adverse Events Diagnostic
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NB	negative binomial
NDA	new drug application
NIS	non-interventional study

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NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	prothrombin time
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
TE	thromboembolism
TEAE	treatment emergent adverse event
TF	tissue factor
TMA	thrombotic microangiopathy
ttPeak	time to peak

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1 Executive Summary

1.1. Product Introduction

Trade Name:	Hemlibra®
Established Name:	Emicizumab-kxwh
Also Known As:	ACE910, RO5534262
Description:	Humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure binding factor IXa and factor X
Dosage Form:	Injection, solution
Pharmacologic Class:	Bispecific factor IXa- and factor X-directed antibody

Hemlibra (emicizumab) is a new biologic product, first-in-class bispecific antibody which bridges activated coagulation factor IXa and factor X to replace the function of missing activated factor VIII that is needed for effective hemostasis. BLA 761083 for Hemlibra was submitted for the proposed indication “for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.” The proposed dosing regimen is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of Hemlibra for the indication “for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.” The recommended dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly.

The recommendation is based on the finding of a decrease in annualized bleeding rate (ABR) with emicizumab prophylaxis compared with no prophylaxis demonstrated in Study HAVEN1. The study also included an intra-patient comparison which demonstrated a decrease in ABR for patients on emicizumab prophylaxis compared to their prior prophylaxis regimen. A single arm study, HAVEN2, showed a low occurrence of bleeds in pediatric patients, similar to the findings in adults.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors have limited treatment options for both the prevention of bleeding episodes (prophylaxis) and treatment of bleeds (on-demand or episodic treatment). The increased occurrence of bleeding events leads to increased morbidity and mortality. Emicizumab is a bispecific antibody which binds to both coagulation factor IXa and X, and mimics the activity of factor VIII. Emicizumab is being developed for the prevention and to reduce the incidence of bleeding in patients with hemophilia A with factor VIII inhibitors.

Study HAVEN1 in adult and adolescent patients with inhibitors demonstrated a significant reduction in treated bleeds between patients who received emicizumab prophylaxis compared to no prophylaxis. All patients received episodic treatment with bypassing agents as needed for bleeds. The randomized part of the trial also demonstrated a significant reduction in all bleeds, treated joint bleeds, treated spontaneous bleeds, and treated target joint bleeds. The randomized patients had an improvement in physical functioning on a hemophilia-specific measure of health-related quality of life. The study also included an intra-patient analysis for patients who were on previous prophylaxis with a bypassing agent, and demonstrated a significant reduction in treated bleeds while on emicizumab prophylaxis compared to patient's prior prophylaxis. Study HAVEN2 in pediatric patients <12 years old with inhibitors demonstrated a low rate of treated bleeds for patients treated with emicizumab prophylaxis. Across both studies, the majority of patients had no treated bleeds.

The safety profile of emicizumab is characterized through a pooled analysis of 189 patients who received at least one dose of emicizumab for prophylaxis. The major safety concern was the occurrence of thrombotic microangiopathy (TMA) and thromboembolism (TE) in patients who receive >100 units/kg/24 hours for more than 24 hours while on emicizumab prophylaxis. The risks of TMA and TE are mitigated by recommendations to avoid aPCC treatment or use the lowest possible dose. Signs and symptoms of TMA and TE are described for prescribers, patients, and caregivers in the prescribing information and medication guide.

Emicizumab represents an additional treatment option for patients with hemophilia A with FVIII inhibitors to prevent or decrease the frequency of bleeding episodes. Emicizumab has a novel mechanism of action that mimics the action of FVIII but can function even in the presence of FVIII inhibitors. The efficacy is robust in both pediatric and adult patients with hemophilia A with inhibitors. The safety is acceptable with rigorous

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management of the risk of TMA and TE which are addressed through appropriate labeling. Emicizumab is an important addition to the treatment armamentarium for prophylaxis of bleeds in patients with hemophilia A with FVIII inhibitors.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none">Hemophilia A occurs in approximately 1 in 5000 males, and 30-35% of patients with hemophilia A will develop inhibitors to factor VIIIPatients with factor VIII inhibitors have more frequent and difficult to treat bleeds which leads to an increase in joint destruction, life-threatening bleeds, and mortality	Hemophilia A with factor VIII inhibitors is rare and serious, and can be life-threatening. The disease affects all pediatric and adult age groups, though inhibitor formation is rare in very young children.
Current Treatment Options	<ul style="list-style-type: none">Patients with factor VIII inhibitors must rely on bypassing agents for prophylaxis or treatment of bleeding episodesFDA-approved therapy for the prophylaxis of bleeds in patients with inhibitors is aPCCNon-FDA-approved therapy also used in this setting is rFVIIa.	The effectiveness of available therapies for prophylaxis of bleeds is variable. There is a need for more effective therapy.
Benefit	<ul style="list-style-type: none">In Study HAVEN1, 53 patients aged 12 years and older who were on prior episodic treatment were randomized 2:1 to emicizumab prophylaxis or no prophylaxis for 24 weeks. The ABR for treated bleeds on emicizumab was 2.9 compared to 23.3 with no prophylaxis.In HAVEN1, patients who were on prior prophylaxis with bypassing agents had bleeding rate on prior prophylaxis compared with emicizumab prophylaxis. The ABR for treated bleeds on prior prophylaxis was 15.7, and on emicizumab prophylaxis was 3.3.In HAVEN2, pediatric patients <12 years old were treated with emicizumab prophylaxis. The ABR for treated bleeds was 0.2 with 87% of patients having zero treated bleeds.	Both HAVEN1 and HAVEN2 provide substantial evidence of effectiveness for emicizumab as prophylaxis in patients with hemophilia A with FVIII inhibitors.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	<ul style="list-style-type: none">In a pooled safety analysis of 189 patients, the most common adverse reactions ($\geq 5\%$) were injection site reactions, headache, arthralgia, pyrexia, diarrhea, and myalgia.Three patients who received aPCC as a bypassing agent to treat an acute bleed while on emicizumab prophylaxis developed thrombotic microangiopathy.Two patients who received aPCC while on emicizumab prophylaxis developed thrombotic events.	Labeling includes a boxed warning for the risk of thrombotic microangiopathy and thrombotic events. Patients should avoid aPCC, if possible. If patients require aPCC treatment, then the lowest possible dose should be used. Information is provided to prescribers, patients, and caregivers regarding the signs and symptoms of thrombotic microangiopathy and thrombotic events in the Prescribing Information and Medication Guide.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
	<input checked="" type="checkbox"/> Patient reported outcome (PRO)	Section 8.1.1 Study endpoints Section 8.1.2 Study results
	<input checked="" type="checkbox"/> Observer reported outcome (ObsRO)	Section 8.1.3 Study endpoints Section 8.1.4 Study results
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input checked="" type="checkbox"/> Observational survey studies designed to capture patient experience data	Section 8.1.2 Study results
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that was not submitted in the application, but was considered in this review.	

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APPEARS THIS WAY ON ORIGINAL

X

X

Lori Ehrlich, MD, PhD
Primary Clinical Reviewer

R. Angelo de Claro, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Hemophilia A is an X-linked bleeding disorder characterized by the congenital deficiency or absence of factor VIII (FVIII). Hemophilia A occurs in 1 in 5000 live male births without ethnic predominance which results in an incidence in the US of about 20,000 people and 400,000 people worldwide (Soucie, Evatt et al. 1998).

The absence of functional FVIII interrupts the coagulation cascade and the ability to form a stable clot in response to trauma. The resulting bleeding complications can be severe and life-threatening and can lead to long-term morbidity from joint damage due to recurrent bleeds. The standard of care in patients with hemophilia A is treatment with recombinant or plasma-derived FVIII concentrates. Treatment can either be in response to a bleeding event (episodic or “on demand” treatment) or scheduled treatment to prevent bleeds (prophylactic treatment). In resource-rich countries, prophylactic treatment initiated prior to any joint bleeds is preferred. In 30-35% of patients with Hemophilia A, a neutralizing antibody, known as a FVIII inhibitor, forms which renders exogenous and endogenous FVIII nonfunctional. Patients with FVIII inhibitors are more difficult to treat in response to bleeding events leading to a higher rate of progressive joint disease from frequent joint bleeds and an increased risk of death from uncontrolled bleeding.

2.2. Analysis of Current Treatment Options

The current standard of care available for Hemophilia A is FVIII replacement with recombinant or plasma-derived factor products. Patients with inhibitors cannot be treated with FVIII replacement as the inhibitor would clear the exogenous FVIII and likely increase the inhibitor titer. To clear the FVIII inhibitor, patients may undergo immune tolerance induction (ITI). ITI involves frequent administrations of high dose FVIII to eliminate the antibody over time and allow patients to resume their prophylactic treatment with FVIII. While this is successful in some patients, there is a failure rate of 20-40%, and those patients who have a resurgence of their antibody after ITI tend to be even more refractory to treatment. It is also a heavy burden for patients both in effort and cost from daily high dose factor VIII infusions.

The available treatments in patients with FVIII inhibitors are episodic treatment with a bypassing agent which bypasses FVIII in the coagulation cascade, often during ITI. Unfortunately, the efficacies of these agents are unstable compared to FVIII infusions for patients without inhibitors. There are two bypassing agents available (see Table 1), NovoSeven® and FEIBA®, and both available agents have product-specific characteristics that limit their usability. NovoSeven is a recombinant activated factor VII (rFVIIa) product which has a short half-life and requires IV

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treatment every 2-3 hours. FEIBA, or Factor Eight Inhibitor Bypassing Activity, is a plasma-derived activated prothrombin complex concentrate (aPCC) which is predominately prothrombin and Factor X, but also contains lesser amounts of Factors VII and IX. This product requires a long infusion time which can be limiting for its use. It also contains small amounts of FVIII, so could augment inhibitor formation in patients not currently undergoing ITI.

Patients with FVIII inhibitors can also receive prophylactic treatment with a bypassing agent. FEIBA was approved in 2013 for this indication. The primary efficacy outcome for the registration trial was annualized bleeding rate (ABR) which is the rate of bleeds normalized to one year. Patients on FEIBA prophylaxis had a median ABR of 8 compared to 29 for patients receiving episodic treatment with FEIBA. Prophylactic treatment is costly and burdensome given the need for every other day IV infusions of FEIBA. NovoSeven is not approved for this indication and therefore the dosing regimens used are not standardized and with variable rates of efficacy.

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Table 1: Summary of Available Treatments for Prophylaxis in Patients with Hemophilia A with FVIII Inhibitors

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
FEIBA® (activated prothrombin complex concentrate, aPCC)	For use in hemophilia A and B patients with inhibitors for: <ul style="list-style-type: none">• Control and prevention of bleeding episodes• Perioperative management• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.	1979	<ul style="list-style-type: none">• Control of bleeding episodes: 50-100 U/kg, frequency by type of bleed• Routine prophylaxis, 85 U/kg, every other day	On demand, median ABR 28.7 Prophylaxis, median ABR 7.9 72% reduction	Boxed warning for thromboembolic events Other serious adverse reactions, hypersensitivity	Given via IV infusion not to exceed 2 U/kg/min, therefore each infusion for prophylaxis is approx. 45 minutes
Other Treatments						
NovoSeven® (recombinant factor VIIa, rFVIIa)	<ul style="list-style-type: none">• Treatment of bleeding episodes in hemophilia A or B with inhibitors and in acquired hemophilia• Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B with inhibitors and in acquired hemophilia	1999	<ul style="list-style-type: none">• Bleeding episodes: 90 mcg/kg, every 2 hours until hemostasis is achieved• Routine prophylaxis: No standard dosing	Published information of prophylaxis report 2-3 bleeds per month (Konkle, Ebbesen et al. 2007)	Boxed warning for thrombotic events	Due to the short half-life, the utility of rFVIIa for routine prophylaxis is limited.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Emicizumab is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The key US presubmission regulatory activities for this submission are as follows:

- 7/30/2013: Pre-IND meeting held with Chugai Pharma and CBER, to discuss the plan to initiate the phase 1b study in the US; this study was ultimately completed in Japan without enrolling in the US.
- 1/10/2014: Orphan designation granted to emicizumab for treatment of hemophilia A, transferred from Chugai to Genentech on 10/31/2014.
- Q2/2014: Chugai licensed the development of RO5534262 for some regions, including the US, to Roche/Genentech
- 7/23/2014 and 5/5/2015: Pre-IND meeting held with Genentech and CDER/DHP to discuss the results of the phase 1b trial and plans for a phase 3 trial
- 8/7/2015: IND 122954 opened with Study BH29884 (phase 3), breakthrough therapy designation request was submitted at the time of the IND filing
- 9/2/2015: BTD granted for patients with hemophilia A with FVIII inhibitors
- 11/16/2015: Pre-phase 3 meeting to discuss the planned study BH29992 for pediatric patients
- 4/1/2016: Type C, written responses only, to discuss study for every 4-week dosing
- 8/29/2016: Type C meeting to discuss content and format of planned BLA, rolling review granted under BTD
- 10/17/2016 and 10/18/2016: Dear investigator letter issued by Sponsor to notify investigators of events of thrombotic microangiopathy and thrombotic events seen in Study BH29884 with risk mitigation strategies
- 11/29/2016: Type C, written responses only to discuss inclusion of intra-patient comparisons
- 1/6/2017: Expanded access protocol submitted
- 3/21/2017: Pre-BLA meeting to discuss the topline results of the pivotal studies
- 5/31/2017: Initial BLA rolling submission with all of Modules 3 and 4 and portions of Modules 1 and 2, primarily non-clinical and CMC
- 6/23/2017: BLA submission completed with the remaining content of Modules 1 and 2 and the clinical data in Module 2 and 5

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

For the emicizumab clinical program, two clinical sites were selected for inspection. Site 289318/291688 (Guy Young, Children's Hospital Los Angeles, Los Angeles, CA) was the highest enrolling US site for pediatric patients, enrolling 7 patients in BH29884 and 2 patients in BH29992. Site 287909 (Christine Kempton, Winship Cancer Institute, Atlanta, GA) was the highest enrolling US site for adult patients, enrolling 4 patients in BH29884. The Sponsor (Genentech) was also investigated.

The preliminary regulatory classification for Drs. Young and Kempton is No Action Indicated (NAI). The preliminary regulatory classification for the inspection of Genentech is No Action Indicated (NAI).

4.2. Product Quality

The drug substance is a recombinant humanized monoclonal modified IgG4 bispecific antibody produced in Chinese hamster ovary cells. The process used in the Phase 1 trial was G1, and the process used in the pivotal studies and planned for commercial material is G2.1. Comparability was demonstrated and confirmed by the CMC reviewer.

The to-be-marketed emicizumab drug product will be provided as [REDACTED] (b) (4) vials for subcutaneous injection in the following vial sizes and concentrations:

- [REDACTED] (b) (4) (30 mg/mL)
- 60 mg/0.4 mL (150 mg/mL)
- 105 mg/0.7 mL (150 mg/mL)
- [REDACTED] (b) (4) (150 mg/mL)

Excipients are L-histidine, L-aspartic acid, L-arginine, poloxamer 188, and [REDACTED] (b) (4)

The drug substance and drug product manufacturing sites were inspected. There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections.

Novel excipients: No

Any impurity of concern: No

4.3. Clinical Microbiology

The emicizumab drug product is presented in [REDACTED] (b) (4) vials without preservatives. The microbiological quality and sterility are controlled and assessed by various measures outlined by the Applicant. The measures were determined to be adequate.

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4.4. Devices and Companion Diagnostic Issues

There are no companion diagnostic devices required for the proposed use of Hemlibra.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

HEMLIBRA (emicizumab) is being developed for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A. Emicizumab is a IgG4 bispecific antibody that binds to activated human coagulation factor IX (hFIXa) and factor X (hFX) and forms a molecular bridge that mimics activated factor VIII (FVIIIa), and can restore the function of missing FVIIIa. Because emicizumab does not share any sequence homology with FVIII, hemostasis may be restored in the presence of FVIII inhibitors. The antibody has little to no potential to induce complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC). The established pharmacological class of “bispecific factor IXa- and factor X-directed antibody” is both scientifically valid and clinically meaningful. The pharmacology and toxicology studies reviewed include: mechanism of action, cytokine release, Fc receptor binding, in vivo pharmacodynamics, pharmacokinetics, and general toxicology.

Emicizumab was shown to bind in a concentration-dependent manner to hFIX and hFX, in addition to their activated forms, hFIXa and hFXa. Upon binding its targets, emicizumab enhances the activation of hFX by hFIXa, and restores downstream hemostatic function at the site of bleeding in hemophilia A patients, irrespective of the presence of FVIII inhibitors. Emicizumab was shown to bind similarly to the corresponding cynomolgus monkey coagulation factors, as such the cynomolgus monkey is a pharmacologically relevant species.

The hemostatic effects of emicizumab were characterized in vitro in hFVIII-deficient plasma from patients with hemophilia and in cyFVIII-neutralized cynomolgus monkey plasma. Several in vitro cofactor reconstitution experiments were conducted to determine which coagulation pathway (intrinsic or extrinsic) was responsive to the effects of emicizumab. Emicizumab's activity was mainly associated with the intrinsic coagulation cascade and relatively ineffective in promoting coagulation through the extrinsic pathway.

In in vitro combination pharmacology studies using emicizumab and recombinant factor VIIa or activated prothrombin complex concentrate (aPCC), thrombin generation was greatest with the emicizumab-aPCC combination. This nonclinical data supports the association of thrombotic microangiopathy (TMA) and thromboembolism (TE) findings in patients receiving aPCC and HEMLIBRA.

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The Applicant also conducted *in vivo* characterization of emicizumab-induced hemostasis in cynomolgus monkey models of acute and chronic hemophilia A. In the acute model, single doses of emicizumab by the subcutaneous (SC) route of administration at doses of 0.3 to 200 mg/kg or intravenous (IV) route at doses of 0.3 to 3 mg/kg prevented a decrease in hemoglobin level and significantly reduced the bruising area on the skin surface. Activated prothrombin time (aPTT) was increased in the acute model and was dose-dependently normalized by emicizumab. In the chronic hemophilia model in cynomolgus monkeys, a single SC dose of 3.97 mg/kg followed by 1 mg/kg/week SC for 8 weeks prevented intra-articular bleeding and other bleeding symptoms characteristic of hemophilia A. Overall, in cynomolgus monkeys, emicizumab was associated with shortening of activated prothrombin time (aPTT), promotion of thrombin generation, reduction of bleeding episodes (in the chronic hemophilia model) and mitigation of adverse events associated with bleeding induced by trauma. Emicizumab had no effect on prothrombin time (PT) in these studies.

Emicizumab was generally well tolerated in a 26-week toxicology study conducted in cynomolgus monkeys administered weekly SC doses of emicizumab at 1, 6, and 30 mg/kg. Notable findings in this study were those associated with the exaggerated pharmacology of emicizumab, and included lesions at the injection sites (reddish patch at subcutis, hemorrhage, white cell infiltrate, edema, in addition to some degeneration and/or necrosis) and hematological changes (increased D-dimer and fibrin degradation products (FDP)). There was no evidence of thrombi in the organs and tissues examined. The pharmacokinetics of emicizumab in monkeys was characterized by: increases in systemic exposures that were roughly proportional to increases in dose; no apparent sex differences; T_{max} of 2-5 days; and a half-life ($T_{1/2}$) of 3-4 weeks. Emicizumab was immunogenic in monkeys. Anti-drug antibodies (ADA) were identified in 9 out of 40 monkeys in the 26-week study, and 4 of those 9 developed neutralizing antibodies (NAb).

Animal reproductive and developmental toxicology studies were not conducted with emicizumab as hemophilia A is inherited in an X-linked recessive manner, thus it would be exceedingly rare for females to be prescribed this drug (99% of the hemophilia A patients are males). It is not known whether HEMLIBRA can adversely impact the development of embryo/ fetus when administered to a pregnant woman. Based on its mechanism of action, emicizumab may potentially reduce pregnancy loss associated with hemophilic bleeding; in the absence of supporting data, this information will not be included in the label. Fertility studies in animals were not conducted with emicizumab. In general toxicology studies in cynomolgus monkeys emicizumab did not cause any toxicological changes in the reproductive organs of males or females at subcutaneous doses of up to 30 mg/kg/week for 26-weeks or at intravenous doses up to 100 mg/kg/week for 4-weeks. There is no information regarding the presence of emicizumab in animal or human milk. Genotoxicity studies were not conducted as these studies are not applicable to biotechnology-derived pharmaceuticals per ICH S6. Carcinogenicity studies have not been conducted with emicizumab because the product is not active in mice or rats; restoring hemostasis is not expected to increase the potential for tumorigenesis.

The nonclinical pharmacology and toxicology data submitted to this BLA are adequate to support the approval of emicizumab for the proposed indication.

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5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

Mode of action (MOA) of emicizumab: bridging FIXa and FXa

In uncompromised hemostasis, FVIIIa forms complexes with FIXa in the presence of Ca²⁺ and phospholipid. This FVIIIa: FIXa complex then functions as a cofactor for the activation of FX. In hemophilia A, FVIII is deficient or missing, and emicizumab acts through molecular mimicry to act as a scaffold for FX activation by binding directly to activated FIXa and FX on the surface of activated platelets.

Binding affinity

Binding of emicizumab to human and cynomolgus monkey, native and activated FIX and FX, was demonstrated to be concentration-dependent (up to 640 nM) using surface plasmon resonance (SPR) technology. The table below summarizes binding characterization.

Table 2: Binding Affinity of Emicizumab to Human Coagulation Factors FIX and FX

	hFIX	hFIXa	hFX	hFXa
Emicizumab				
Dissociation constant K _D	1.6 μM	1.5 μM	1.8 μM	0.9 μM

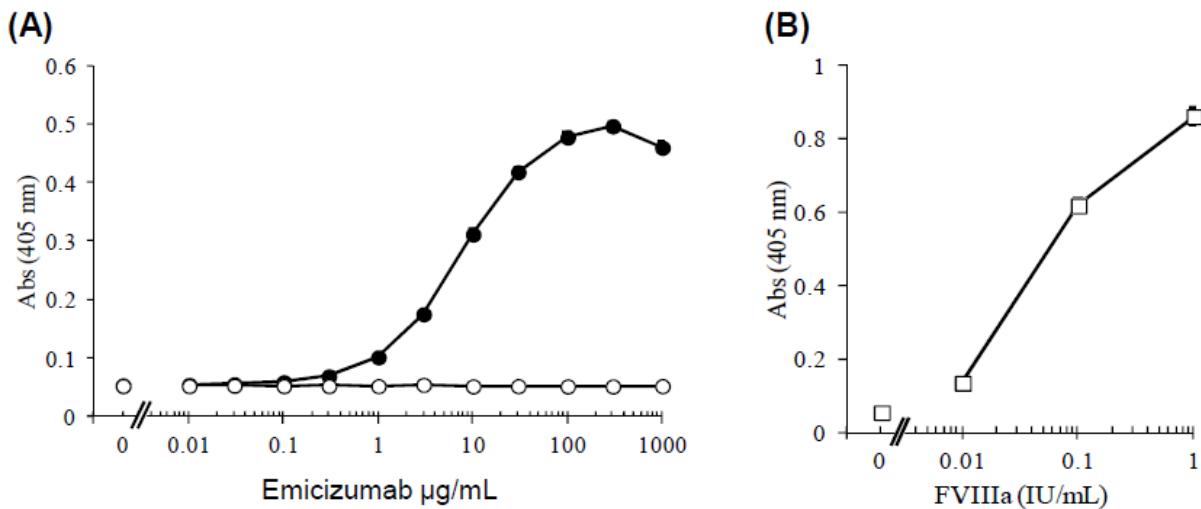
Cofactor FVIII activity of emicizumab on human and cynomolgus monkey cofactors

An enzymatic assay was utilized to assess activation of purified hFX by emicizumab and hFIXa. This study showed concentration-dependent increases in FXa when FIXa was present, but not in the absence of FIXa. A similar effect was seen when emicizumab was replaced with FVIIIa.

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Figure 1: Effect of Emicizumab on FIXa-Induced FX activation



(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 \pm 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.

Source: Figure from the Applicant

In a similar experiment using cynomolgus monkey FX (cyFX), emicizumab treatment resulted in similar effects (data not shown). In experiments using mouse or rat FIXa and FX, emicizumab treatment did not result in FX activation (data not shown).

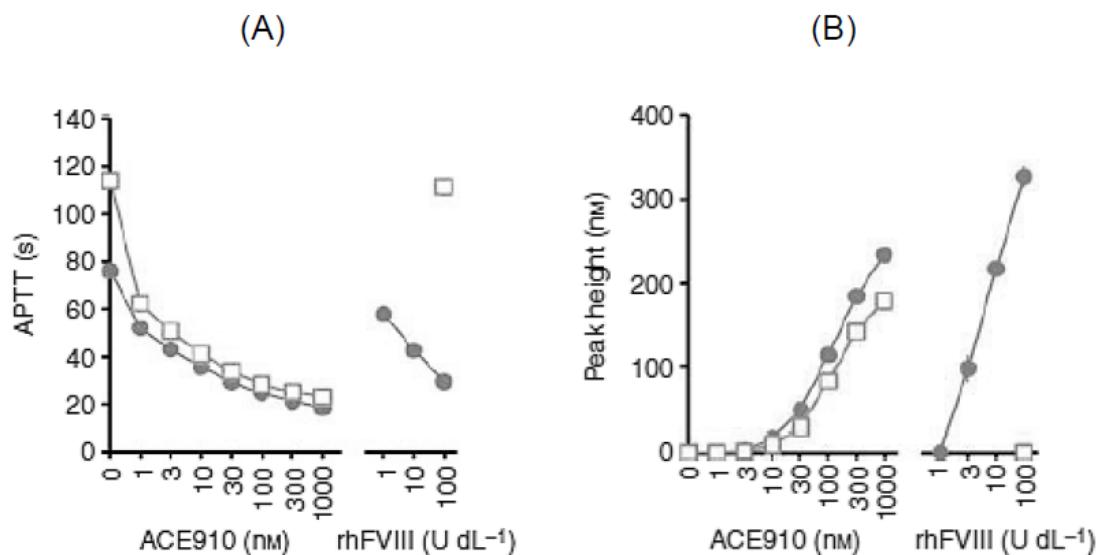
The FVIIIa-like activity of emicizumab in human hemophilia A plasma in the presence of FVIII inhibitors

The effects of emicizumab on both shortening of aPTT and on thrombin generation were found to be unaffected by FVIII inhibitors [the IgG antibodies that sometimes develop to recombinant antihemophilic FVIII (rhFVIII) therapy], as reported by Muto et al., 2014 (see Figure 2)(Muto, Yoshihashi et al. 2014). On the other hand, the procoagulant activity of rhFVIII itself was completely neutralized in the presence of FVIII inhibitors.

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Figure 2: Emicizumab Activity in Human FVIII-Deficient Plasma in the Presence and Absence of FVIII Inhibitors



Procoagulant activity of emicizumab (i.e., ACE910 in the figure) in human FVIII-deficient plasma in the presence (open squares) and absence (filled circles) of FVIII inhibitors. Human recombinant FVIII (rhFVIII) was used as a comparator. Procoagulant activity was shown by aPTT (A) and peak height of thrombin generation assay (B). Data are expressed as mean \pm SD ($n = 3$).

Source: Figure from the Applicant, based on Muto et al., 2014

Prothrombotic potential of emicizumab In vitro studies

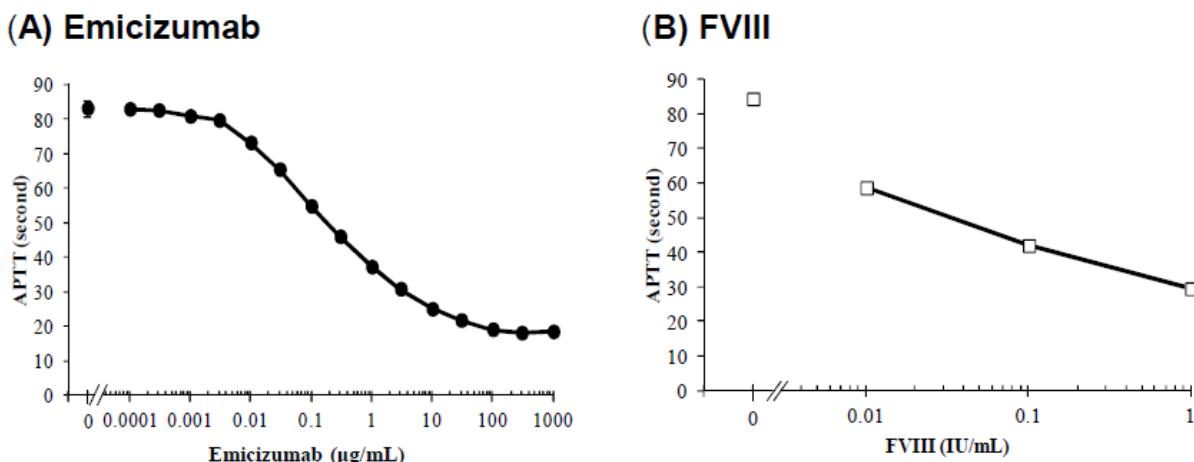
Shortening aPTT

Plasma from patients with hemophilia A have greatly reduced FVIII activity and prolonged aPTT. In an assay system using the aPTT reagent thrombocheck APTT-SLA and Ca²⁺, emicizumab was shown to reduce or normalize aPTT, in a concentration-dependent manner, similar to the way in which the positive control hFVIII shortened aPTT.

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Figure 3: Effect of Emicizumab on aPTT in FVIII-Deficient Human Plasma



A: Mean \pm SD ($n = 5$ independent experiments); B: Median values

Source: Figure from the Applicant

Thrombin generation

The effect of emicizumab on thrombin generation with FIXa as a starting reagent was determined in human plasma from a patient with hemophilia A, as well as in FVIII-deficient cynomolgus monkey plasma. The thrombin generated over time was measured in an enzymatic activity utilizing a fluorogenic thrombin substrate. The characterization included determination of lag time, peak height, time-to-the peak (ttPeak), and endogenous thrombin potential (ETP).^{1,2}

Emicizumab shortened the lag time and increased the peak height in a concentration-dependent manner. Emicizumab also shortened ttPeak and increased ETP in a concentration-dependent manner with a minimal effective concentration of 0.3 $\mu\text{g/mL}$. Under the current assay conditions, absence of thrombin generation was noted in blank plasma lacking emicizumab. In the absence of FVIII, such improvements of FIXa-induced thrombin generation with emicizumab, illustrated the cofactor FVIII activity of emicizumab.

¹ Lag time: time to the start of thrombin generation (minute); Peak height (Peak): peak free thrombin concentration (nmol/L); Time to the peak (ttPeak): time to the peak free thrombin concentration (min); Endogenous thrombin potential (ETP): overall thrombin-forming capacity of the plasma sample (nmol/L x min).

² The parameters of lag time and ttPeak assess the rate of coagulation in the initial phase and prolongation phase of coagulation, respectively, while peak height and ETP assess the maximal and total thrombin activity produced, respectively. The thrombin generation assay is considered more relevant to assess an anti- or pro-thrombotic tendency than general clotting tests.

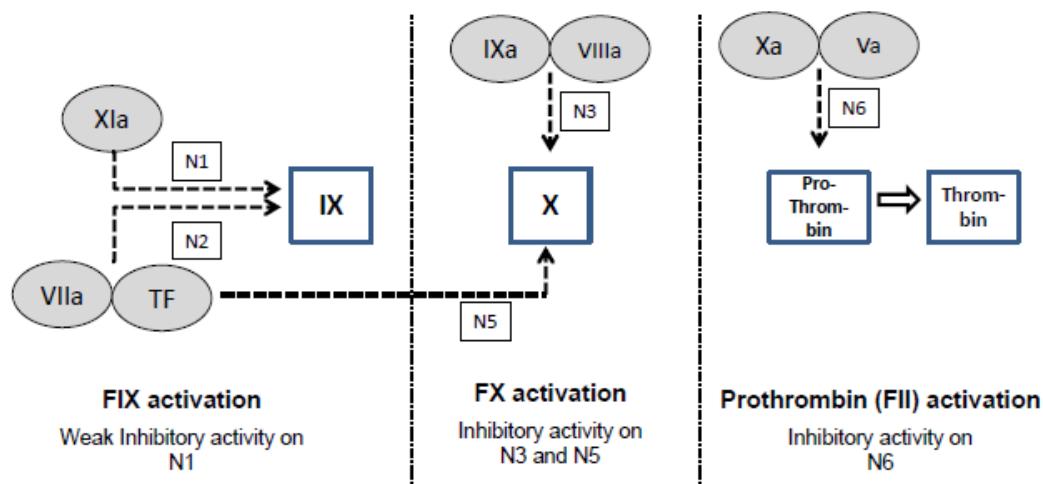
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Inhibitory potential of emicizumab on human FIX and FX-related activation reactions

The Applicant conducted a series of experiments to assess where emicizumab interfered with the networking of FIX and FX clotting factors. Emicizumab significantly inhibited activity in three FIX- and FX-dependent reaction steps (shown below): FX activation by FIXa/FVIIIa (N3 reaction), FX activation by FVIIa/TF (N5 reaction) and prothrombin activation by FXa/Va (N6 reaction). Under the *in vitro* assay conditions, emicizumab exhibited potential to inhibit FX-dependent coagulation reactions. The anticoagulant potential of emicizumab identified in this series of *in vitro* tests did not translate into an *in vivo* liability of systemic bleeding in any of the *in vivo* cynomolgus monkey pharmacology models or general toxicology studies (e.g., no major bruising or histopathological data to indicate bleeding or anticoagulation).

Figure 4: Overview of the Assay to Test the Inhibitory Potential of Emicizumab on FIX and FX-Related Activation Pathways



FII = factor II; FIX = factor IX; FX = factor X; TF = tissue factor.

An overview of the test system using the catalytic activity of isolated human clotting factors as a marker of activation (large boxes). Reagents used for activation are depicted in oval circles; their activation pathways are illustrated with dotted lines and for convenience, numbered from N1 to N6.

Source: Figure from the Applicant

In vivo studies

The *in vivo* pharmacological effects of emicizumab were assessed in cynomolgus monkey models of acute and chronic hemophilia A as described below.

- Acute hemophilia A models: FVIII deficiency was experimentally induced by a single IV injection of a FVIII-depleting mouse mAb.
- Chronic hemophilia A model: FVIII deficiency was experimentally induced via 10 mg/kg once weekly injections of a mouse:cynomolgus monkey chimeric mAb.

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Acute hemophilia A model

- Preventative treatment of emicizumab via SC administration

Escalating single SC doses of emicizumab at 0.3, 1, 3, 10, 50, or 200 mg/kg were given 4 days prior to bleeding induction (Day -4). After needle-induced bleeding (Day 0), the effect of emicizumab on bleeding-related adverse outcomes, as indicated by anemia (decreases in hemoglobin levels) and area of bruising on the skin surface of the subcutaneous bleeding site was determined. The plasma concentration of emicizumab on Day 0 was also determined.

- On demand treatment of emicizumab via IV administration

Immediately following bleeding induction (Day 0), escalating single IV doses of emicizumab at 0.3, 1, or 3 mg/kg, or recombinant porcine FVIII (rpFVIII) at 3.4 and 10 U/kg were administered. There were five administration timepoints: one time on Day 0 after induction of bleeding and twice daily on Day 1 and 2. The effect of emicizumab on reducing bleeding-related adverse outcomes was determined on Day 3.

- In both SC and IV settings, rpFVIII served as the positive control and restored hemostasis.

Results:

Needle-induced bleeding

SC administrations (Preventative treatment of emicizumab prior to bleeding)

Treatment	Results
Amelioration of the adverse effects following needle-induced bleeding	
0.3, 1, and 3 mg/kg	Emicizumab induced concentration-dependent mitigation of the effects of bleeding compared to controls. Hemoglobin levels were increased and bruising on the surface of the skin was significantly reduced at doses of 1 and 3 mg/kg.
10 and 50 mg/kg	Similar results to 1 and 3 mg/kg, with further improvements in bleeding-induced hemoglobin loss and in bruising. The effect was significant at 50 mg/kg with the final hemoglobin level close to the non-bleeding pre-test condition.
200 mg/kg	Further restoration of hemostasis from was observed: <ul style="list-style-type: none">• significantly elevated hemoglobin level (102%) compared with the control (54%).• reduced the mean area of bruising on Day 3 (6 cm² versus 208 cm² in the control group).
Bleeding time (thrombin time: PT and aPTT)	
0.3 and 1mg/kg	Dose-dependent trend for normalization of prolonged aPTT in comparison with the control
3, 10, 50, and 200 mg/kg	Complete normalization of aPTT
Plasma concentration of emicizumab	
0.3-50 mg/kg	Increased dose proportionally
50-200 mg/kg	Increased greater than dose proportionally

IV administrations

(On demand treatment of emicizumab following bleeding)

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Following bleeding induction, IV administration of emicizumab for 3 days resulted in a hemostatic effect in FVIII-deficient monkeys.

Table 3: Overview of the Assay to Test the Inhibitory Potential of Emicizumab on FIX and FX-Related Activation Pathways

Summary of Intravenous Administration of Emicizumab on Blood Hemoglobin Concentration and on Skin Surface Bruised Area on Day 3

	Number of Animals / Group	Hgb on Day 3 (% of Day 0)	Bruised Area on Day 3 (cm²)	Emicizumab Plasma Concentration* (µg/mL) ±SD *
Control	6	54±22	208±50	NA
rpFVIII 3.4 U/kg IV	4	67±11	142±79	NA
rpFVIII 10 U/kg IV	4	84±12 ^a	74±83 ^b	NA
Emicizumab 0.3 mg/kg IV	4	61±10	145±50	6.6 ± 0.6
Emicizumab 1.0 mg/kg IV	4	76±23	75±16 ^b	25.7 ± 2.5
Emicizumab 3.0 mg/kg IV	4	82±9	104±49 ^a	60.8±3.3

NA= not applicable

Mean ± SD (n = 6 in control group and n = 4 in all other groups).

* plasma concentrations determined within 7 to 17 minutes after administration of emicizumab at study Day 0.

^a: P < 0.05 vs. control group (Dunnett's multiple comparison test).^b: P < 0.01 vs. control group (Dunnett's multiple comparison test).

Source: Table from the Applicant

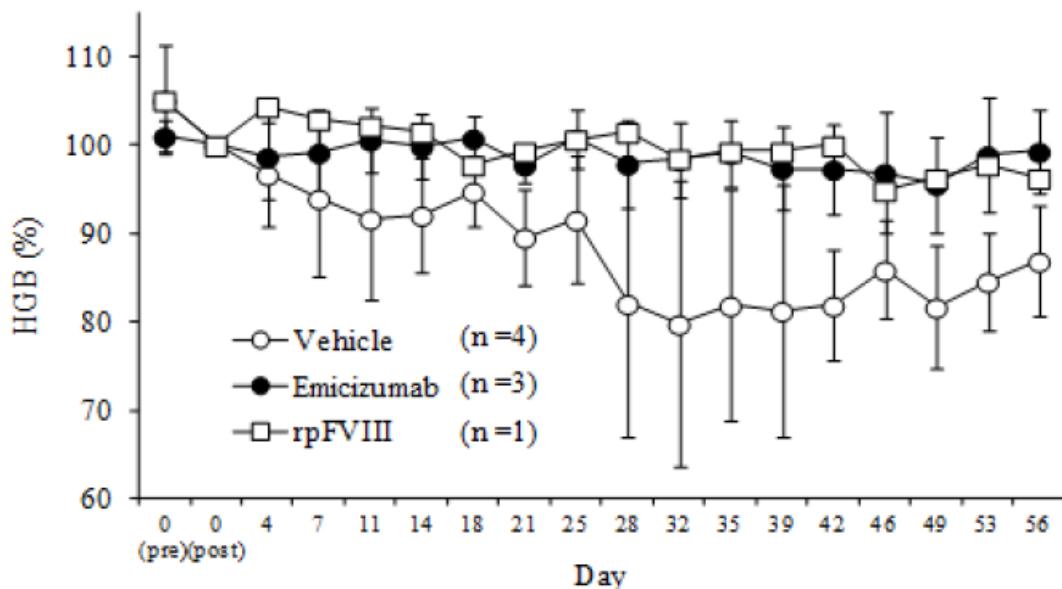
Chronic hemophilia A model**Spontaneous-bleeding model**

In a 56-day study of emicizumab in the cynomolgus monkey model of chronic hemophilia A, the endpoints of blood hemoglobin concentration, days of no bleeding symptoms, and the number of joints with intra-articular bleeding were evaluated. As shown below, treatment with emicizumab resulted in: the ability for monkeys to maintain approximately 100% of their blood hemoglobin concentrations, prolonged number of days with no bleeding symptoms (from less than 10 days to more than 30 days), and significantly decreased number of joints with intra-articular bleeding, at Day 56 necropsy. Plasma emicizumab concentrations remained stable from Day 4 to Day 56, with mean values ≥30 µg/mL (data not shown).

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Figure 5: Time Profile of Relative Blood Hemoglobin Concentration (FVIII Neutralized Hemophilia A/Spontaneous Bleeding Model)



Mean \pm SD (Vehicle group: n = 4; Emicizumab group: n = 3), rpFVIII group: n = 1. Day 0 (pre): Before administration of cyFVIII (functional) depleting antibody. Day 0 (post): Approximately 2 hours after administration of cyFVIII (functional) depleting antibody.

Source: Figure from the Applicant

Combination with FVIII and bypass agents FVII and aPCC

In vitro studies

In vitro investigations on the effects of emicizumab in combinations with FVIII and bypassing agents, rFVIIa and aPCC, revealed that thrombin generation increased with both aPCC-emicizumab and rFVIIa-emicizumab combinations. Enhanced thrombin generation was also observed in the combination with FVIII (0.01 and 0.1 U/mL), while no additional effects were observed when the FVIII concentration was increased (1 U/mL).

In vivo studies

A venous stasis model was developed to assess whether in vivo emicizumab administration would increase the risk for, or size of, thrombus formation when added-on to bypassing agents. In one experiment in normocoagulative cynomolgus monkeys, the effect of emicizumab on thrombus formation was compared with the effect of rFVIIa and FVIII treatment. In another experiment in the FVIII-depleted cynomolgus monkey model of hemophilia A, the co-administration of emicizumab and bypassing agents (rFVIIa and aPCC) on thrombus formation was investigated.

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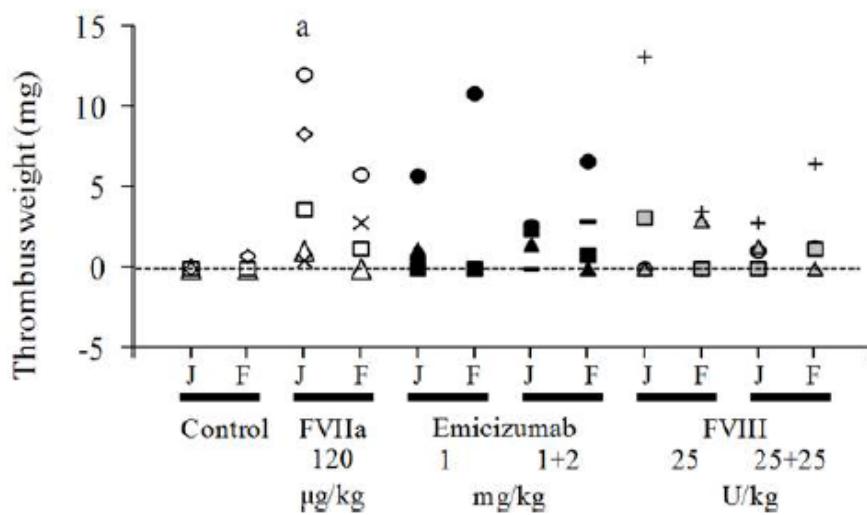
To induce stasis, veins were ligated proximally and distally, and stasis occurred between the ligatures. Left and right Jugular veins and femoral veins were used. The test substances were administered before induction of stasis. The thrombi that had formed at each stasis site were weighed at 1.5 hours after induction of stasis, and the effect of the test substances on thrombosis formation was assessed.

Venous stasis model in normocoagulative cynomolgus monkeys

Thrombus formation by emicizumab was equal to the thrombus formation induced by rFVIIa and FVIII suggesting the risk of emicizumab causing thrombosis does not markedly exceed the risk of rFVIIa or FVIII preparations causing thrombosis (see below).

In a model of venous stasis, male cynomolgus monkeys were treated with rFVII (120 µg/kg), emicizumab (1 and/or 2 mg/kg), FVIII (25 U/kg, one or two doses), or remained untreated (control). The thrombus weight was used as the measure of hemostatic effect of the agents. The following figure is the summary of the result.

Figure 6: Effect of Emicizumab on Thrombin Formation: Venous Stasis in Cynomolgus Monkey Model



F=femoral vein; J=jugular vein

n = 5 in control group (femoral vein), n = 5 in FVIIa group (jugular vein), and n = 4 in all other groups

a, b: P < 0.05 vs. control group (Wilcoxon test)

Source: Figure from the Applicant

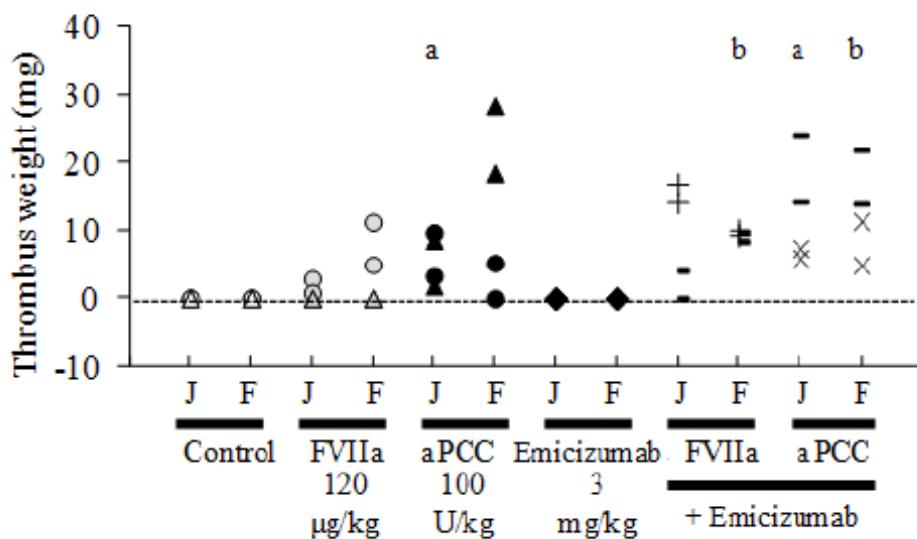
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Venous stasis model in cynomolgus monkey model of hemophilia A

- Thrombus weights increased in groups treated with the bypass agents rFVIIa or aPCC alone compared to controls.
- The sum of thrombus weights in the groups where rFVIIa or aPCC was co-administered with emicizumab increased above the levels noted in the rFVIIa and aPCC alone groups, although the individual measured thrombi did not exceed the levels observed with either bypass agent alone (see Figure 7).

Figure 7: Thrombus Weight in Emicizumab, rFVIIa and aPCC Treated Monkeys



F: Femoral vein. J: Jugular vein

Treatment: vehicle control (n = 2), rFVIIa (n = 2), aPCC (n = 2), emicizumab (n = 3), rFVIIa + emicizumab (n = 2) and aPCC + emicizumab (n = 2).

Source: Figure from the Applicant

This nonclinical data supports the association of thrombotic microangiopathy (TMA) and thromboembolism (TE) findings in patients receiving aPCC and HEMLIBRA.

Secondary Pharmacology

The Applicant conducted several studies to characterize the secondary pharmacodynamics of emicizumab. Antibody effector function was assessed by determining emicizumab binding to human and cynomolgus monkey Fc_y receptors (Fc_yRs). Binding to Fc_yRs was measured by surface plasmon resonance, and emicizumab binding was compared with other therapeutic antibodies rituximab and natalizumab. The results of the Fc_yRs analysis suggest emicizumab has a low potential to induce ADCC effector function. Antibody residence time was characterized by studying the binding activity of emicizumab to the neonatal Fc receptor (FcRn). The results suggest the FcRn recycles a certain amount of emicizumab back to the systemic circulation, which

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may increase its terminal half-life. The potential for emicizumab to have CDC activity was assessed by studying the binding of emicizumab to human complement C1q. Emicizumab and natalizumab showed a markedly weaker binding activity to C1q protein than rituximab, suggesting that emicizumab retains the low C1q binding property typical of IgG4-isotypes and is unlikely to induce CDC effector functions via the classical pathway.

Safety Pharmacology

Safety assessment of vital organs was incorporated in the toxicology studies in monkeys.

5.4. ADME/PK

Type of Study	Major Findings								
Absorption Pharmacokinetics of emicizumab in cynomolgus monkeys following a single subcutaneous dose of 0.06, 0.6 and 6 mg/kg /Study report no. 1060139	Dose (mg/kg)	Sex		AUC _{0-7d} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	AUC _{inf} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	C _{max} ($\mu\text{g}/\text{mL}$)	T _{max} (d)	t _{1/2} (d)	F (%)
	0.06	M	Mean ^a	3.55	24.6	0.602	3.00	26.5	NA
	0.6	M	Mean	28.6	189	5.10	5.00	24.7	NA
			SD	1.6	45	0.21	1.73	8.1	NA
	6	M	Mean	249	1670	45.7	5.33	23.6	102.3
			SD	17	140	5.2	2.89	3.2	NA
AUC _{0-7d} =area under the plasma concentration-time curve from 0 to 7 days; AUC _{inf} =area under the plasma concentration-time curve extrapolated to infinity; C _{max} =maximum plasma concentration; F=bioavailability; t _{1/2} =half-life; T _{max} =time to maximum plasma concentration; n=3									
^a One animal with confirmed presence of anti-RO5534262 antibodies excluded. <ul style="list-style-type: none">● Increase in exposure was dose proportional.									
26-week repeated SC dose study in monkeys /Study report no. 1060134									

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Type of Study	Major Findings											
	Dose (mg/kg)	Sex	C _{max} (µg/mL)			t _{max} (day)			AUC _{0-7d} (d·µg/mL)			
			1st dose	13th dose	26th dose	1st dose	13th dose	26th dose	1st dose	13th dose	26th dose	
1	M	Mean	10.1	44.2 ^a	52.0 ^a	3.6	1.0 ^a	2.8 ^a	58.3	280 ^a	339 ^a	
		SD	0.4	4.1	5.6	0.5	0.0	1.3	3.2	23	34	
	F	Mean	10.4	38.8 ^b	48.2 ^b	3.0	1.0 ^b	1.0 ^b	61.8	253 ^b	284 ^b	
		SD	1.0	7.0	16.4	0.0	0.0	0.0	5.8	48	78	
6	M	Mean	59.7	315 ^a	358 ^a	2.8	1.5 ^a	2.8 ^a	352	1990 ^a	2360 ^a	
		SD	12.0	43	89	1.1	1.0	1.3	62	350	650	
	F	Mean	54.4	196 ^a	262 ^a	3.2	1.5 ^a	2.3 ^a	313	1290 ^a	1670 ^a	
		SD	6.1	27	31	0.4	1.0	1.5	38	180	220	
30	M	Mean	288	1200 ^a	1340 ^a	1.8	1.0 ^a	3.3 ^a	1690	7560 ^a	8680 ^a	
		SD	40	250	240	1.1	0.0	1.5	230	1290	1540	
	F	Mean	307	1240	1370	4.2	1.8	1.6	1770	7970	8830	
		SD	34	190	310	1.6	1.1	1.3	170	1510	1910	

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

n=5/sex in each dose group; n=4 only for the 26th dose in the 6 mg/kg male group.
 Animals with confirmed ADA presence were excluded regardless of neutralizing activity:

^a One animal excluded.
^b Two animals excluded.

Immunogenicity (ADA positivity): males and females combined

	Dosing phase (n=10/group)	Recovery phase (n=4/group)	Neutralizing ADA (n=10/group)
0 mg/kg (control)	N=0	N=0	N=0
1 mg/kg (LD)	N=3	N=3*	N=3
6 mg/kg (MD)	N=2	N=1	N=1
30 mg/kg (HD)	N=1	N=1	N=0

*2 animals dosed with 1 mg/kg were ADA positive during the dosing phase.

- Product accumulation was observed upon repeated dosing.
- Increases in exposure were generally dose proportional when animals with ADA were excluded.
- ADAs were formed mostly in the dosing phase.
- ADA-positive animals had faster elimination of emicizumab and were excluded from the TK evaluation.

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5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: 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 / Study report no. 1060134

Key Study Findings:

- One male at the 6 mg/kg dose level was prematurely sacrificed with severe injection site reaction, including acute necrotizing vasculitis and chronic vasculitis accompanied by severe hemorrhagic changes, which were correlated with the clinical and necropsy findings.
- Local injection site reactions were found in several administered sites treated with the test article.
- At injection sites, subcutis reddish patch at necropsy and hemorrhage/hemosiderin deposition with mononuclear cell infiltration, neutrophil infiltration, eosinophil infiltration, perivascular mononuclear cell/plasma cell infiltration, swelling of endothelium, edema and/or degeneration/necrosis of subcutis were observed histopathologically.
- ADAs occurred in 9/40 animals; NAbs occurred in 4 of the ADA-positive animals.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 1, 6, and 30 mg/kg; once weekly for 26 weeks (27 doses)
Route of administration:	Subcutaneous
Formulation/Vehicle:	20 mmol/L histidine-aspartate buffer containing 150 mmol/L arginine-aspartate and 0.5 mg/mL poloxamer 188 (or, 0.05% w/v), pH 6.0
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	3 (main study groups); 2 (recovery groups)
Age:	4-6 years
Satellite groups/ unique design:	None / Immunogenicity (ADA) assay
Deviation from study protocol affecting interpretation of results:	No

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Observations and Results: changes from control

Parameters	Major findings						
Mortality	No treatment-related mortality. One animal at 6 mg/kg was sacrificed early (Day 149, following the 22 nd injection) for having an undetectable plasma level of emicizumab. Positive ADA identification was before the 3 rd dose of emicizumab. Plasma concentration of emicizumab was below the limit of quantitation (BLQ) by the 20 th injection.						
Clinical Signs	The one animal sacrificed early exhibited inflammation/swelling at the injection site. These findings were considered to coincide with the histopathological feature of Arthus reaction, a local immune complex disease which is classified as type III hypersensitivity.						
Body Weights	Not remarkable						
Ophthalmoscopy	Not remarkable						
ECG	Not remarkable						
Hematology: % change from control	Males						
		Day 141			Day 183		
	Dose (mg/kg/day)	1	6	30	1	6	
	Eosinophil	-28	+70	-56	-48	-48	
	FDP	+7	+40	+17	+23	+13	
	D Dimer	+88	+369	+291	+284	+260	
	Nucleated Cell count (bone marrow)	0	0	0	+16	-8	
						-3	
	Bolted numbers indicate statistically significant changes.						
	Females						
		Day 141			Day 183		
	Dose (mg/kg/day)	1	6	30	1	6	
	Eosinophil	+59	-27	-27	+40	+10	
	FDP	-6	0	-4	-2	+2	
	D Dimer	+9	-19	+89	+30	-7	
						+38	
	Findings resolved at the end of recovery period.						
	Clinical Chemistry	Not remarkable					
	Urinalysis	Not remarkable					
	Gross Pathology	Not remarkable					
	Organ Weights	Not remarkable					
Histopathology	Findings were mainly at injection sites, with no apparent dose relationship or sex differences. Findings were noted at the end of treatment and recovery periods, although some reversibility of the lesions was noted in the recovery animals. These findings at injection sites are listed as follows, and wherever applicable the corresponding gross pathological findings are also included.						
Adequate battery: Yes	<ul style="list-style-type: none"> • Subcutis reddish patch: Hemorrhage/hemosiderin deposition (slight to moderate); mononuclear cell infiltration, neutrophil infiltration, eosinophil infiltration, swelling of endothelium, edema, and/or degeneration/necrosis. 						

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	<ul style="list-style-type: none">• Also, minimal mononuclear cell infiltration, swelling of endothelium and/or edema were found in some animals wherein no corresponding gross findings were noticed.• Perivascular mononuclear cell/plasma cell infiltration (slight); findings in some of these animals were also accompanied by minimal mononuclear cell infiltration and/or eosinophil infiltration. <p>There were no remarkable findings in the other organs and tissues examined. There was no embolism, thrombi, or hemorrhage observed in other organs or tissues.</p> <p>Lipoid hyperplasia of the fascicular zone of the adrenal gland was noted in one high dose male. In this animal, other findings were seen in: bone marrow (decreased cellularity), bone (a decrease of trabecular bone) and minimal to slight immaturity of male reproductive organs (e.g. immaturity of testes, prostate gland and seminal vesicle). The relationship to emicizumab administration is unclear.</p>
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Repeat-Dose Toxicity; additional studies

Repeat-dose toxicity was also evaluated in cynomolgus monkeys dosed once weekly in a 4-week IV dose toxicity study (1060140) and 4- and 13-week SC dose toxicity studies (1060133 and 1060134). Shortening of aPTT was observed in all emicizumab-treated groups and was attributed to the pharmacology of emicizumab. No other systemic toxicological changes attributable to IV or SC emicizumab were observed. In the 4-week IV toxicity study there was one case (100 mg/kg/week group) of spontaneous polyarteritis.

5.5.2. Genetic Toxicology

Genotoxicity studies were not conducted as these types of studies are not applicable to biotechnology-derived pharmaceuticals (per ICH S6).

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5.5.3. Carcinogenicity

Carcinogenicity studies were not conducted due to lack of a pharmacologically relevant rodent species.

5.5.4. Reproductive and Developmental Toxicology

Animal reproductive and developmental toxicology studies were not conducted with emicizumab as hemophilia A is inherited in an X-linked recessive manner. Males represent 99% of the patients with hemophilia A, thus it would be exceedingly rare for females to be prescribed this drug. It is not known whether HEMLIBRA can cause fetal harm when administered to a pregnant woman or affects reproductive capacity. Fertility studies in animals were not conducted with emicizumab. In general toxicology studies in cynomolgus monkeys emicizumab did not cause any toxicologically significant changes in the reproductive organs of males or females at SC doses of up to 30 mg/kg/week for 26-weeks, or at IV doses up to 100 mg/kg/week for 4-weeks. There is no information regarding the presence of emicizumab in animal or human milk.

5.5.5. Other Toxicology Studies

Tissue cross-reactivity study with normal human tissues /Study report no. 1060174

The tissue cross-reactivity of emicizumab was evaluated in a panel of human tissue cryosections at two concentrations (10 and 50 µg/mL). Staining was observed in hepatocytes and Kupffer cells (potential sites of FIX and FX synthesis). Additionally, staining was observed in adrenal tissue (cortical cells of the zona reticularis), thyroid tissue (follicular epithelial cells), and bone marrow (bone marrow cells). Most of this staining was cytoplasmic in nature and is not a toxicological concern, because it is unlikely that emicizumab will cross cell membranes or interact directly with components of the cytoplasm.

In vitro cytokine release assay /Study report no. 1060175

Peripheral blood from 10 healthy human volunteers was mixed with emicizumab (0.1 to 100 µg/mL) and incubated for 24 hours. Positive and negative control antibodies were included in the experiment. The cytokine assessment included measurement of interleukins (IL) IL-8, IL-6, and tumor necrosis factor- α (TNF- α). The results of the assay indicated emicizumab has a low risk for eliciting cytokine release.

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Shwu-Luan Lee, PhD
Primary Reviewer

Christopher Sheth, PhD
Team Leader

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6 Clinical Pharmacology

6.1 Executive Summary

The applicant seeks approval of emicizumab for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in pediatric and adult patients with hemophilia A with factor VIII (FVIII) inhibitors. The proposed dose is 3 mg/kg by subcutaneous (SC) injection once weekly for the first 4 weeks, followed by a dose of 1.5 mg/kg by SC injection once weekly. The efficacy and safety of emicizumab in the proposed patient population was supported by two trials, trial BH29884 in adult and adolescent patients and trial BH29992 in pediatric patients younger than 12 years old. Additional safety data was provided from trial ACE001JP/ACE002JP, a dose finding trial conducted in adults and adolescents.

The proposed dose for the treatment of pediatric and adult patients with hemophilia A with FVIII inhibitors is approvable. The dose was selected using available data from the dose finding trial (ACE001JP/ACE002JP) to conduct a quantitative characterization of the exposure-response (ER) relationship of emicizumab; the results of this analysis suggested that a median annualized bleeding rate (ABR) of 0 would be achieved at emicizumab steady state trough plasma concentration ($C_{ss, \text{trough}}$) ≥ 45 mcg/mL. In the safety and efficacy trials (BH29884 and BH29992), the mean ($\pm SD$) $C_{ss, \text{trough}}$ was 52.2 ± 13.5 mcg/mL following injection of the loading dose (3 mg/kg/week) for 4 weeks and maintenance dose (1.5 mg/kg/week). The results of the ER analysis using data from these safety and efficacy trials confirmed a positive relationship trend between emicizumab exposure and the absolute ABR and the probability for achieving an ABR of 0. No evident relationship between emicizumab exposure and safety endpoints, including injection site reaction (ISR) and thrombotic microangiopathy (TMA) or thromboembolic events (TE), was identified. A weight-based dose is supported by the positive correlation between body weight and the apparent clearance and volume of distribution. These data collectively support the proposed dosing regimen.

Only 2.8% of patient developed anti-emicizumab antibodies, but the immunogenicity assay was not sensitive to detect anti-emicizumab antibodies at the observed $C_{ss, \text{trough}}$. A post marketing commitment (PMC) will be issued to request characterization of the incidence of anti-emicizumab antibodies and their effect on safety, efficacy and PK following the development of adequately validated assays for binding and neutralizing antibodies.

Recommendations

The Office of Clinical Pharmacology recommends approval of the BLA761083 from a clinical pharmacology perspective, if the applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language. The review focuses on the clinical pharmacology aspects mentioned above.

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6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Emicizumab is a monoclonal antibody that bridges activated factor IX and factor X to restore the function for effective hemostasis in presence of missing activated FVIII.

Emicizumab exhibited dose-proportional PK over a dose range of 0.3 mg/kg/week to 3 mg/kg/week following SC administration. Following multiple doses, the mean (\pm SD) trough plasma concentrations of emicizumab was $52.8 \pm 13.5 \mu\text{g/mL}$. See section 19.4.2 for additional details.

Absorption

Following SC administration, the mean (\pm SD) absorption half-life was 1.7 ± 0.9 days.

The absolute bioavailability following SC administration of 1 mg/kg was between 80.4% and 93.1%. Similar PK profiles were observed following SC administration in the abdomen, upper arm, and thigh.

Distribution

The mean apparent volume of distribution was 11.4 L [95% confidence interval (CI) (10.6, 12.1)].

Elimination

The mean apparent clearance (95% CI) was 0.24 L/day (0.22, 0.26) and the mean elimination apparent elimination half-life (\pm SD) was 27.8 ± 8.1 days.

Specific Populations

Body weight (14.2 to 131 kg) is positively correlated to apparent clearance and volume of distribution. Age (3 to 75 years), race (White 54%, Black 8.5% and Asian 30.5%), inhibitor status (inhibitor present, 92%), mild hepatic impairment [defined as total bilirubin 1x to < 1.5x the upper limit of normal (ULN) and any aspartate transaminase (AST) level] or moderate hepatic impairment (defined as total bilirubin 1.5x to ≥ 3 x ULN and any AST level) have no clinically meaningful effect on emicizumab PK.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose is 3 mg/kg by SC injection once weekly for the first 4 weeks, followed by 1.5 mg/kg by SC injection once weekly. The dose was selected based on the results of an ER analysis conducted using data from adolescents and adults (trial ACE001JP) which suggested that a median ABR of 0 would be achieved at a Css,trough $\geq 45 \mu\text{g/mL}$. The same dose was evaluated in pediatrics ≤ 12 years, because the same disease process and mechanism of action is expected for pediatrics as compared to adults.

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The proposed dose is acceptable from clinical pharmacology. A Css,trough above 50 mcg/mL was achieved following injection of the loading dose (3 mg/kg/week) for 4 weeks; the mean (\pm SD) Css,trough was 52.2 ± 13.5 mcg/mL in the efficacy and safety trials. The ER analysis for safety and efficacy using data from the safety and efficacy trials further supports the dose; a positive relationship trend between emicizumab exposure and absolute ABR and the probability for achieving an ABR of 0 and no evident relationship between emicizumab exposure and key adverse events was observed. Furthermore, the Css,trough in pediatrics 3 years to 12 years is similar to the Css,trough in adolescent and adult patients. Subsequently, the PK data for two children (~1-year-old) was submitted as part of the 90-day safety update. The treatment duration for these children were 2 weeks and 5 weeks. One child < 2 years old had a Css,trough of 51.8 mcg/mL at week 5 suggesting that the dose is acceptable for pediatrics < 2 years old. Collectively, the available data supports the proposed dose in pediatrics and adults.

Therapeutic Individualization

The applicant proposed dosing based on body weight. The results of the population PK analysis support weight-based dosing, as body weight is positively correlated to apparent clearance and volume of distribution. No dose individualization is recommended based on age, race, mild and moderate hepatic impairment, and inhibitor status.

No drug interactions are anticipated with emicizumab, as it is a monoclonal antibody (mAb).

Outstanding Issues

No outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Emicizumab is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure. Emicizumab bridges activated factor IX (FIXa) and FX to restore the function of missing activated FVIII that is needed for effective hemostasis. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII.

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General Information	
Bioanalysis	<p>The validated bioanalytical method is acceptable to measure emicizumab plasma concentrations in samples collected from trial BH29884 and trial BH29992. Emicizumab concentrations were analyzed using a validated ELISA. The lower and upper limits of quantification were 100 ng/mL and 6400 ng/mL, respectively. The precision and accuracy of the assay ranged from 9.5% to 13.3% (precision) and from 97.6% to 103.2% (accuracy). Long-term storage stability at the relevant storage conditions was demonstrated. Refer to section 19.4.1 for additional detail.</p> <p>A bioanalytical report for anti-emicizumab antibody determination was submitted. The immunogenicity assay was inadequately developed and PMCs will be issued to develop new assays.</p>
PK Model	A one-compartment model with first-order absorption and first-order elimination adequately described emicizumab's concentration-time data. The model is considered acceptable based on model evaluation criteria, including goodness-of-fit plots, visual predictive check, and plausibility of model parameters.
Drug Exposure at Steady State	Steady state was achieved around week 5 in both adult and pediatric patients. The mean $C_{ss, \text{trough}}$ at steady state was 52.8 ± 13.5 mcg/mL in pediatrics (> 3 years of age) and adults. The mean $C_{ss, \text{trough}}$ was 53.6 ug/mL in children (≥ 1 year of age) as provided in the 90-day safety update.
Dose Linearity	Emicizumab exhibits linear PK at dose range of 0.3 mg/kg/wk to 3 mg/kg/wk.
Body Weight	Body weight was positively correlated with apparent clearance (CL/F) and apparent volume of distribution (V/F) with a power of 1.02 and 0.96 for CL/F and V/F, respectively.
Renal or Hepatic Impairment	No dose adjustment is recommended for patients with mild and moderate hepatic impairment as defined by the NCI ODWG. The effect of renal impairment on emicizumab PK or safety was not investigated, as all patients enrolled in trial BH29884 and trial BH29992 had $\text{ClCr} > 86$ mL/min.
ADME	
Absorption	Emicizumab was administered as a SC injection. Absolute bioavailability was 80% to 93% with injection sites in abdomen, upper arm and thigh.
Distribution	The estimated mean (95% CI) apparent volume of distribution of emicizumab was 11.4 L (10.6, 12.1).
Elimination	The estimated mean apparent clearance (95% CI) at steady state was 0.24 L/day (0.22, 0.26). As emicizumab is a mAb, it is expected to be metabolized into peptides and amino acids via catabolic pathway. The estimated mean (SD) terminal elimination half-life is 27.8 ± 8.1 days.

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Immunogenicity	
Incidence	The percentage of evaluable patients who tested positive for anti-emicizumab antibodies was 2.8% (4 of 141). No patients in trial BH29884 and trial BH29992 tested positive for anti-product antibodies (APA); however, the PK profiles of two patients suggest the presence of the anti-emicizumab antibodies. Neutralizing antibodies were not evaluated. Since the binding assay has limited sensitivity in the presence of the observed Css,trough, a PMC will be issued to reevaluate the incidence of anti-emicizumab antibodies following the development of new validated assays for binding and neutralizing antibodies.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The available clinical pharmacology information supports the proposed dose for the treatment of pediatric and adult patients with hemophilia A with FVIII inhibitors. The applicant selected the dose based on PK, safety and efficacy data from the dosing finding trial ACE001JP (18 Japanese adolescents and adults). The applicant supported the selected dose based on the following observations:

- Substantial reduction in bleeding events with a dose 0.3 mg/kg/week to 3 mg/kg/week;
- Css,trough \geq 45 ug/mL provided a median ABR = 0 based on results of an ER analysis;
- This Css,trough can be reached rapidly with a dose of 3 mg/kg/week for 4 weeks followed by 1.5 mg/kg/week based on modeling and simulation;
- This dose should provide similar activity and safety in children as compared to adolescents and adults, as the disease process and mechanism of action is the same for pediatric and adult patients.

In the efficacy and safety trials, the mean (\pm SD) Css,trough was 52.2 ± 13.5 mcg/mL following the proposed dose, demonstrating that the target exposure (Css,trough \geq 45 ug/mL) was observed in most patients. The ER analysis for safety and efficacy using the data from the safety and efficacy trials further supports the dose; a positive relationship trend between emicizumab exposure and absolute ABR and the probability for achieving an ABR of 0, and no evident relationship between emicizumab exposure and key adverse events was observed. Furthermore, the Css,trough in pediatrics 3 years to 12 years is similar to the Css,trough in adolescent and adult patients. Subsequently, the PK data for two children (1-year-old) was submitted as part of the 90-day safety update. The treatment duration for these children were 2 weeks and 5 weeks. One child had a Css,trough of 51.8 mcg/mL at week 5 suggesting that the dose is acceptable for pediatrics < 2 years old. Collectively, the available data supports the proposed dose in pediatrics and adults.

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Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dose of 3 mg/kg by SC injection once weekly for the first 4 weeks, followed by 1.5 mg/kg by SC injection once weekly is approvable for the proposed population. The results of two efficacy and safety trials demonstrate the effectiveness of emicizumab in patients with hemophilia A with factor VIII inhibitors. Based on the following factors, the proposed indication is approvable in all pediatric populations.

- The available PK data from two pediatrics (\leq 2 years old) suggests that the PK in this subgroup is similar to pediatrics ($>$ 2 years old) and adults.
- The mechanism of action and disease is similar in pediatrics \leq 2 years as other populations.
- Literature shows FIX and FX levels in infants could reach to 80% of adult normal values within 6 months after birth.

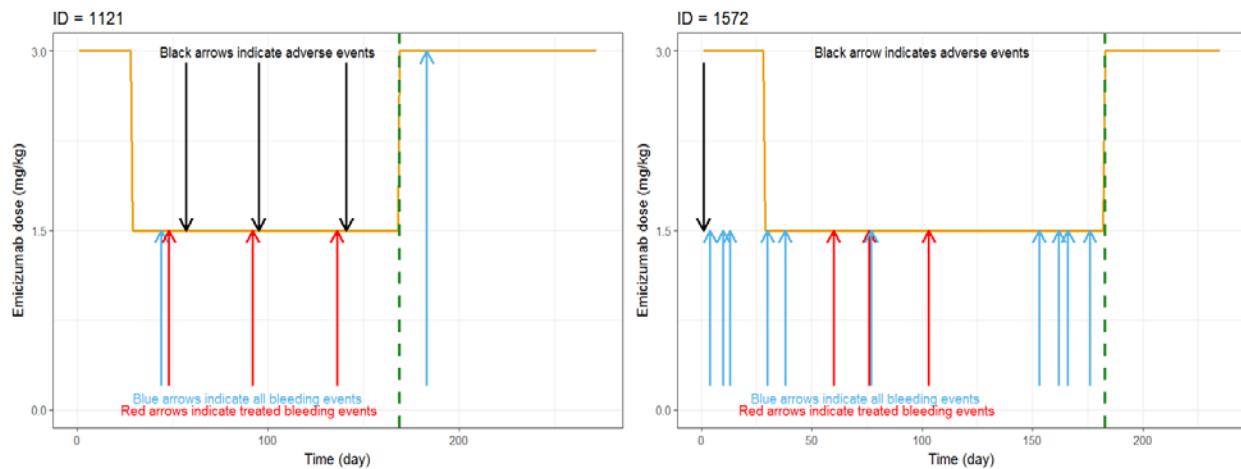
In addition to the proposed dosing regimen, we also recommend permitting up-titration of the maintenance dose. Dose up-titration from 1.5 mg/kg/week to 3 mg/kg/week was allowed in trial BH29884 if two spontaneous and clinically significant bleeds occurred in last 24 weeks on emicizumab. The ER analysis for safety and efficacy support the up-titration. No evident relationship between emicizumab exposure and safety endpoints, including injection site reaction (ISR) and thrombotic microangiopathy (TMA) or thromboembolic events (TE), was identified. Additionally, the results of the ER analysis for efficacy showed positive relationship trend between emicizumab exposure and absolute ABR or the probability for achieving ABR of 0 at the proposed dose (refer to section of reviewer's analysis for results and details).

The efficacy and safety data from two patients enrolled in trial BH29884 (Figure 8) and four subjects enrolled in trial ACE001JP (Table 4) who underwent up-titration suggests that dose up-titration resulted in fewer bleeds and no significant safety issues.

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Figure 8: Time Course of Dose Changes, Efficacy and Safety Events for Subjects Who Underwent Dose Up-Titration in Trial BH29884



Note: Yellow lines indicate emicizumab dose changes. Black arrows indicate adverse events. Red arrows indicate treated bleeding events and blue arrows indicate all other bleeding events.

Table 4. Efficacy Results for Subjects Who Underwent Dose Escalation in Study ACE002JP

Patient	1	2	3	4
ABR in pre-treatment	36.5	8.1	77.1	14.2
ABR in 0.3 mg/kg/week	18.5 (316)	1.6 (671)	59.6 (86)	-
ABR in 1 mg/kg/week	15.5 (189)	0.7 (536)	29.1 (176)	2.6 (567)
ABR in 3 mg/kg/week	3.5 (729)	-	10.0 (729)	0 (490)

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The proposed dose is weight-based, which is supported by the positive correlations between body weight and apparent clearance and volume of distribution. No alternative dosing regimen is needed for other specific populations based the results of the population PK analysis.

The population PK analysis evaluated the effects of age (3 to 75 years), body weight (14.2 to 131 Kg), serum albumin (16.8 to 54.93 g/L), post-baseline APA, factor VIII inhibitor, race, site of injection, and hepatic function (BIL: 3.2 to 46 µmol/L; AST: 11 to 89 IU/L; ALT: 5 to 210 IU/L) on emicizumab apparent clearance and volume of distribution. The analysis results showed body

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weight had significant effects on both PK parameters with a power of 1.02 and 0.96 for apparent clearance and volume of distribution, respectively.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interactions are not applicable as emicizumab is administered as a SC injection. Cytochrome P450 mediated drug interactions were not evaluated, because emicizumab undergoes proteolytic catabolism and it has no clinically significant effect on cytokine levels.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 5: Listing of Clinical Trial Relevant to BLA 761083

Trial Identity	Trial Design	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	Centers/ Countries
Controlled Studies to Support Efficacy and Safety						
BH29884 (HAVEN1) NCT02622321	Randomized, open-label, Phase 3 study, with two additional nonrandomized arms Objectives: safety, efficacy, PK Primary endpoint: Treated bleed rate Arm A (emicizumab prophylaxis) vs. Arm B (no prophylaxis)	Emicizumab SQ 3 mg/kg/week for 4 weeks, then 1.5 mg/kg/week	Patients who continue to derive clinical benefit may continue receiving prophylactic emicizumab	Randomized: Arm A: N = 35 Arm B: N = 18 Non-randomized: Arm C: N = 49 Arm D: N = 7	Adult and adolescent patients (≥ 12 years old) with hemophilia A with FVIII inhibitors	USA: 11 Japan: 7 France: 4 Poland: 4 Germany: 3 Spain: 3 UK: 3 Australia: 2 Costa Rica: 1 Italy: 1 South Korea: 1 New Zealand: 1 South Africa: 1 Taiwan: 1
BH29992 (HAVEN2) NCT02795767	Single-arm, open-label Study Objectives: safety, efficacy, PK	Emicizumab SQ 3 mg/kg/week for 4 weeks followed by 1.5 mg/kg/week	Patients who continue to derive clinical benefit may continue receiving prophylactic emicizumab	N = 20 at interim analysis N = 60 at safety update	Pediatric patients (< 12 years old) with hemophilia A with FVIII inhibitors	USA: 8 Japan: 5 Turkey: 3 Spain: 2 UK: 1 Germany: 1 Italy: 1 Costa Rica: 1 France: 1 South Africa: 1

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BH29768 NCT02476942	Multicenter, non-interventional study Objectives: Document number, types, and treatment of bleeds under routine clinical practice	None	N/A	Cohort A: N = 103 Cohort B: N = 24 Cohort C: N = not provided	<u>Cohort A:</u> Adult and adolescent patients with hemophilia A with FVIII inhibitors <u>Cohort B:</u> Pediatric patients (<12 years old) with hemophilia A with FVIII inhibitors <u>Cohort C:</u> Adult and adolescent patients with severe hemophilia A without inhibitors	N/A
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Other studies pertinent to the review of efficacy or safety

ACE001JP	Parts A + B: Randomized, double blind single ascending dose in Japanese and Caucasian HV Part C: Open-label multiple ascending dose in Japanese patients Objectives: tolerability, safety, PK and PD	Emicizumab SQ Parts A + B: Single doses cohorts: 0.001 mg/kg 0.01 mg/kg 0.1 mg/kg 0.3 mg/kg 1 mg/kg placebo Part C: <u>Cohort C-1:</u> 1 mg/kg loading dose, then 0.3 mg/kg/week <u>Cohort C-2:</u> 3 mg/kg loading dose, then 1 mg/kg/week <u>Cohort C-3:</u> 3 mg/kg/week	Parts A + B: Single dose Part C: 12 weeks	Part A: N = 40 Part B: N = 24 Part C: N = 18	Parts A + B: Healthy volunteers Part C: Adult and adolescent Japanese patients (\geq 12 years old) with hemophilia A with or without FVIII inhibitors	Japan
ACE002JP	Open-label extension of ACE001JP Objectives: safety, exploratory efficacy	Emicizumab SQ <u>Cohort C-1:</u> 1 mg/kg loading dose, then 0.3 mg/kg/week <u>Cohort C-2:</u> 3 mg/kg loading dose, then 1 mg/kg/week <u>Cohort C-3:</u> 3 mg/kg/week	Until the marketing approval date or the date of notification of development discontinuation	N = 16	Adult and adolescent Japanese patients (\geq 12 years old) with hemophilia A with or without FVIII inhibitors	Japan

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7.2. Review Strategy

The key material used for this review of efficacy and safety includes:

- IND 122954
- BLA 761083
- Relevant published literature
- Relevant information in the public domain

Study HAVEN1 was used for the primary efficacy analysis in adult and adolescent patients. Study HAVEN2 was used for the efficacy analysis in pediatric patients <12 years old. Intra-patient analysis for both HAVEN1 and HAVEN2 were performed only for patients who enrolled in the non-interventional study (NIS, BH29768) prior to the treatment trials. Study ACE001JP and the extension study ACE002JP were used for safety information.

Data sources include applicant study reports, protocol and amendments, SAP and amendments, data sets, and literature referenced for study HAVEN1.

Electronic data sets in the legacy format and SAS programs were located at:
\\CDSESUB1\evsprod\BLA761083\0002\m5\datasets.

Section 8.1 contains a review of efficacy from studies HAVEN1 and HAVEN2. The statistical reviewer conducted the analyses independent of the Applicant's results except where indicated. Both the statistical and clinical reviewers provide commentary on the results. The analyses of safety presented in Section 8.2 are those of the clinical reviewer using MAED and JMP except for a few areas where the Applicant's results were not independently verified where indicated.

Summaries of data and statistical analysis by the clinical reviewer were performed using JMP 11.1.1 (SAS Institute, Inc., Cary, NC). MedDRA Adverse Events Diagnostic 1.3 (MAED) (FDA, Silver Spring, MD) was also used to look for safety signals. For the results of the primary efficacy analysis the methodologies used were SAS version 9.4.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. BH29884/HAVEN1

Trial Design

The pivotal trial BH29884, referred to as HAVEN1, titled “A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients with inhibitors” is a randomized, multicenter, open label, phase III clinical study which enrolled patients aged 12 years or older with hemophilia A who have inhibitors against FVIII. A total of 53 patients with inhibitors who received episodic treatment with bypassing agents prior to study entry were enrolled at a 2:1 randomization ratio to receive either prophylactic emicizumab (Arm A) or no prophylaxis (Arm B). Emicizumab was given at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously thereafter. A central block-based randomization method was used.

Randomization was stratified by:

- Number of bleeds the patients experienced over the last 24 weeks prior to study entry (<9 vs. ≥ 9)

All patients in Arm A and Arm B continued to receive episodic bypassing agent therapy to treat breakthrough bleeds, preferably with rFVIIa at the lowest expected dose to achieve hemostasis.

To obtain additional safety and efficacy data, patients who had been randomized to not receive emicizumab (control arm, Arm B) would be offered treatment with prophylactic emicizumab at the same dose and schedule once they completed 24 weeks in the study. After 24 weeks on prophylactic emicizumab, all patients were able to continue their 1.5 mg/kg/week maintenance dose or may be provided the option to increase their dose to 3 mg/kg/week if they meet protocol defined criteria of suboptimal response and receive approval from the Medical Monitor to do so. Patients who continue to derive clinical benefit were given the opportunity to continue receiving prophylactic emicizumab as part of this or a future, separate extension study.

Patients with hemophilia A with inhibitors who were treated with bypassing agents on a prophylactic basis before enrollment were enrolled in Arm C to receive prophylactic emicizumab at the same dose and schedule as Arm A.

Patients who were on episodic bypassing agents and participated in Study BH29768 (a non-interventional study) but were unable to enroll in Arms A or B were enrolled in Arm D. Patients on prophylactic bypassing agents who were unable to enroll in Arm C were also enrolled in Arm

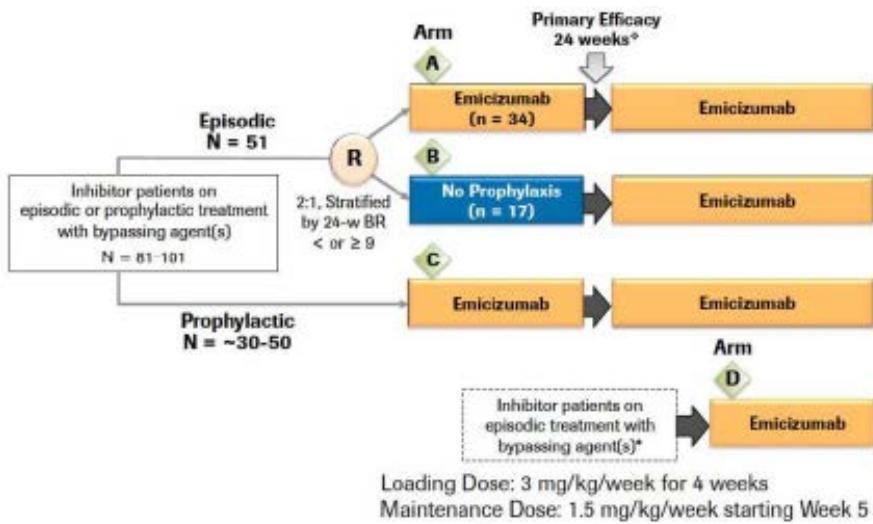
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D.

The Study Schema for HAVEN1 is shown in the Figure below.

Figure 9: BH29884/HAVEN1 Study Schema



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

Source: Figure 1, Applicant's Clinical Study Report for BH29884

Eligibility Criteria (summarized)

- Aged 12 years or older
- Body weight ≥ 40 kg
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥ 5 BU)
- ≥ 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)
- Adequate hematologic function (platelet count of ≥ 100 × 10⁹ cells/L and hemoglobin ≥ 8 g/dL)
- Adequate hepatic function (total bilirubin ≤ 1.5 × ULN and both AST and ALT ≤ 3 × ULN; no known cirrhosis)
- Adequate renal function (serum creatinine ≤ 2.5 × ULN and creatinine clearance > 30 mL/min/1.73m²)
- Patients were excluded if they were undergoing ITI or prophylaxis treatment with FVIII
- Patients were excluded if they had a history of thromboembolic disease, with exception of previous catheter-associated thrombosis without ongoing anti-thrombotic treatment
- Patients were excluded if they were at high risk of TMA (in Protocol Amendment 2)

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Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint is the number of treated bleeds over the efficacy period. A bleed is a “treated bleed” if it is directly followed by a hemophilia medication reported to be a “treatment for bleed”, irrespective of the time between the treatment and the preceding bleed. Bleeds due to surgery/procedure are not included in the primary analysis.

72-Hour Rule: Two bleeds of the same type (e.g., “joint”, “muscle”, or “other”) and at the same anatomical location are considered to be one bleed if the second occurs within 72 hours from the last treatment for the first bleed. The last treatment is defined as the last treatment before a new bleed occurs, either in the same or in a different location.

Secondary Efficacy Endpoints

- All bleeds – Comprises both treated and non-treated bleeds, irrespective of treatment with coagulation factors, with the exception of bleeds due to surgery/procedure. It also fulfills the 72-hour rule.
- Treated joint bleed – Defined as treated bleeds that fulfill the 72-hour rule, and bleed type is “joint” and unusual sensation (e.g. tingling) has been observed in combination with at least one of the following symptoms: swelling or warmth, pain or decreased range of motion, or difficulty moving the joint compared with usual.
- Treated spontaneous bleed – Defined as treated bleeds that fulfill the 72-hour rule and classified as “spontaneous” if there is no other known contributing factor such as trauma or procedure/surgery.
- Treated target joint bleeds – Target joints are major joints into which repeated bleeds occur (i.e. ≥ 3 bleeds into the same joint over the last 24 weeks prior to study entry). The target joints prior to study entry are identified through the eCRF. The bleeds in target joints during the efficacy period are defined by first selecting the bleeds that fulfill the definition of a treated joint bleed and then counting how many of these occurred in a target joint identified prior to study entry. The locations to be taken into account are: shoulder, elbow, wrist, fingers/thumb, hip, knee, ankle, sole/heel, and toes. Left and right side of the same joint type are considered to be separate joints.
- PRO endpoint—Due to the concern of using EQ-5D-5L (which is not specific for hemophilia A; per COA review), only the PRO endpoint based on Haem-A-QoL (physical function; total scores) will be described here:

For Haem-A-QoL, only adult and adolescent data were included in the analysis.

For reporting purposes, the individual items are combined to scales (e.g. physical health) and the scales were combined to form an overall total score. Per Applicant, there are 3 steps in the process of deriving the transformed scale score which is used for all the analyses:

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1. Raw Scale Score: Derived as the sum of all items in a scale., e.g. the raw score for physical health is the sum of the 5 items from this scale. A total score is calculated by summing up all of the raw and reverse coded items in the available scales.
2. Standardized Scale Score: To get the standardized scale score, the raw scale score is divided by the number of items in the scale. That way a comparison of scores across scales per patient is possible.
3. Transformed Scale Score: The scores for each scale is normalized to a 100-point scale. This is done with the following formula:

$$\begin{aligned} \text{TSC} &= 100 \times \frac{(\text{raw scale score} - \text{minimal possible raw score})}{\text{possible range of raw scale scores}} \\ &= 100 \times \frac{(\text{standardized scale score} - 1)}{4} \end{aligned}$$

The transformed Scale Score is the score used for all analyses in the CSR.

Statistical Analysis Plan

Sample Size Determination

The sample size for this study was based on clinical rather than statistical considerations, taking into account the limited number of patients with hemophilia A with inhibitors available for participation in clinical studies and in an effort to collect sufficient data to address the safety and efficacy of emicizumab. As such the study sample size was not based on detecting a hypothesized treatment effect.

A statistical simulation also showed that the proposed sample size has sufficient power to demonstrate the target treatment effect.

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Table 6 Power Calculation for Sample Size Determination

Rate for Control Treatment Arm B $(\lambda_c, n_c = 15)$	Rate for Experimental Treatment Arm A $(\lambda_t, n_t = 30)$			
	1 ($\gamma_t = 0.11$)	2 ($\gamma_t = 0.22$)	3 ($\gamma_t = 0.33$)	4 ($\gamma_t = 0.44$)
18 ($\gamma_c = 2$)	1 $(\lambda_t / \lambda_c = 0.056)$	0.999 $(\lambda_t / \lambda_c = 0.111)$	0.99 $(\lambda_t / \lambda_c = 0.167)$	0.952 $(\lambda_t / \lambda_c = 0.222)$
25 ($\gamma_c = 2.78$)	1 $(\lambda_t / \lambda_c = 0.04)$	1 $(\lambda_t / \lambda_c = 0.08)$	0.994 $(\lambda_t / \lambda_c = 0.12)$	0.973 $(\lambda_t / \lambda_c = 0.16)$
30 ($\gamma_c = .33$)	1 $(\lambda_t / \lambda_c = 0.033)$	0.999 $(\lambda_t / \lambda_c = 0.067)$	0.995 $(\lambda_t / \lambda_c = 0.1)$	0.978 $(\lambda_t / \lambda_c = 0.133)$

Source: BH 29884, Statistical Analysis Plan, Table 2, page

Reviewer's comments:

- *Sample size calculations were performed with East®, version 6 (Cytel, Cambridge, MA), which allows specific shape parameters for both the treatment and control groups.*
- *Descriptions of these design parameters are presented in the following:*

Test Type	2-Sided
Type I Error (α)	0.05
Type II Error (β)	0.10
Power ($1-\beta$)	0.90
Allocation Ratio (n_t / n_c)	2:1
Rate for Control Treatment Arm (λ_c)	18, 25, and 30 events/year
Rate for Experimental Treatment Arm (λ_t)	1, 2, 3, and 4 events/year
Ratio of Rates ($\Theta_1 = \lambda_t / \lambda_c$)	Range from 0.055 up to 0.133
Follow-up Time (D) in years, defined as pre-specified (known) amount of time for which subjects will be followed	0.5 If non-convergence occurred, D is taken as close as possible to 0.5 in order to allow convergence.
Shape Parameter for Control Treatment Arm (γ_c)	$\gamma_c = (\lambda_c)^2 / (\text{Variance} - \lambda_c)$, with variance defined as 10 times of λ_c
Shape Parameter for Experimental Treatment Arm (γ_t)	$\gamma_t = (\lambda_t)^2 / (\text{Variance} - \lambda_t)$, with variance defined as 10 times of λ_t

- The allocation ratio (n_t / n_c) describes the ratio of patients in each arm. An allocation ratio of 2:1 indicates that 66% of the patients are randomized to the treatment arm and 33% to the control.
- This calculation assumed 6 months follow-up, 2-sided 5% significance level, 90% power and 10% drop-out rate.

Source: *Per Applicant's responses to the Agency's information request (dated 6/20/2015)*

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Analysis Population

For bleeding related primary and secondary efficacy endpoints, the primary analysis population is intent to treat (ITT) population, defined as all randomized patients, and with patients grouped according to the treatment assigned at randomization.

For patient reported outcome, Haem-A-QoL, the primary analysis population is all adult patients (age ≥ 18) in the ITT population, because Haem-A-QoL was used for adult patient only.

Analysis Method

Primary Efficacy Endpoint –

Primary Analysis Method

The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic emicizumab vs. no prophylaxis (Arm A vs. Arm B), was planned to be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinued study participation, whichever occurs first.

The comparison of number of bleeds over time between the randomized treatment Arms A and B was performed using a negative binomial (NB) regression model, which accounts for different follow up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (< 9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in randomization.

This analytic model estimates the rate ratio, λ_t / λ_c , which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level, and the estimated risk ratio is compared with 1.

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

$$\text{ABR} = (\text{Number of bleeds}/\text{number of days during the efficacy period}) \times 365.25$$

Sensitivity Analysis Methods

Sensitivity analysis methods include zero inflated negative binomial regression, which takes account of excessive zeros in the data, the Van Elteren test, unstratified negative binomial model and Wilcoxon Rank Sum test.

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Secondary Efficacy Endpoints (Bleed Related Endpoints) -

Randomized Comparison

The number of all bleeds (i.e., those treated and not treated with coagulation factors), spontaneous bleeds, joint bleeds, and target joint bleeds over time in patients who receive prophylactic emicizumab (Arm A) compared with no prophylaxis (Arm B) was evaluated by the NB regression model, as specified for the primary efficacy endpoint.

The number of bleeds was also annualized for each patient using the same formula for the primary endpoint

$$\text{ABR} = (\text{Number of bleeds}/\text{number of days during the efficacy period}) \times 365.25$$

Intra-Patient Comparison

The number of treated bleeds and all bleeds over time was compared with patients' bleed rate prior to study entry.

In the intra-patient comparison, only patients who participated in the non-interventional study (NIS) BH29768 are included. Of note, for some patients who participated in NIS BH29758, the total time in that study prior to enrollment in Study BH29884 may be less than 24 weeks. The efficacy period in NIS BH29758 is defined as the time from the first entry on the electronic, handheld device or site data entry system to the day the patient completed the study. The analysis method is the NB regression model as for the primary endpoint with the exception that the SAS GENMOD procedure includes a REPEATED statement to account for the intra-patient comparison.

Secondary Efficacy Endpoint (Patient Reported Outcomes) -

Haem-A-QoL and EQ-5D-5L were assessed on a regular basis, as per the schedule of assessments. Health status was also assessed in the event of a bleed.

Adherence with the PRO measures was summarized. Because the Haem-A-QoL was administered to adult patients only, all calculations and analyses were conducted for adult patients. Scale scores for the PRO were calculated and summarized descriptively. The Haem-A-QoL scale scores for all patients were evaluated at 25 weeks. For each treatment arm, paired t-tests were used to compare the 25-week and baseline scale scores. Within-subject and between-group changes from baseline on the scale scores were also calculated at 25 weeks. The ANCOVA model adjusted for baseline score and baseline by treatment group interaction.

For the assessments of the EQ-5D-5L performed every 4 weeks, the number and percentage of patients in each of the five categories for each question for each group was assessed. Changes in the EQ-5D-5L index utility score from baseline was compared between groups. In addition,

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summary statistics, including the mean, standard deviation, median, minimum and maximum, were displayed for the patients' health state using the EQ-VAS both within and between groups. The proportion of patients who reported changes in each group exceeding the clinically meaningful threshold on the EQ-5D-5L index and EQ-VAS scores was reported at 25 weeks.

For the analyses of Haem-A-QoL and EQ-5D-5L at 25 weeks, analysis of variance (ANOVA) was used for the analysis of the score between treatment groups. The model includes treatment group, baseline score, and treatment group by baseline interaction term as covariates.

Multiplicity Control

Type I error is controlled through the hierarchical testing framework. The α level is 2-sided 0.05. The endpoints would be tested if the primary efficacy endpoint was tested statistically significant. The secondary efficacy endpoint is tested in the following order:

- | | |
|---|----------------------------------|
| • All bleeds | (Arm A vs. Arm B) |
| • All bleeds | (Arm A intra-patient comparison) |
| • Treated bleeds | (Arm A intra-patient comparison) |
| • Treated joint bleeds | (Arm A vs. Arm B) |
| • All bleeds | (Arm C intra-patient comparison) |
| • Treated bleeds | (Arm C intra-patient comparison) |
| • Treated spontaneous bleeds | (Arm A vs. Arm B) |
| • Treated target joint bleeds | (Arm A vs. Arm B) |
| • Haem-A-QoL physical health subscale at 25 weeks | (Arm A vs. Arm B) |
| • Haem-A-QoL total score at 25 weeks | (Arm A vs. Arm B) |
| • EQ-5D-5L VAS at 25 weeks | (Arm A vs. Arm B) |
| • EQ-5D-5L index utility score at 25 weeks | (Arm A vs. Arm B) |

Interim Analysis

No efficacy interim analysis was planned or conducted.

Analysis Time

The primary analysis takes place at the earliest time when all randomized patients reach 24 weeks in the study or have withdrawn. The primary comparison consists of Arms A and B.

At this time, not all patients in Arms C and D have been in the study for 24 weeks. However, all available data from these patients was analyzed at this time point as well.

Reviewer comment: Results for Arms C and D need to be interpreted with caution due to the short follow-up for some patients.

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Missing Data

The applicant collected the bleed-related endpoint on an electronic, handheld device. The device does not allow the patient to leave questions unanswered or enter partial data. The data for the primary and secondary bleed-related endpoints based on this device are complete and there is no missing data.

In general, a domain score can be calculated if $\geq 50\%$ of the Haem-A-QoL items have been answered otherwise it is set to missing even if 1 item have been answered. In current study, the questionnaire is being administered electronically and patients are not able to skip items and therefore the data is complete.

Of note, patients can answer “Not applicable” in the Haem-A-QoL to questions in the sports and leisure, work and school, and family planning scales. In this case, the minimum number of items that needs to be completed and not responded to as “Not applicable” is:

- Sports and leisure: 3
- Work and school: 2
- Family planning: 2

The total score took into account the individual item of the domain even if $<50\%$ of the items for a domain have been answered. A complete questionnaire can be missing if a patient did not complete the whole questionnaire.

Statistical reviewer's comments:

For PRO endpoints, the applicant proposed missing at random mechanism for the missing observations (2 patients [13%] in the no prophylaxis arm and 6 patients [19%] in the emicizumab prophylaxis arm), and used observed data in the analysis without imputation. Per Agency's request, sensitivity analyses were performed (see result section).

Protocol Amendments

Significant changes at each protocol amendment are provided below.

Protocol Amendment 1:

- Planned enrollment for Arm C increased from 10-20 to 30-50 due to rapid enrollment
- Arm D added for patients who had participated in NIS BH29768 but were unable to enroll in Arm A or Arm B before those arms closed
- Secondary endpoint added for all bleeds (treated and not treated)
- Interim analysis removed due to rapid enrollment

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Urgent Changes prior to Protocol Amendment 2:

- Two Dear Investigator Letters (DILs) were issued to report 2 patients with thromboembolic events and 2 patients with thrombotic microangiopathy
- Recommended that the use of aPCC or other bypassing agents should be avoided or limited, and if needed to treat breakthrough bleeds, rFVIIa should be used if possible.
- Temporary halt of enrollment until iDMC review, patients reconsented

Protocol Amendment 2:

- Incorporated urgent changes reflected in DILs
- Microangiopathic hemolytic anemia/ thrombotic microangiopathy was newly classified as an AESI, and an exclusion criterion to exclude patients at high risk to experience thrombotic microangiopathy was added
- Spontaneous bleed rate was added as a secondary efficacy objective

Data Quality and Integrity

The quality of the efficacy data submitted was adequate to allow substantial primary review. The Applicant provided analysis-ready datasets for the study BH29884.

8.1.2. BH29884 Study Results

Compliance with Good Clinical Practices

The Applicant stated in Module 2.5, Section 1.7 that all studies included in this submission were conducted in accordance with the principles of Good Clinical Practice, the principles of the Declaration of Helsinki, and the local laws and regulations of the countries in which the studies were conducted. Ethics Committees and Institutional Review Boards reviewed and approved all studies.

Financial Disclosure

A summary of financial disclosures for the studies included in the submission is provided in Appendix 19.2. The Applicant submitted financial disclosure information from all the investigators and subinvestigators from Study BH29884. One investigator, (b) (6) Site (b) (6) was identified to have (b) (6) financial disclosure of receiving significant payment from the Sponsor. This site enrolled (b) (6) patients in Study BH29884. With the small number of patients enrolled at any site, the enrollment of patients by this investigator is not expected to bias the outcome of the study results.

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Patient Disposition

A total of 114 patients were screened, and 5 were excluded based on enrollment criteria, resulting in 109 eligible patients enrolled. Twenty-four patients in each Arm A and C were enrolled in NIS BH29768 prior to HAVEN1 and are included in the intra-patient comparison secondary endpoints.

One patient randomized to Arm A withdrew prior to receiving a dose of emicizumab (patient decision). This patient is included in the ITT, but is excluded from safety analyses. Three patients withdrew from emicizumab treatment, all in Arm A. Two were for AEs (see safety section below), and one was due to physician decision.

Thirty-one of 35 patients in Arm A (88.6%) and all patients in Arm B completed at least 24 weeks on study. In Arms C and D, 22 of 49 (44.9%) and 0 of 7 patients, respectively, had completed at least 24 weeks treatment on study. Two patients in Arm A (5.7%) had their dose up-titrated to 3 mg/kg/week from 1.5 mg/kg/week.

Table 7: Patient Disposition

Status	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)
Patients randomized/enrolled	18 (100.0%)	35 (100.0%)	49 (100.0%)	7 (100.0%)	109 (100.0%)
Patients who participated in NIS	11 (61.1%)	24 (68.6%)	24 (49.0%)	7 (100.0%)	66 (60.6%)
Patients who started the study	18 (100.0%)	34 (97.1%)	49 (100.0%)	7 (100.0%)	108 (99.1%)
Patients who discontinued prematurely prior to study day 1	0	1 (2.9%)	0	0	1 (0.9%)
Patients with duration of efficacy period <24 weeks	0	4 (11.4%)	27 (55.1%)	7 (100.0%)	38 (34.9%)
Patients who completed 24 weeks in the study	18 (100.0%)	31 (88.6%)	22 (44.9%)	0	71 (65.1%)
Patients in arm B who switched to receive emicizumab	13 (72.2%)	0	0	0	13 (11.9%)
Patients whose dose was up-titrated	0	2 (5.7%)	0	0	2 (1.8%)
Patients who started follow up	0	3 (8.6%)	0	0	3 (2.8%)
Patients who completed the safety follow up	0	0	0	0	0
Patients who discontinued from the study	0	1 (2.9%)	0	0	1 (0.9%)
Patients who completed the study	0	0	0	0	0

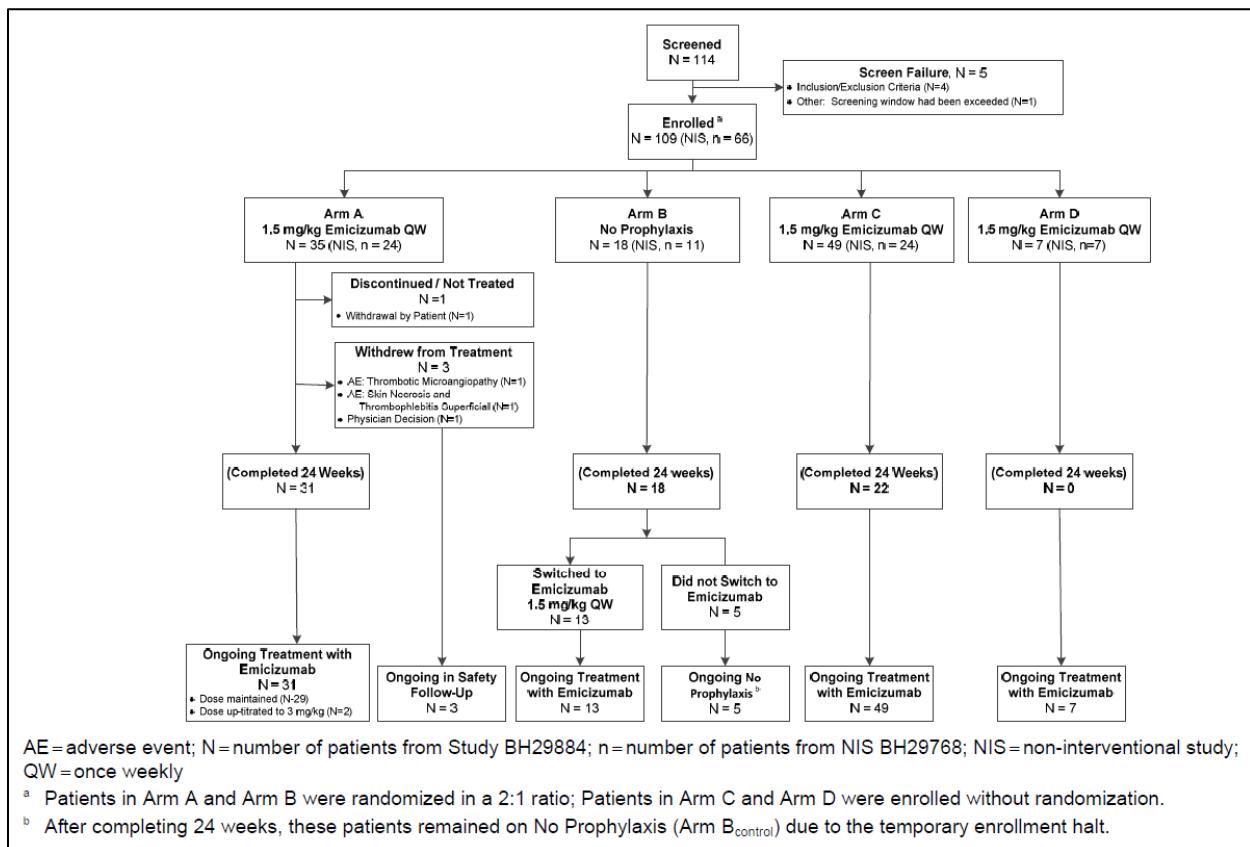
Arm A and B patients on no previous prophylaxis randomized to emicizumab or no prophylaxis; Arm C patients on previous prophylaxis with bypassing agent; Arm D patients on no previous prophylaxis
Patients exposed to emicizumab started with loading dose 3mg/kg/week for 4 weeks

Source: Study BH 29884, CSR, patient disposition table

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Figure 10: Patient Disposition



Source: Study BH 29884, CSR, Figure 2

Reviewer comment:

The shorter duration on study in Arms C and D is expected because the primary analysis was triggered based on the randomized part of the trial. Arm D opened to enrollment later than the other parts of the trial.

Protocol Violations/Deviations

In the randomized part of the trial, 12 major protocol deviations were reported in 10 of 53 patients enrolled. Two were dosing deviations, and the remaining were procedural, primarily missing laboratory or HRQoL measurements. An additional 25 major protocol deviations were reported in 14 of 69 patients treated with emicizumab, including Arm B after starting emicizumab prophylaxis. Four were related to medication administration, and the remaining were procedural.

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Table of Demographic Characteristics

In general, the distributions of demographic and baseline characteristics are comparable between treatment arms (A vs B). Some imbalance was observed with more African American or Black patients enrolled in Arm B while more Asian patients were enrolled in Arm A.

Table 8: BH29884/HAVEN1, Demographic characteristics

Demographic Parameters	Randomized Arms (N=53)		Non-Randomized Arms (N = 56)		Total (N=109) n (%)
	Arm A Emicizumab Prophylaxis (N =35) n (%)	Arm B No prophylaxis (N =18) n (%)	Arm C (N = 49) n (%)	Arm D (N = 7) n (%)	
Sex					
Male	35 (100.0)	18 (100.0)	49 (100.0)	7 (100.0)	109 (100.0)
Age					
Mean years (SD)	35.8 (13.9)	37.2 (13.7)	25.6 (16.8)	30.3 (10.8)	31.1 (15.8)
Median (years)	38.0	35.5	17.0	26.0	28.0
Min, max (years)	12, 68	13, 65	12, 75	19, 49	12, 75
Age Group					
< 65 years	34 (97.1)	17 (94.4)	47 (95.9)	7 (100.0)	105 (96.3)
≥ 65 years	1 (2.9)	1 (5.6)	2 (4.1)	0	4 (3.7)
Race					
White	21 (60.0)	10 (55.6)	33 (67.3)	7 (100.0)	71 (65.1)
Black or African American	4 (11.4)	4 (22.2)	3 (6.1)	0	11 (10.1)
Asian	10 (28.6)	3 (16.7)	8 (16.3)	0	21 (19.3)
American Indian or Alaska Native	0	0	1 (2.0)	0	1 (0.9)
Native Hawaiian or Other Pacific Islander	0	1 (5.6)	0	0	1 (0.9)
Unknown	0	0	4 (8.2)	0	4 (3.7)
Ethnicity					
Hispanic or Latino	4 (11.4)	1 (5.6)	12 (24.5)	1 (14.3)	18 (16.5)
Not Hispanic or Latino	31 (88.6)	17 (94.4)	37 (75.5)	6 (85.7)	91 (83.5)
Region					
Africa	3 (8.6)	3 (16.7)	0	0	6 (5.5)
Asia	8 (22.9)	3 (16.7)	6 (12.2)	0	17 (15.6)
Australia and Oceania	3 (8.6)	1 (5.6)	2 (4.1)	0	6 (5.5)
Central America	2 (5.7)	0	3 (6.1)	0	5 (4.6)
Europe	12 (34.3)	5 (27.8)	19 (38.8)	3 (42.9)	39 (35.8)
North America	7 (20.0)	6 (33.3)	19 (38.8)	4 (57.1)	36 (33.0)

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Reviewer comment: The imbalances in distribution by race are likely due to the small sample sizes in each arm. A subgroup analysis by race did not show a substantial impact of the imbalance. Refer to “Additional analyses” at the end of this Section.

Other Baseline Characteristics

Table 9: BH29882, Baseline Disease Characteristics

	Randomized Arms (N=53)		Non-Randomized Arms (N = 56)		Total (N=109) n (%)
	Arm A Emicizumab Prophylaxis (N =35) n (%)	Arm B No prophylaxis (N =18) n (%)	Arm C (N = 49) n (%)	Arm D (N = 7) n (%)	
Baseline ABR					
<9	11 (31.4)	5 (27.8)	23 (46.9)	4 (57.1)	43 (39.4)
≥9	24 (68.6)	13 (72.2)	26 (53.1)	3 (42.9)	66 (60.6)
Target joints					
None	10 (28.6)	5 (27.8)	15 (30.6)	3 (42.9)	33 (30.3)
1	7 (20.0)	3 (16.7)	10 (20.4)	3 (42.9)	23 (21.1)
>1	18 (51.4)	10 (55.6)	24 (49.0)	1 (14.33)	53 (48.6)
Previous ITI*					
Yes	14 (40.0)	7 (38.9)	33 (67.3)	3 (42.9)	57 (52.3)
No	21 (60.0)	11 (61.1)	16 (32.7)	4 (57.1)	52 (47.7)

* ITI: immune tolerance induction

Source: FDA reviewer analysis

Reviewer comment: There were no imbalances in distribution by baseline ABR (stratification factor), target joints, or previous ITI in the randomized portion of the trial (Arm A vs. Arm B). Refer to “Additional analyses” at the end of this Section for analyses by baseline ABR and target joints. The lower rate of baseline ABR ≥9 for Arm C is reflective of patients’ prior prophylaxis with a bypassing agent in that arm. More patients in Arm C attempted prior ITI which is likely reflective of patient management for patients who chose prophylaxis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Information on bleeds and hemophilia medications, including emicizumab and bypassing agents, was collected on a handheld device using the Bleeds and Medication Questionnaire (BMQ). The patient could enter bleeds and medications for the preceding 7 days. If no bleeds occurred or the patient did not need any treatments for a week, the patient was asked to fill out the BMQ to confirm this. Overall compliance with the BMQ was 93-100% in each arm of BH29884.

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Treatment compliance was high with only 8% of patients missing one or more doses. Rescue medication (bypassing agent) use was captured in the efficacy data on bleeds requiring treatment. The use of other concomitant medications was similar between Arms A, B, and C (59–72%). The most common concomitant medications were analgesics (28%), antihistamines (13%), penicillins (13%), cough preparations (10%), hemostatics (10%), NSAIDs (10%), and steroids (10%).

Efficacy Results – Primary Endpoint

Primary Analysis

The primary efficacy endpoint is treated bleed rate. The annualized bleeding rate was 2.9 for emicizumab prophylaxis arm (Arm A), and 23.3 for no prophylaxis arm (Arm B). The ABR ratio is 0.13 (95% CI [0.057, 0.277]) with the p-value < 0.0001 indicating a statistically significant test result.

Table 10: Primary Endpoint, Treated Bleeds, Arm A vs. Arm B

	Arm A: Emicizumab Prophylaxis (N = 35)	Arm B: No Prophylaxis (N = 18)
Model based ABR (95% CI) ^a	2.9 (1.7, 5.0)	23.3 (12.3, 43.9)
Model based ABR ratio (95% CI), p value ^a	0.13 (0.057, 0.277), < 0.0001	
Formula based ABR, Median (IQR) ^{b c}	0 (0, 3.7)	18.8 (13.0, 35.1)
Number of Patients with zero bleed (%)	22 (62.9)	1 (27.3)

^a Based on negative binomial model

^b Based on formula ABR = Number of bleeds/number of days during the efficacy period) X 365.25

^c IQR = Interquartile range, 25th percentile to 75th percentile

Source: FDA Reviewer Analysis

Reviewer comment: The study met its primary endpoint of treated bleeds in Arm A vs. Arm B with an 87% reduction in treated bleeds. The median ABR of zero represents an improvement over available therapies for patients with hemophilia A with FVIII inhibitors.

Sensitivity Analysis

Zero inflated negative binomial model is for modeling count variable with excessive zeros. In the study BH29884, 22 of 35 patients (62.9%) in the emicizumab prophylaxis arm and 1 of 18 patients (5.6%) in the no prophylaxis arm had zero bleed. Based on zero inflated negative binomial models, the ABR ratio is 0.28 (95% CI [0.16, 0.49]), with 2-sided p-value < 0.0001, supporting the primary analysis results.

The applicant also specified Van Elteren test, Wilcoxon Rank Sum test and unstratified negative binomial model. Both the Van Elteren test and the Wilcoxon rank sum test showed statistically

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significant test results with $p < 0.0001$ for both tests. Based on unstratified negative binomial model, the ABR ratio is 0.12 (95% CI [0.05, 0.27]), supporting the primary analysis results.

Efficacy Results – Secondary endpoints, comparison between emicizumab prophylaxis (Arm A) vs. no prophylaxis (Arm B)

The number of bleed in patients on the emicizumab prophylaxis arm is compared to that on the no prophylaxis arm on the secondary endpoints including

- All bleed
- Treated joint bleed
- Treated spontaneous bleed
- Treated target joint bleed.

The analysis results are summarized in the Table below.

All bleed

The model based ABR was 5.5 for emicizumab prophylaxis arm (Arm A), and 28.3 for no prophylaxis arm (Arm B). The ABR ratio is 0.20 (95% CI [0.102, 0.375]) with the p-value < 0.0001 , showing a statistically significant test result.

Treated Joint Bleed

The model based ABR was 0.8 for emicizumab prophylaxis arm (Arm A), and 6.7 for no prophylaxis arm (Arm B). The ABR ratio is 0.11 (95% CI [0.025, 0.520]) with the p-value < 0.0001 showing a statistically significant test result.

Treated Spontaneous Bleed

The annualized ABR was 1.3 for emicizumab prophylaxis arm (Arm A), and 16.8 for no prophylaxis arm (Arm B). The ABR ratio is 0.08 (95% CI [0.037, 0.154]) with the p-value < 0.0001 from the Wald test, which is statistically significant.

Treated Target Joint Bleed

The model based ABR was 0.1 for emicizumab prophylaxis arm (Arm A), and 3.0 for no prophylaxis arm (Arm B). The ABR ratio is 0.05 (95% CI [0.009, 0.227]) with the p-value 0.0002 from the Wald test, which is statistically significant.

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Table 11: Secondary Bleeding Related Endpoint, Arm A vs. Arm B

	Arm A: Emicizumab Prophylaxis (N = 35)	Arm B: No Prophylaxis (N = 18)
All Bleed		
Model Based ABR (95% CI) ^a	5.5 (3.58, 8.60)	28.3 (16.79, 47.76)
Model Based ABR ratio (95% CI), p value ^a	0.20 (0.102, 0.375), < 0.0001	
Formula based ABR, Median (IQR) ^{b c}	2.0 (0, 9.9)	30.2 (18.3, 39.4)
# of Patients with zero bleed (%)	1 (5.6)	13 (37.1)
Treated Joint Bleed		
Model based ABR (95% CI) ^a	0.8 (0.26, 2.20)	6.7 (1.99, 22.4)
Model based ABR ratio (95% CI), p-value ^a	0.11 (0.025, 0.520), 0.0050	
Formula based ABR, Median (IQR) ^{b c}	0 (0, 0)	1 (0, 14.4)
# of Patients with zero bleed (%)	30 (85.7)	9 (50.0)
Treated Spontaneous Bleed		
Model based ABR (95% CI) ^a	1.3 (0.73, 2.19)	16.8 (9.9, 28.30)
Model based ABR ratio (95% CI), p-value ^a	0.08 (0.037, 0.154), < 0.0001	
Formula based ABR, Median (IQR) ^{b c}	0 (0, 3.3)	15.2 (6.6, 30.4)
# of Patients with zero bleed (%)	24 (68.6)	2 (11.1)
Treated Target Joint Bleed		
Model Based ABR (95% CI) ^a	0.1 (0.03, 0.58)	3.0 (0.96, 9.13)
Model Based ABR ratio (95% CI), p value ^a	0.05 (0.009, 0.227), 0.0002	
Formula based ABR, Median (IQR) ^{b c}	0 (0, 0)	1.0 (0, 6.52)
# of Patients with zero bleed (%)	33 (94.3)	9 (50.0)

^a Based on negative binomial model

^b Based on the formula ABR = Number of bleeds/number of days during the efficacy period) X 365.25

^c IQR = Interquartile range, 25th percentile to 75th percentile

Source: FDA Reviewer Analysis

Efficacy Results – Secondary endpoints, comparison within Arm A or Arm C (intra-patient comparison)

The number of bleed in patients in arm A or Arm C during the trial BH 29884 was compared with that during the NIS BH29768 in the following endpoints

- Treated bleed
- All bleed

Treated Bleed (Intra-patient Comparison within Arm C)

For the 24 subjects from Arm C who were also enrolled in the NIS study, the ABR for all bleeds is 3.3 (95% CI [1.33, 8.08]) during emicizumab prophylaxis treatment, compared with 15.7 (95% CI

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[11.08, 22.29]) during previous prophylactic bypassing agent therapy. The ABR ratio is 0.21 (95% CI [0.089, 0.486]) with 2-sided p value 0.0003.

All bleed (Intra-patient Comparison within Arm C)

For the 24 subjects from Arm C who were also enrolled in the NIS study, the ABR for all bleeds is 5.5 (95% CI [2.98, 10.26]) during emicizumab prophylaxis treatment, compared with 24.3 (95% CI [18.11, 32.67]) during previous prophylactic bypassing agent therapy. The ABR ratio is 0.23 (95% CI [0.119, 0.435]) with 2-sided p value < 0.0001.

Treated bleeds (Intra-patient Comparison within Arm A)

For the 24 subjects from Arm A who were also enrolled in the NIS study, the ABR for treated bleed is 1.7 (95% CI [0.71, 4.06]) during emicizumab prophylaxis treatment, compared with 21.6 (95% CI [15.40, 30.22]) during previous episodic bypassing agent treatment. The ABR ratio is 0.08 (95% CI [0.031, 0.198]) with 2-sided p value < 0.0001 from the Wald test.

Reviewer comment: The intra-patient comparison in Arm C compared patients' prior prophylaxis with a bypassing agent with emicizumab prophylaxis. Only patients previously enrolled in NIS BH29768 were included to insure robust collection of bleeding information prior to emicizumab prophylaxis and while on emicizumab prophylaxis. The study was not designed to demonstrate superiority over prophylaxis with any bypassing agents. However, the comparisons were to aPCC and rFVIIa which are the only agents available for prophylaxis for patients with FVIII inhibitors. Superiority over other products has not been proven, and results should be interpreted with caution.

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Table 12: Secondary Bleeding Related Endpoint, Intra-Patient Comparison within Arm A

	BH 29884 Emicizumab Prophylaxis	NIS Study
Number of Subjects		24
Treated Bleed		
Model based ABR (95% CI) ^a	1.7 (0.7, 4.1)	21.6 (15.4, 30.2)
Model based ABR ratio (95% CI), p value ^a	0.08 (0.031, 0.198), < 0.0001	
Formula based ABR, Median (IQR) ^{b c}	0 (0.0, 2.4)	17.0 (10.0, 26.6)
# of patients with zero bleed (%)	17 (70.8)	2 (8.3)
All Bleed		
Model based ABR (95% CI) ^a	4.1 (2.10, 8.02)	37.7 (28.4, 50.04)
Model based ABR ratio (95% CI), p value ^a	0.11 (0.055, 0.218), < 0.0001	
Formula based ABR, Median (IQR) ^{b c}	0.5 (0.0, 5.1)	26.9 (16.4, 56.9)
# of patients with zero bleed (%)	12 (50.0)	0.0 (0.0)

^a Based on negative binomial model

^b Based on the formula ABR = Number of bleeds/number of days during the efficacy period) X 365.25

^c IQR = Interquartile range, 25th percentile to 75th percentile

Source: FDA Reviewer Analysis

Table 13 Secondary Bleeding Related Endpoint, Intra-Patient Comparison within Arm C

	BH 29884 Emicizumab Prophylaxis	NIS Study
Number of Subjects		24
Treated Bleed		
Model based ABR (95% CI) ^a	3.3 (1.33, 8.08)	15.7 (11.08, 22.29)
Model based ABR ratio (95% CI), p value ^a	0.21 (0.089, 0.486), 0.0003	
Formula based ABR, Median (IQR) ^{b c}	0 (0, 2.2)	12 (5.7, 24.2)
# of patients with zero bleed (%)	17 (70.8)	3 (12.5)
All Bleed		
Model based ABR (95% CI) ^a	5.5 (2.98, 10.26)	24.3 (18.11, 32.67)
Model based ABR ratio (95% CI), p value ^a	0.23 (0.119, 0.435), < 0.0001	
Formula based ABR, Median (IQR) ^{b c}	0.7 (0.0, 7.0)	17.2 (10.5, 38.7)
# of patients with zero bleed (%)	12 (50.0)	0 (0.0)

^a Based on negative binomial model

^b Based on the formula ABR = Number of bleeds/number of days during the efficacy period) X 365.25

^c IQR = Interquartile range, 25th percentile to 75th percentile

Source: FDA Reviewer Analysis

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Reviewer comment: The rate of treated bleeds and all bleeds for the intra-patient comparison for Arms A (prior episodic treatment) and Arm C (prior prophylaxis) were pre-specified secondary endpoints. The Arm C intra-patient comparison was proposed for inclusion in the prescribing information. For Arm C, the rate of treated bleeds and all bleeds comparing patient's prior prophylaxis to emicizumab prophylaxis showed statistically significant reductions. The patients also demonstrated reductions in treated joint bleeds and treated spontaneous bleeds (data not shown) which lends supportive data to the efficacy of emicizumab prophylaxis.

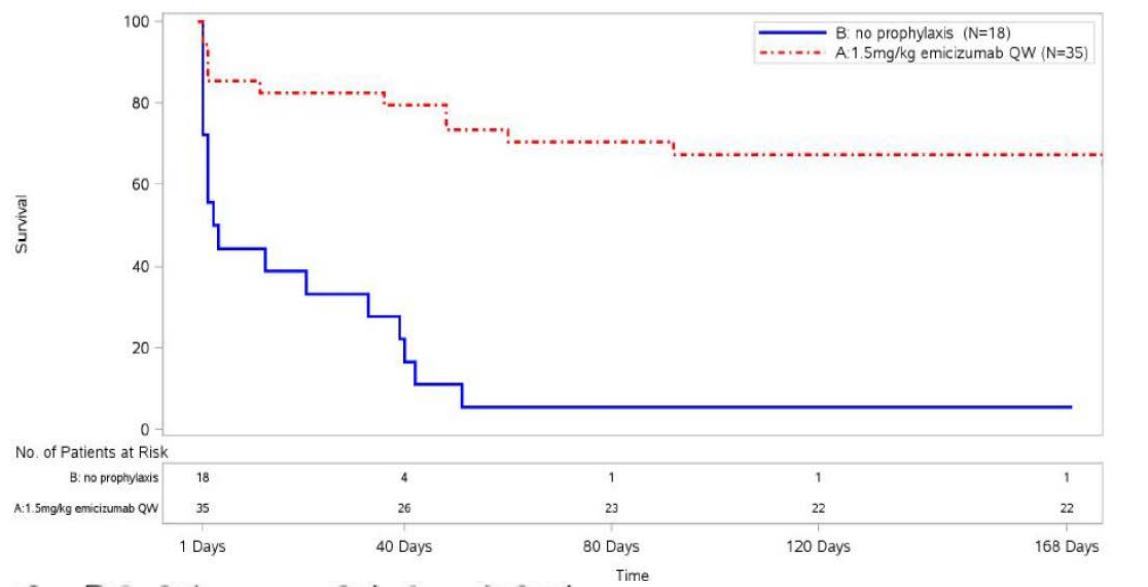
Dose/Dose Response

All patients in Study HAVEN1 received the same dose of emicizumab. Two patients up-titrated. See the clinical pharmacology section for discussion of the up-titration.

Durability of Response

Per the Agency's request, the Applicant performed time to first treated bleed analysis, the KM plots are presented below for Arm A vs. Arm B (Arm B includes prophylaxis period only; prior to up-titration):

Figure 11: Kaplan Meier Estimates for time to the first treated bleed (ITT; Cutoff: 10/25/2016): Arm A vs. Arm B

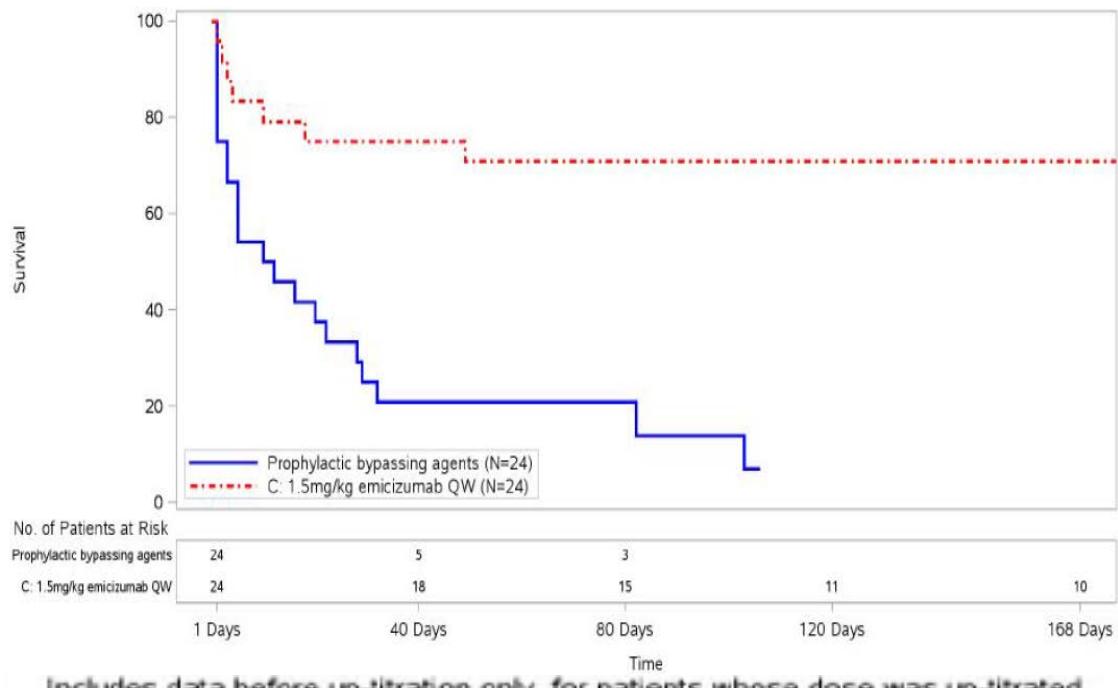


Source: Applicant's response to IR (dated 9/21/2017)

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Figure 12: Kaplan Meier Estimates for time to the first treated bleed (ITT; Cutoff: 10/25/2016): Intra-patient comparison -- Arm C vs. NIS patients



Source: Applicant's response to IR (dated 9/21/2017)

Reviewer comment: Based on this time to the first treated bleed analysis, the KM curve for Arm A appears to stay flat (i.e. over 70% of patients stay treated bleeding free) at ~50-60 days until up to 168 days of observation period, while almost all patients (except one patient) experienced treated bleeding by approximately day 50 in Arm B. Similar trend (over 70% of patients stay treated bleeding free at ~50 days until up to 168 days) was observed while receiving emicizumab in Arm C. This analysis demonstrates that high proportions of patients (~70%) appear to stay treated bleeding free over the observation period in the emicizumab treated arm.

Persistence of Effect

An insufficient number of patients discontinued emicizumab to allow an analysis of persistence of effect after discontinuation. However, persistence is not expected after the antibody concentration falls below therapeutic levels.

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Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The PRO secondary endpoints include the Haem-A-QoL and EQ-5D-5L scores.

(b) (4)

this review focuses on the Haem-A-QoL Physical Health Score and Total Score. Please refer to the COA review for more details.

The Haem-A-QoL questionnaire was administered only to adult patients 18 years of age and older, so the analyses are based on a subpopulation of patients ages ≥ 18 years. Two of 18 patients (11.1%) and 4 of 35 patients (11.4%) were younger than 18 years old in the emicizumab prophylaxis arm and no prophylaxis arm respectively, and therefore were not included in the analysis population of Haem-A-QoL.

PRO Endpoint – Haem-A-QoL Physical Health and Total Score

The following table summarizes the completion rate (patients without missing data) of the Haem-A-QoL questionnaire for patients ages ≥ 18 years. The completion rate ranged from 83.9% to 93.5% in the emicizumab prophylaxis arm, and 87.5% to 100% in the no prophylaxis arm.

Table 14: Haem-A-QoL Questionnaire Completion Rate

	Arm A: Emicizumab Prophylaxis (N = 31)^a	Arm B No Prophylaxis (N = 16)^a
Baseline	29 (93.5%)	16 (100%)
Week 5	26 (83.9%)	16 (100%)
Week 9	26 (83.9%)	14 (87.5%)
Week 13	27 (87.1%)	15 (93.8%)
Week 17	27 (87.1%)	15 (93.8%)
Week 21	27 (87.1%)	14 (87.5%)
Week 25	25 (80.6%)	14 (87.5%)

^a Adult patients ≥ 18 years old

Source: FDA reviewer analysis

The patients mean Haem-A-QoL physical health scores (transformed, raw, and standardized scores) and total scores (transformed, raw, and standardized scores) over time by treatment arms were plotted in the following figures. Lower scores indicate better patient-reported health-related quality of life.

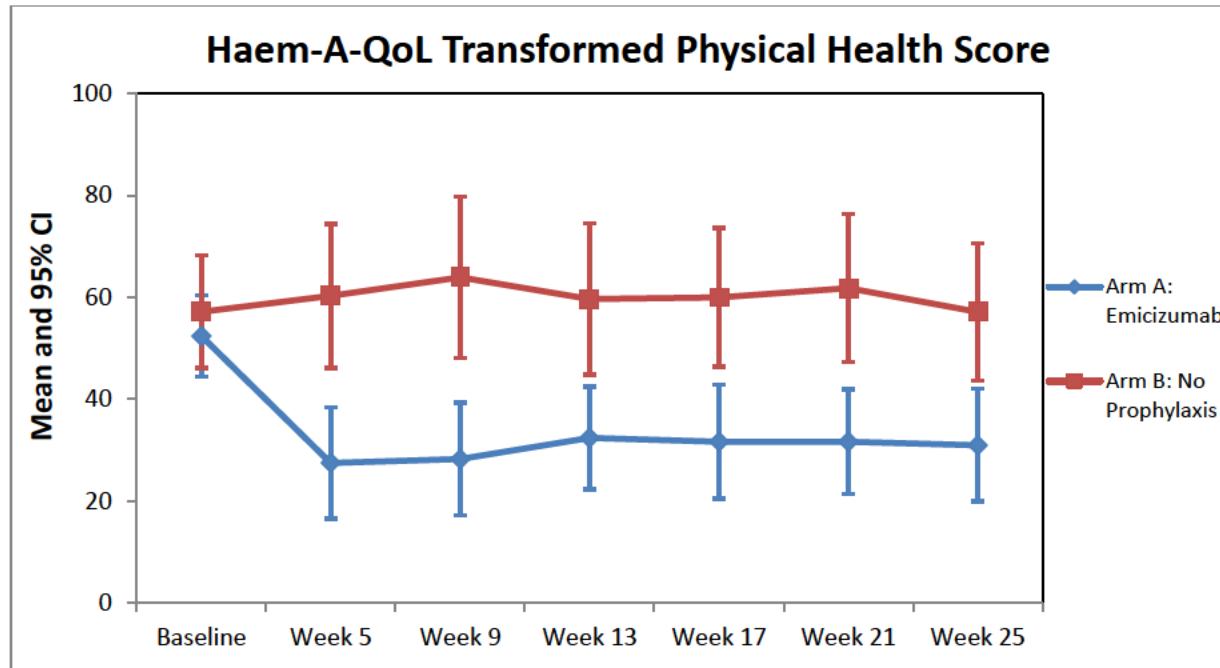
Patients on the emicizumab prophylaxis treatment arm (Arm A) and the no prophylaxis control arm (Arm B) reported comparable Haem-A-QoL physical health scores at baseline (baseline mean Arm A = 52.4 and Arm B = 57.2) and comparable Haem-A-QoL total scores at baseline (baseline mean Arm A = 41.1 and Arm B = 44.6). Over the course of 24 weeks, lower Haem-A-QoL physical

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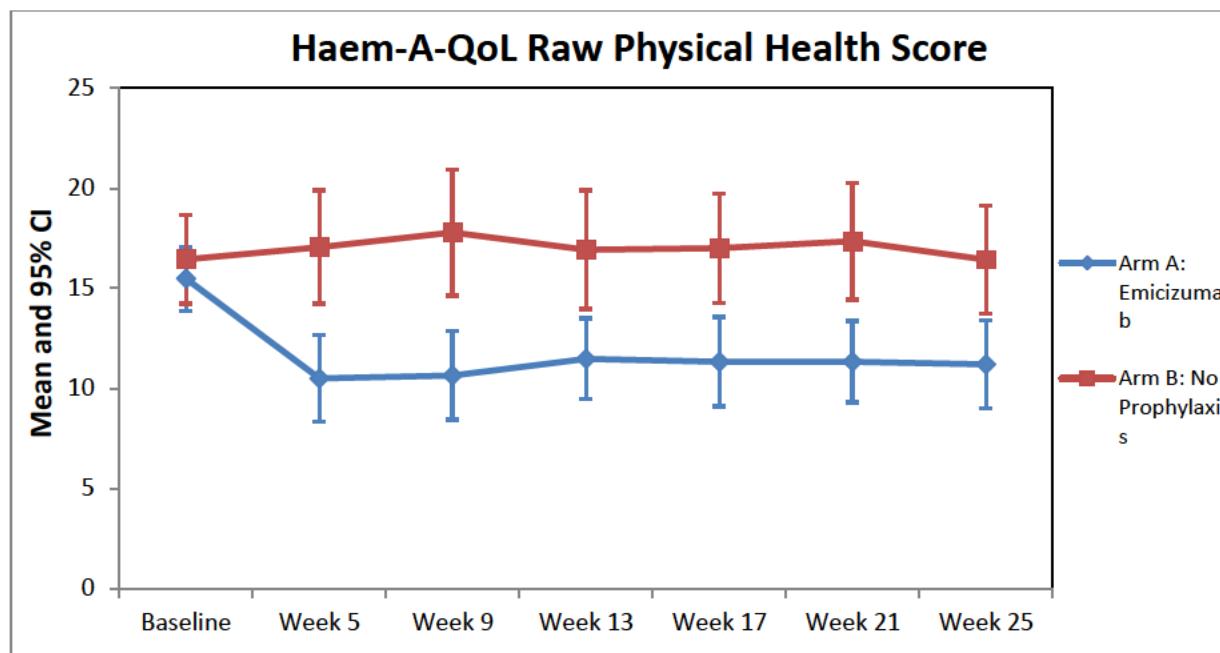
health and total scores were observed on Arm A compared with Arm B, suggesting an improvement in patient-reported physical health over time on the treatment arm.

Figure 13: Mean Haem-A-QoL Transformed Physical Health Score over Time



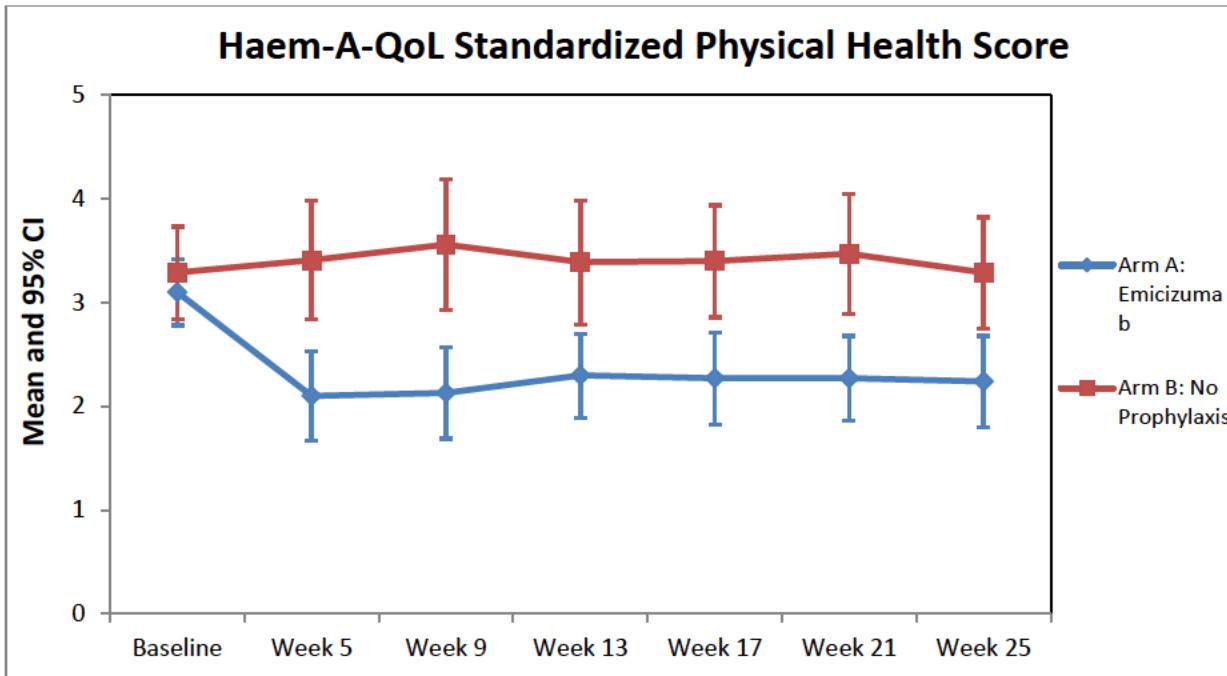
Source: FDA reviewer's analysis

Figure 12: Mean Haem-A-QoL Raw Physical Health Score over Time



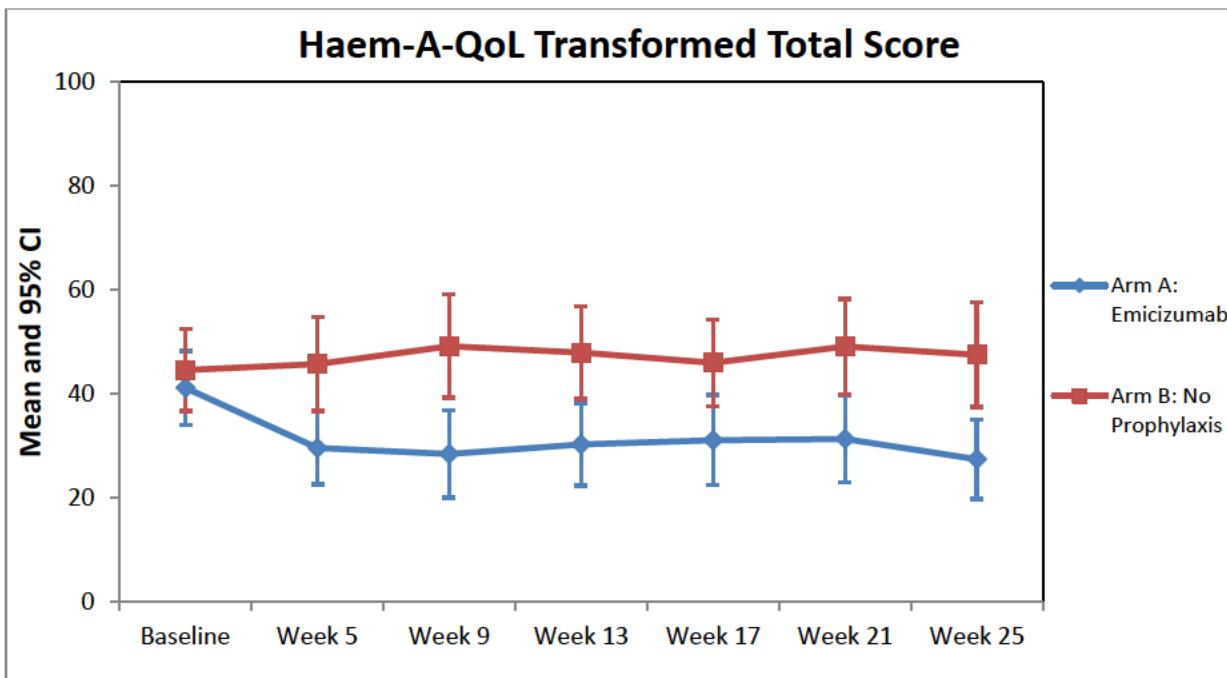
Source: FDA reviewer's analysis

Figure 13: Mean Haem-A-QoL Standardized Physical Health Score over Time



Source: FDA reviewer's analysis

Figure 14: Mean Haem-A-QoL Transformed Total Score over Time

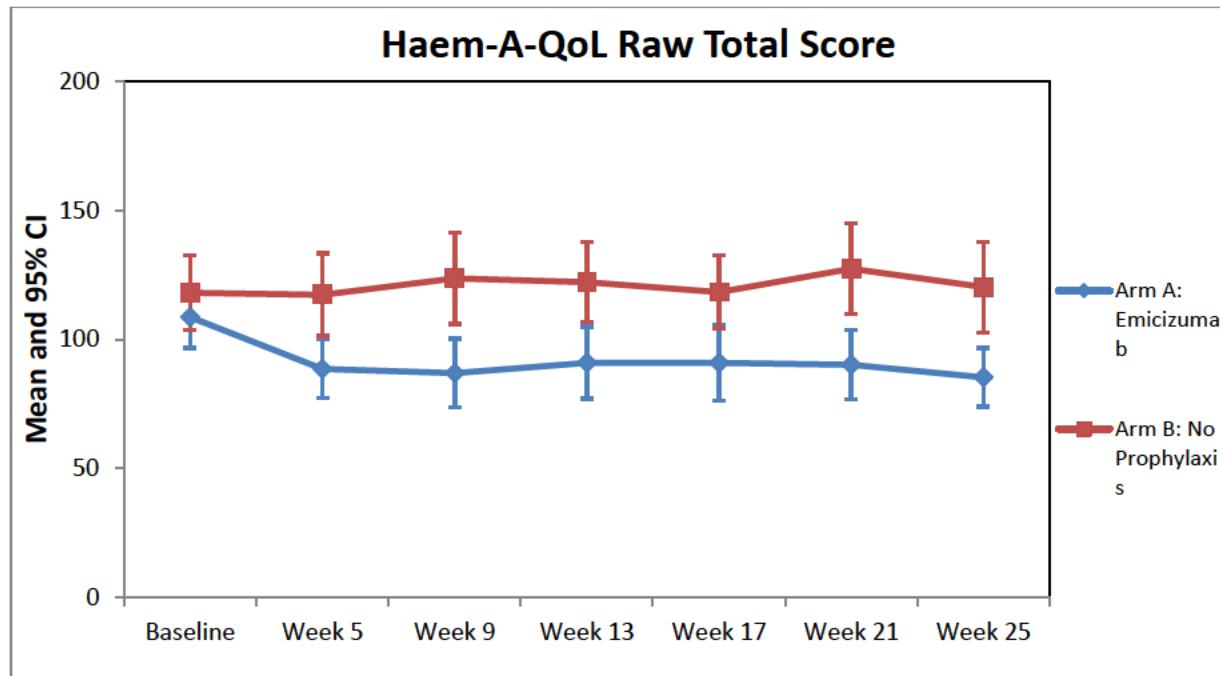


Source: FDA reviewer's analysis

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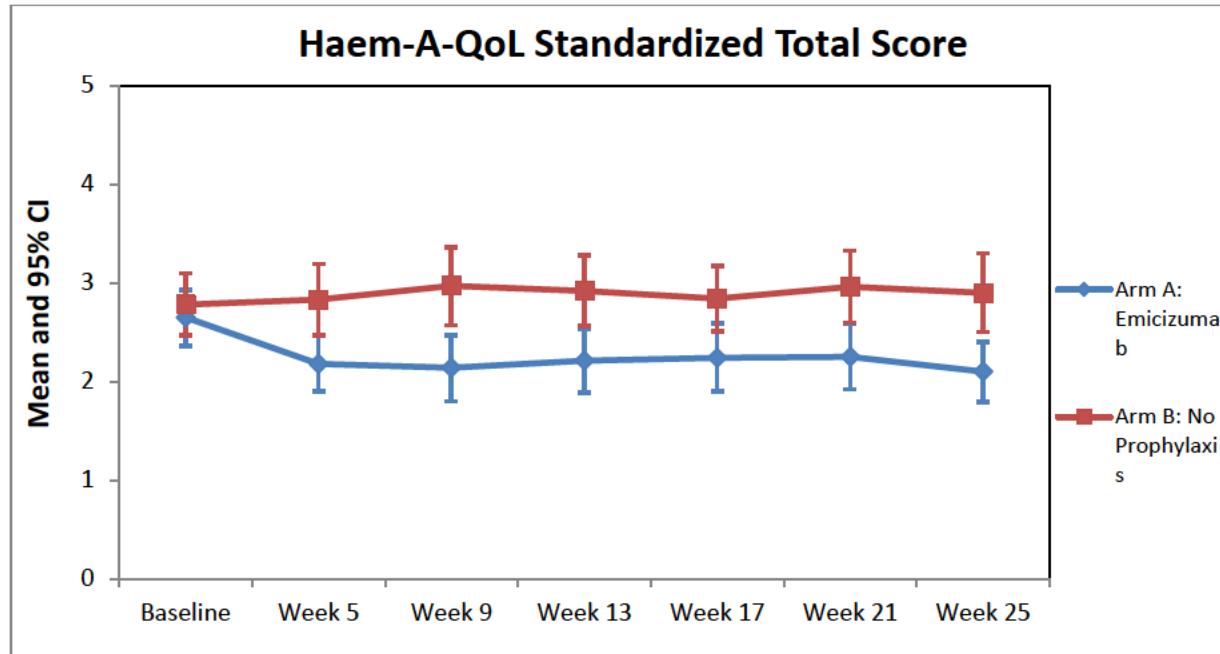
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Figure 15: Mean Haem-A-QoL Raw Total Score over Time



Source: FDA reviewer's analysis

Figure 16: Mean Haem-A-QoL Standardized Total Score over Time



Source: FDA reviewer's analysis

The following table summarizes the analysis results of the Haem-A-QoL physical health score and total score at week 25 based on the ANCOVA model.

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The adjusted mean of the transformed physical health score is 32.6 (95% CI [24.58, 40.75]) and 54.2 (95% CI [43.19, 65.15]) in the emicizumab prophylaxis arm and no prophylaxis arm, respectively. The difference of the adjusted mean is 21.6 (95% CI [7.89, 35.22], p-value = 0.0029).

The adjusted mean of the transformed total score is 29.2 (95% CI [24.24, 34.16]) and 43.2 (95% CI [36.37, 50.04]) in the emicizumab prophylaxis arm and no prophylaxis arm, respectively. The difference of the adjusted mean is 14.0 (95% CI [5.56, 22.45]).

As lower scores indicate better quality of life, the analysis results suggest that quality of life was improved at week 25 comparing emicizumab prophylaxis with no prophylaxis.

Table 15: ANCOVA for Haem-A-QoL at Week 25

	Arm A: Emicizumab Prophylaxis (N = 25) *	Arm B: No Prophylaxis (N = 14) *
Transformed Physical Health Score		
Adjusted Mean (95% CI)	32.6 (24.48, 40.75)	54.2 (43.19, 65.15)
Difference in Adjusted Means (95% CI)		21.55 (7.89, 35.22)
Raw Physical Health Score		
Adjusted Mean (95% CI)	11.52 (9.90, 13.15)	15.83 (13.64, 18.03)
Difference in Adjusted Means (95% CI)		4.31 (1.58, 7.04)
Standardized Physical Health Score		
Adjusted Mean (95% CI)	2.30 (1.98, 2.63)	3.17 (2.73, 3.61)
Difference in Adjusted Means (95% CI)		0.86 (0.32, 1.41)
Transformed Total Score		
Adjusted Mean (95% CI)	29.2 (24.24, 34.16)	43.2 (36.37, 50.04)
Difference in Adjusted Means (95% CI)		14.0 (5.56, 22.45)
Raw Total Score		
Adjusted Mean (95% CI)	89.01 (81.07, 96.95)	110.11 (98.91, 121.31)
Difference in Adjusted Means (95% CI)		21.10 (7.37, 34.83)
Standardized Total Score		
Adjusted Mean (95% CI)	2.17 (1.97, 2.37)	2.73 (2.45, 3.00)
Difference in Adjusted Means (95% CI)		0.56 (0.22, 0.90)

* Adult patients who completed the Haem-A-QoL questionnaire

Source: FDA reviewer's analysis

Reviewer Comment:

- The analysis of Haem-A-QoL physical health score and total score was based on a sub-population of HAVEN 1 study with patients' age ≥ 18 years. There were also patients with missing questionnaires at week 25, who were further excluded from the analyses of Haem-A-QoL. The p-value was based on a sub-population, and therefore is difficult to interpret.

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Due to the concern that the analyses were not based on ITT population and the results may be biased, and per Agency's request during the late cycle communication (10/24/2017), the Applicant performed sensitivity analysis to demonstrate the robustness of the results (submitted on 10/27/2017). Among all 8 patients who had missing week 25 assessments (6 patients in Arm A and 2 patients in Arm B), two patients from Arm A withdrew before week 25 due to AE, while the reasons of missing week 25 assessments for the rest of the patients were not related to treatment. In one sensitivity analysis treating these two missing assessments due to AE to have the worst scores, the nominal p-value (0.028) appears to be supportive of the pre-specified analysis. Other sensitivity analysis results presented in the submission also appear to be supportive.

- *Due to the concern of content validity of the total score and the total score results are driven by the physical score, the Agency does not agree that the total score can fully capture the patient benefit from emicizumab.*
- *In the CSR, the Applicant used a threshold* (b) (4)
In the response to the Agency's information request (9/25/2017), the Applicant also used anchor based method and distribution method (Probability distribution function; Cumulative distribution function) to justify the threshold. However, it is not clear if the approaches can fully justify the threshold. Without an agreed upon threshold, it is very difficult to interpret the PRO results or put the results into context.
- *While the results appear to be robust, it lacks acceptable clinical meaningful threshold, and the interpretation of the results in the context open-label nature of the design should viewed cautiously.*

Additional Analyses Conducted on the Individual Trial

A subgroup analysis of the randomized portion of the trial (Arm A vs. Arm B) was completed by age (<18 vs. ≥18 and <65 vs. ≥65), baseline ABR (<9 vs. ≥9), race, and target joints.

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Table 16: HAVEN1, Arm A vs. Arm B subgroup analyses

		Arm A (N=35) Emicizumab prophylaxis		Arm B (N=18) No prophylaxis		ABR ratio (95% CI)
		# subjects	ABR	# subjects	ABR	
Age	< 18	4	0.4	2	10.9	0.04 (0.005, 0.314)
	≥ 18	31	3.6	16	28.1	0.13 (0.055, 0.301)
	< 65	34	3.2	17	26.7	0.12 (0.051, 0.286)
	≥ 65	1	3.4	1	18.3	0.18 (0.008, 4.376)
Race	White	21	4.7	10	31.9	0.15 (0.052, 0.407)
	Asian	10	1.6	3	36.8	0.04 (0.011, 0.164)
	Black/AA	4	0.5	4	7.1	0.07 (0.008, 0.600)
	Other	0	NE	1	NE	NE
Baseline ABR	< 9	11	2.4	5	18.1	0.13 (0.043, 0.384)
	≥ 9	24	3.7	13	29.4	0.12 (0.045, 0.343)
Target joints	Yes	25	3.5	13	32.6	0.11 (0.045, 0.255)
	No	10	2.5	5	9.8	0.25 (0.051, 1.240)

NE = not evaluable

Source: FDA reviewer analysis

Reviewer comment: Due to the small sample of the overall randomized portion of the trial, each subgroup analysis is limited by size. However, the ABR ratio for treated bleeds is consistent among all subgroups analyzed.

8.1.3. BH29992/HAVEN2

Trial Design

The pediatric trial BH29992, referred to as HAVEN2, titled “A single-arm, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of once weekly subcutaneous administration of emicizumab in hemophilia A pediatric patients with inhibitors”

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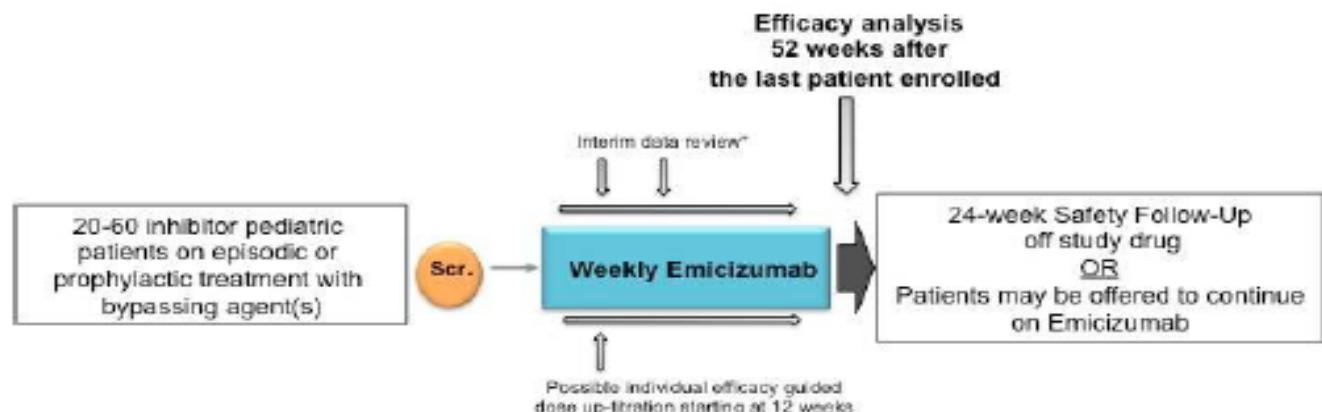
is a non-randomized, single arm, multicenter, open label, clinical study which enrolled patients aged younger than 12 years with hemophilia A who have inhibitors against FVIII. The protocol allowed enrollment of patients 12-17 years of age who weigh <40 kg as patients had to be ≥40 kg to enroll in HAVEN1. Patients could have been either on prophylaxis or episodic treatment with bypassing agents prior to study enrollment. A total of 20 patients were enrolled at the interim analysis for the initial BLA submission. At the 90-day safety update, 60 patients were enrolled, and updated analyses for both efficacy and safety were provided.

Emicizumab was given at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously thereafter. All patients in Arm A and Arm B continued to receive episodic bypassing agent therapy to treat breakthrough bleeds, preferably with rFVIIa at the lowest expected dose to achieve hemostasis.

During the 52 weeks on study, patients could up-titrate their dose for suboptimal bleeding control on emicizumab. Patients who continue to derive clinical benefit were given the opportunity to continue receiving prophylactic emicizumab as part of this or a future, separate extension study.

The Study Schema for HAVEN2 is shown in the Figure below.

Figure 14: BH29992/HAVEN2, Study Schema



Source: Figure 1, Applicant's Clinical Study Report for BH29992

Eligibility Criteria (summarized)

- <12 years of age with allowance for
- 12-17 years who weighed <40 kg
- <2 years of age only after interim review
- Weight >3 kg*
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (≥ 5 BU)
- For patients > 2 years of age:

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If on an episodic bypassing agent regimen: 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 of age: determined by investigator to be in high unmet medical need
- Adequate hematologic function (platelet count of $\geq 100 \times 10^9$ cells/L and hemoglobin ≥ 8 g/dL)
- Adequate hepatic function (total bilirubin $\leq 1.5 \times$ age adapted ULN and both AST and ALT $\leq 3 \times$ age adapted ULN)
- Adequate renal function (serum creatinine $\leq 1.5 \times$ ULN for age or creatinine clearance > 70 mL/min/1.73m²)
- Patients were excluded if they were undergoing ITI or prophylaxis treatment with FVIII
- Patients were excluded if they had a history of thromboembolic disease, with exception of previous catheter-associated thrombosis without ongoing anti-thrombotic treatment

Study Endpoints

Efficacy objectives for HAVEN2 were annualized bleeding rate (for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds) intra-patient comparison for patients previously enrolled in NIS BH29768, and HRQoL (by Haemo-QoL-SF and Adapted Inhib-QoL).

Definitions of bleeds and treatments, including the 72-hour rule, were as in HAVEN1. See Section 8.1.1 for details.

Reviewer comment: HAVEN2 included an endpoint to characterize the efficacy of up-titration. No patients in HAVEN2 up-titrated their dose, and this objective is not discussed in the context of this study.

Statistical Analysis Plan

No formal hypothesis testing was planned for HAVEN2. Annualized bleeding rates were reported using the negative binomial regression model as described above for HAVEN1.

Protocol Amendments

Significant changes at each protocol amendment are provided below.

Protocol Amendment 1:

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- Recruitment temporarily halted after 20 patients to allow Joint Monitoring Committee to evaluate the appropriateness of the maintenance dose
- Added additional efficacy objectives to evaluate all bleeds (both treated and untreated) and spontaneous bleeds
- Increased the maximum enrollment from 40 to approximately 60 with allowance for more to ensure at least 5 patients <2 years old

Protocol Amendment 2:

- Added safety findings of thromboembolic events and TMA events observed in Study BH29884, required laboratory monitoring of coagulation status following bypassing agent use
- Microangiopathic hemolytic anemia/TMA was classified as an AESI, exclusion criterion to exclude patients at high risk to experience TMA
- Guidance provided for use of bypassing agents

Data Quality and Integrity

The quality of the efficacy data submitted was adequate to allow substantial primary review. The Applicant provided analysis-ready datasets for the study BH29992.

8.1.4. BH29992 Study Results

Compliance with Good Clinical Practices

The Applicant stated in Module 2.5, Section 1.7 that all studies included in this submission were conducted in accordance with the principles of Good Clinical Practice, the principles of the Declaration of Helsinki, and the local laws and regulations of the countries in which the studies were conducted. Ethics Committees and Institutional Review Boards reviewed and approved all studies.

Financial Disclosure

A summary of financial disclosures for the studies included in the submission is provided in Appendix 19.2. The Applicant submitted financial disclosure information from all the investigators and subinvestigators from Study BH29992. One investigator, (b) (6) Site (b) (6) was identified to have financial disclosure of receiving significant payment from the Sponsor. This site enrolled (b) (6) patients in Study BH29992. With the small number of patients enrolled at any site, the enrollment of patients by this investigator is not expected to bias the outcome of the study results.

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Patient Disposition

At the cutoff date (May 8, 2017) of the updated interim report submitted with the 90-day safety update, 60 patients were enrolled. Of the 60 patients, 24 patients (40%) had completed at least 12 weeks on study, and 19 had participated in NIS BH29768 (13 of whom completed 12 weeks). No patients discontinued study treatment or had their dose up-titrated.

Protocol Violations/Deviations

At the initial clinical cutoff for the interim report with 20 patients enrolled, 11 major protocol deviations were reported in 7 patients. Two were reported as protocol deviations related to medications: one related to an incorrect emicizumab dose which was reported in error and one related to receiving a prohibited therapy (ibuprofen). Five protocol deviations were related to HRQoL assessments missing due to a technical problem with the device which was resolved.

Demographic Characteristics

All patients in this study are males and over 50% of patients are White. Approximately 70% of patients are from ex-US.

Table 17: BH29992/HAVEN2, Demographic Characteristics

	All Enrolled Patient N = 60 n (%)	Efficacy Population¹ N = 23 n (%)
Age		
Median (Min, Max)	7.1 (1.1, 15.9)	8.1 (3.2, 12.0)
Mean (SD)	7.2 (3.3)	8.0 (2.6)
Gender		
Male	60 (100%)	23 (100%)
Female	0 (0%)	0 (0%)
Race		
White	32 (53.3%)	14 (60.9%)
Asian	10 (16.7%)	4 (17.4%)
African-American	10 (16.7%)	1 (4.4%)
Other/unknown	8 (13.3%)	4 (17.4%)
Country		
US	17 (28.3%)	7 (30.4%)
Ex-US	43 (71.7%)	16 (69.6%)

¹ Efficacy population: include subjects younger than 12 years old who had been receiving emicizumab prophylaxis for at least 12 weeks.

Source: FDA reviewer analysis

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**Table 18: BH29992/HAVEN2, Baseline Disease Characteristics**

	All Enrolled Patient N = 60 n (%)	Efficacy Population ¹ N = 23 n (%)
Baseline hemophilia severity		
Mild	2 (3)	1 (4)
Moderate	1 (2)	0 (0)
Severe	57 (95)	22 (96)
Treatment in the past 24 weeks		
Episodic	25 (42)	4 (17)
Prophylactic	46 (77)	22 (96)
Baseline ABR ²		
Median	13	15
Range	(0, 337)	(0,76)
Target Joints		
Yes	23 (38)	8 (35)
No	37 (62)	15 (65)
Previous ITI*		
Yes	43 (72)	21 (91)
No	17 (28)	2 (9)

¹ Efficacy population: include subjects younger than 12 years old who had been receiving emicizumab prophylaxis for at least 12 weeks.

* ITI: immune tolerance induction

² calculated based on: (# bleeding over 24 weeks/168) X 365.25

Source: FDA reviewer analysis

Reviewer comment: The disease characteristics were reflective of standard of care in resource-rich areas. The majority of patients have tried previous immune tolerance and were on prophylaxis with a bypassing agent.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was high with no patients missing one or more doses. Rescue medication (bypassing agent) use was captured in the efficacy data on bleeds requiring treatment. The use of other concomitant medications was 70%, similar to the reported use of concomitant medications in BH29884. The most common concomitant medications were analgesics (20%, 4 patients). Other concomitant medications were used in 3 patients or fewer.

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Reviewer comment: Concomitant medication use was based on the original analysis population, and not the population submitted at the 90-day safety update. Significant differences are not expected.

Efficacy Results

At the time of the interim analysis at the 90-day safety update, the study BH29992 enrolled a total of 60 subjects, and there were 23 subjects younger than 12 years old who had been receiving emicizumab prophylaxis for at least 12 weeks (efficacy population).

Observation Time

The median observation time for the 23 subjects who completed at least 12 weeks on study was 38.1 weeks (min. 12.7 weeks; max 41.6 weeks).

Table 19: HAVEN2 Observation Time

	>12 to ≤ 16 weeks	> 32 to ≤ 36 weeks	> 36 to ≤ 40 weeks	> 40 weeks
Number of Patients (%)	4 (17.4)	4 (17.4)	10 (43.5)	5 (21.7)

Source: FDA reviewer analysis

Reviewer Comment: The observation time in the BH29992 study is comparably shorter than the observation time in the BH29884 study. The ABR analysis results may not be stable due to the short observation time, and the analysis result should be interpreted with caution.

Efficacy Endpoint, BH29992 Single Arm Study

The analysis results on treated bleed, all bleed, treated spontaneous bleed, treated joint bleed and treated target bleed during the observation time are shown in the following table.

Based on negative binomial model, the ABR is fewer than 1 for treated bleed, treated spontaneous bleed and treated joint bleed, and 2.9 for all bleed. The ABR is not estimable for treated target joint bleed because all patients have zero bleed during the efficacy period.

Using the formula that ABR = Number of bleeds/Number of days during the efficacy period) x 365.25, the median ABR was zero for all types of bleed, except for all bleed, which is 1.5.

Majority of patients have zero bleed event for treated bleed, treated spontaneous bleed, treated joint bleed, and target joint bleed. There were 8 of 23 patients (34.8%) with all bleeds.

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Table 20: HAVEN2, Bleed Events (Efficacy Population)

Bleed Type	ABR (95% CI) ^a N = 23	Median ABR (IQR) ^{b c} N = 23	# of Patients with Zero Bleed, % (95% CI) N = 23
Treated Bleed	0.2 (0.06, 0.62)	0 (0, 0)	20, 87% (66.4%, 97.2%)
All Bleed	2.9 (1.75, 4.94)	1.5 (0, 4.53)	8, 34.8% (16.4%, 57.3%)
Treated Spontaneous Bleed	0.1 (0.01, 0.47)	0 (0, 0)	22, 95.7% (78.1%, 99.9%)
Treated Joint Bleed	0.1 (0.01, 0.47)	0 (0, 0)	22, 95.7% (78.1%, 99.9%)
Treated Target Joint Bleed	NE ^d	0 (0, 0)	23, 100% (85.2%, 100%)

^a Based on negative binomial regression

^b Based on formula ABR = Number of bleeds/number of days during the efficacy period) X 365.25

^c IQR = Interquartile range, 25th percentile to 75th percentile

^d Not estimable due to zero bleed for all patients in the analysis population

Source: FDA reviewer analysis

Reviewer's Comment: The analysis population has a small sample size (n = 23), which leads to wide confidence intervals.

Efficacy Endpoint – Intra - Patient Comparison

Among these 23 patients whose observation time longer than 12 weeks, there were 13 patients who were enrolled in the NIS study before enrolling in the BH29992 study. Of the 13 patients, 12 were receiving prophylaxis with a bypassing agent, and 1 was receiving episodic treatment with a bypassing agent prior to emicizumab prophylaxis. The ABR when receiving prophylaxis treatment were compared with that when receiving bypassing agent treatment during the NIS study.

Table 21: Bleed Event, Intra-Patient Comparison

	Emicizumab Prophylaxis (N = 13)	Previous Bypassing Agent Treatment (N = 13)
Treated Bleed		
Model based ABR (95% CI) ^a	0.2 (0.06, 0.76)	17.2 (12.38, 23.76)
Model based ABR ratio (95% CI) ^a		0.01 (0.004, 0.044)
Formula based ABR, Median (IQR) ^{b c}	0 (0, 0)	14.3 (11.02, 24.35)
# of patients with zero bleed (%)	11 (84.6%)	1 (7.7%)

^a Based on negative binomial regression

^b Based on formula ABR = Number of bleeds/number of days during the efficacy period) X 365.25

^c IQR = Interquartile range, 25th percentile to 75th percentile

^d Not estimable due to zero bleed for all patients in the analysis population

Source: FDA reviewer analysis

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Reviewer Comment: Only a small number of patients had both baseline assessments (from NIS study) and week 12 assessments (n=13). The limited number of patients evaluable for the intra-patient comparison limits the reliability of this analysis. However, the trend of improvement in ABR for treated bleeds in the intra-patient analysis is similar to the analysis in HAVEN1 and is supportive of efficacy in pediatric patients <12 years.

HAVEN2 enrolled patients as young as 1.1 years old, and efficacy data supports the indication for pediatric patients with hemophilia A with FVIII inhibitors. The mechanism of the disease is the same across all age groups, including patients less than 1 year old. However, at birth most coagulation factors exceed adult levels, then trend down over the first few months of life approaching adult levels by age 6 months (Williams, Chalmers et al. 2002). The higher levels of FIXa and FX in infants may increase the drug clearance and possibly affect efficacy. In support of including all age groups despite potential differences in drug clearance is that the therapeutic window is wide (see Section 19.4.2) and additional safety concerns would not be expected with increased clearance. The incidence of high-titer FVIII inhibitors is rare in patients <6 months old (Kulkarni, Presley et al. 2017). Overall, the clinical team did not identify a reason to limit the age group of the indication in the pediatric population.

Dose/Dose Response

All patients received the same dose of emicizumab prophylaxis, and a dose response cannot be determined in this trial. See clinical pharmacology sections for an exposure-response assessment.

Durability of Response

Median time on treatment for patients enrolled for patients included in the efficacy analysis in HAVEN2 was 38.1 weeks (range 12.7-41.6). Durability of response cannot be determined at the time of the interim analysis.

Persistence of Effect

No patients discontinued emicizumab to allow an analysis of persistence of effect after discontinuation. However, persistence is not expected after the antibody concentration falls below therapeutic levels.

Additional Analyses Conducted on the Individual Trial

N/A

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8.1.5. ACE001JP/ACE002JP Study Design

Trial Design

The dose-finding trial, ACE001JP, was conducted in healthy volunteers and adolescent and adult patients with hemophilia A in Japan. The extension study, ACE002JP, included adolescent and adults with hemophilia A who either had FVIII inhibitors or had severe hemophilia at baseline.

ACE001JP include 3 parts: (A) healthy Japanese volunteers, (B) healthy Caucasian volunteers, (C) Adult and adolescent Japanese patients (≥ 12 years old) with hemophilia A with or without FVIII inhibitors. Parts A and B included single-dose cohorts ranging from 0.001 mg/kg to 0.3 mg/kg. Part C had three dosing cohorts as follows:

- Cohort C-1: 1 mg/kg loading dose, then 0.3 mg/kg/week
- Cohort C-2: 3 mg/kg loading dose, then 1 mg/kg/week
- Cohort C-3: 3 mg/kg/week

The primary objectives were safety, tolerability, PK/PD, and exploratory efficacy.

Reviewer comment: For efficacy, Study ACE002JP provided supportive data for long-term efficacy only. The study enrolled patients with and without FVIII inhibitors, and only 16 patients entered the extension study. However, these patients represent the longest duration on study drug. The discussion of the trial design is abbreviated, and discussion is provided regarding long-term efficacy. All 18 patients who received at least one dose of the study drug were included in Section 8.2 for discussion of safety.

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8.1.6. ACE001JP/ACE002JP Study Results**Table of Demographic Characteristics****Table 22: ACE001JP, Demographics**

	All Enrolled Patient N = 18 n (%)
Age	
Median (Min, Max)	30 (12, 58)
Mean (SD)	32.9 (15.4)
Gender	
Male	18 (100%)
Female	0 (0%)
Race	
White	0 (0%)
Asian	18 (100%)
African-American	0 (0%)
Country	
US	0 (0%)
Ex-US	18 (100%)

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**Table 23: ACE001JP, Baseline Disease Characteristics**

	All Enrolled Patient N = 60 n (%)
Baseline hemophilia severity	
Mild	0 (0%)
Moderate	0 (0%)
Severe	18 (100%)
Treatment at Baseline ^a	
Episodic	8 (26.7%)
Prophylactic	10 (73.3%)
Target joint	
Yes	15 (83.3%)
No	3 (16.7%)
Current inhibitor	
Yes	11 (61.1%)
No	7 (38.9%)
Previous ITI*	
Yes	8 (44.4%)
No	10 (55.6%)

^a includes prophylaxis with FVIII for patients without inhibitors

* ITI = immune tolerance induction

Efficacy Results

Two patients discontinued emicizumab treatment in ACE001JP. One patient discontinued for injection site reactions at day 29. The other patient completed 12 weeks in ACE001JP and chose not to continue on the extension study. At the data cutoff for this submission, the remaining 16 patients were still receiving emicizumab prophylaxis for at least 121 weeks (2.3 years).

Of 16 patients, 6 patients experienced no bleeding episodes with treatment periods ranging from 848 to 1207 days.

Mean and median ABR for treated bleeds was calculated per dose cohort. Four patients up-titrated dose and are included in analysis for original dose and increased dose, so the total N in the table is 18, though this represents only 16 patients.

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Table 24: ACE002JP, ABR for treated bleeds per dose cohort

	Cohort C-1: 0.3 m/kg/week maintenance N=6*	Cohort C-2: 1 mg/kg/week maintenance N=6*	Cohort C-3: 3 mg/kg/week maintenance N=6
Mean ABR (95% CI)	5.0 (1.6-11.6)	0.8 (0.01-5.1)	0.2 (0.0-4.1)
Median ABR (IQR)	1.1 (0.9-9.2)	0.2 (0-1.4)	0 (0-0.4)

* includes analysis of ABR prior to dose up-titration

Source: Applicant's ISE, Table 9, analysis not independently verified

Reviewer comment: The results from ACE002JP demonstrate durability of response for more than 2 years. All patients who continued treatment maintained efficacy with a low rate of treated bleeds.

Dose/Dose Response

ABR per dose cohort is presented in Table 24. See clinical pharmacology assessment for dose-response evaluation.

Durability of Response

See efficacy results above in support of durability of response for patients enrolled on ACE002JP. At the data cutoff, 16 patients have received treatment for more than 121 weeks.

8.1.7. Assessment of Efficacy Across Trials

Methods

The Applicant proposed the indication “for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors”, which includes the full adult and pediatric age ranges. The clinical development program for emicizumab included two pivotal trials, one for adolescents and adults and one for pediatric patients <12 years old. Both trials were positive and supportive of the proposed indication.

Across the two trials, the age and prior bypassing agent regimen differed between groups. The duration on study varied widely at the interim analyses for both trials. However, a pooled analysis was performed for any patient in HAVEN1 or HAVEN2 who completed 12 weeks on emicizumab treatment.

The numbers of patients from each treatment arm in each trial were summarized in the following table. The median observation time for these patients was 31.9 weeks (min 12.1 weeks, max 48.9

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weeks)

Table 25: Pooled analysis, patients per study arm who completed 12 weeks on emicizumab

	Treatment Arm	Number of Patients N = 97
HAVEN1	A	32 (33.0%)
	B	3 (3.1%)
	C	37 (38.1%)
	D	1 (1.0%)
HAVEN2	Emicizumab	24 (24.7%)

Source: FDA reviewer analysis

Primary Endpoints

The main efficacy endpoint for consideration for efficacy is the occurrence of treated bleeds while on emicizumab prophylaxis. The pooled analysis for patients in HAVEN1 and HAVEN2 who completed at least 12 weeks on study is shown below.

Table 26: Pooled analysis, treated bleed rate

Bleed Type	ABR (95% CI) ^a N = 97	Median ABR (IQR) ^b N = 97	Patients with Zero Bleeds n, % (95% CI) N = 97
Treated Bleed	3.2 (1.8, 5.6)	0 (0, 1.5)	67, 69.1% (58.9%, 78.1%)
All Bleed	5.5 (3.9, 7.9)	1.5 (0, 6.4)	42, 43.3% (33.3%, 53.8%)
Treated Spontaneous Bleed	1.7 (0.9, 3.3)	0 (0, 0)	75, 77.3% (67.7%, 85.2%)
Treated Joint Bleed	0.6 (0.3, 1.3)	0 (0, 0)	85, 87.6% (79.4%, 93.4%)
Treated Target Joint Bleed	0.2 (0.1, 0.7)	0 (0, 0)	91, 93.8% (87.0%, 97.7%)

^a Based on negative binomial regression

^b Based on formula

Source: FDA reviewer analysis

Secondary and Other Endpoints

An analysis of other bleed categories (all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds) was performed for the pooled analysis of any patient who completed 12 weeks on emicizumab prophylaxis. See above.

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Reviewer comment: The pooled analysis provides supportive information showing a low rate of treated bleeds in patients treated with emicizumab. The pooled analysis provides an overview of the larger group of 97 patients across all pediatric and adult age ranges. There are no significant differences in the findings of the pooled analysis compared to the analyses of the individual studies and treatment arms.

Subpopulations

Subgroup analyses by age, race, baseline bleed rate, and baseline target joints is provided for randomized patients in Arm A vs. Arm B of HAVEN1. See Section 8.1.2 for results. No additional subgroup analyses were performed.

8.1.8. Integrated Assessment of Effectiveness

The efficacy of emicizumab in adult and pediatric patients with hemophilia A with FVIII inhibitors has been established based on the results of the randomized phase 3 study in adults and adolescents and the single-arm study in pediatric patients. The key analyses were treated bleeds in the following:

- Emicizumab prophylaxis (Arm A) vs. no prophylaxis (Arm B) in patients who were on prior episodic bypassing agents: ABR 2.9 vs. 23.3
- Prior prophylaxis with bypassing agents (Arm C_{NIS}) vs. emicizumab prophylaxis (Arm C) in patients who were on prior prophylaxis: ABR 15.7 vs. 3.3
- Emicizumab prophylaxis in pediatric patients < 12 years: ABR 0.2

Supportive data was also provided by the rate other bleed categories (all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds) in the analysis populations.

8.2. Review of Safety

8.2.1. Safety Review Approach

Three studies were included in the safety database for emicizumab; see Table 5 for details. HAVEN1 was the phase 3 study for the treatment of adolescent and adult patients with hemophilia A with FVIII inhibitors. HAVEN2 was the single-arm study for pediatric patients <12 years old with hemophilia A with FVIII inhibitors. ACE001JP and its extension study ACE002JP were the phase 1b trials conducted in Japan for patients with hemophilia A with or without FVIII inhibitors.

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The safety population of 189 patients includes any patient who received at least one dose of emicizumab across the clinical development program. The data presented are an updated analysis from the 90-day safety update. This analysis was proposed to be included in the initial labeling to provide an increased number of patients in the pediatric study.

In HAVEN1, 111 patients were included; 1 patient in Arm A withdrew prior to the first dose of emicizumab and 1 patient enrolled in Arm B is on no prophylaxis and has not yet reached 24 weeks to initiate emicizumab prophylaxis; an additional 4 in Arm D were enrolled after the initial analysis. All 60 patients from HAVEN2 are included for safety. From ACE001JP, 18 patients received emicizumab. Seven of the patients in the phase 1b trial did not have high titer inhibitors, but the safety profile is not expected to be significantly different, so those patients are included in the safety evaluation. Table 27 shows the enrollment by age group in each trial.

Table 27: Safety Population by Trial and Age Group

Age Groups	HAVEN1 N=111	HAVEN2 N=60	ACE001JP N=18	Overall N=189
0 - 2	-	2		2
2 - <6	-	17		17
6 - <12	-	38		38
12 - <18	32	3	3	38
Adult	79	-	15 ^a	94

^a Includes 7 patients without high-titer inhibitors

Source: FDA reviewer analysis

8.2.2. Review of the Safety Database

Overall Exposure

The overall exposure in 189 patients across the three submitted studies was 157.9 patient-years. The median exposure was 38.0 weeks (range 0.8-177.2 weeks). Duration of exposure by study and arm is presented in the table below.

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Table 28: Summary of Emicizumab Exposure

	HAVEN1					HAVEN2
	Arm A N=34	Arm B N=17	Arm C N=49	Arm D N=11	Total N=111	All N=60
Duration						
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
By duration						
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

Source: Adapted from Table 3 in Applicant's 90-day Safety Update Report. Analysis not independently verified.

In Study ACE001JP, 16 of 18 patients continue on emicizumab, and all have been exposed for >52 weeks. The median duration of exposure in the study was 149.6 weeks (range 3.0-177.2 weeks).

Relevant characteristics of the safety population:

Table 29: Safety Population, Demographics and Baseline Disease Characteristics

	All patients N=189 n (%)
Age	
Mean (SD)	24.1 (17.7)
Median	17.0
Min-Max	1.1 - 75
Sex	
Male	189 (100%)
Female	0
Baseline hemophilia severity	
Mild	5 (2.6%)
Moderate	5 (2.6%)
Severe	179 (94.7%)
Highest historical inhibitor titer*	

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Mean (SD)	661.0 (1112.9)
Median	204.8
Min-Max	5 - 7200
Prior ITI	
Yes	108 (57.1%)
No	81 (42.9%)
Target joint	
Yes	115 (60.8%)
No	74 (39.2%)

*Data available from N=173

Source: FDA reviewer analysis

Reviewer comment: All patients except for 2 adults enrolled in HAVEN1 have received at least one dose of emicizumab. The demographics and baseline disease characteristics reflect that of each study as discussed in 8.1 above.

Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with emicizumab prophylaxis. Because the data are all from single arm trials, the contribution of the underlying disease and patients usual state of health to adverse reactions is difficult to estimate. Patients with hemophilia A with FVIII inhibitors are generally do not have comorbidities that would not be expected by age. The population in this analysis is a good representation of the US population. The adverse reactions were evaluated over all doses of emicizumab, but all patients except those in the phase 1b study received the same dosing regimen. Few patients discontinued treatment and only two patients in HAVEN1 up-titrated their dose. The duration of treatment is adequate to allow assessment of adverse reactions over time, and all trials in the current review are still ongoing.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the safety data submitted was adequate to allow substantial primary review. The Applicant provided analysis-ready datasets for each individual study as well as an integrated dataset reporting AEs in all patients treated with emicizumab prophylaxis. The Applicant also provided narratives for all patients with AEs resulting in death, SAEs, AEs leading to discontinuation of the study, and AEs of interest.

Categorization of Adverse Events

Adverse events were reported down to the verbatim term. The adverse events were coded using MedDRA. For the initial submission, MedDRA version 19.1 was used for individual trials and the

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pooled safety analysis. For the pooled safety analysis at the 90-day safety update, the Applicant recoded all studies using MedDRA version 20.0. For infusion related reactions, AEs are presented as high level term (HLT).

Routine Clinical Tests

The frequency of clinical assessments is adequate to assess the risks of serious safety signals. Refer to the review of efficacy for the relevant trials for the general schedule of assessments.

8.2.4. Safety Results

Deaths

There were no deaths in emicizumab clinical trials by the clinical cut-off date. After the cut-off date, one patient died from rectal hemorrhage after developing TMA and declining blood transfusion. See Significant Adverse Events below for further details.

Serious Adverse Events

Serious adverse events (SAEs) were uncommon, occurring in 12% of patients overall. SAEs that occurred in more than 1 event were thrombotic microangiopathy (TMA), thromboses, appendicitis, and hemophilia which occurred in 2 patients each.

Dropouts and/or Discontinuations Due to Adverse Effects

AEs leading to discontinuation occurred in only 3 patients: one of the patients with TMA, one of the patients with a thrombosis, and 1 adolescent patient with injection site reactions.

Study drug was interrupted in 5 patients for TMA, cerebral sinus thrombosis, mesenteric hematoma, petechiae, and hematuria. All 5 patients restarted without further occurrence. There were no dose adjustments for AEs.

Significant Adverse Events

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Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) is a rare disorder where blood clots in small blood vessels cause damage to red blood cells, resulting in anemia, and may cause harm to kidneys or other organs. Signs and symptoms may be vague and can include confusion, weakness, swelling of arms and legs, yellowing of skin and eyes, vague abdominal or back pain, nausea, vomiting, feeling sick, or decreased urination (George and Nester 2014).

During the clinical trial, three patients experienced thrombotic microangiopathy. In all three patients, the events occurred after receiving multiple doses of aPCC as a bypassing agent for a suspected bleed. A brief description of each event follows:

Patient 1811 (36 year old): On study day 48, the patient developed a left knee bleed which was treated with 1 dose of aPCC. The following day, he developed a left elbow bleed which was treated with one additional dose of aPCC. On day 50, he had pain in his back suspected to be a bleed, so he administered 2 doses of rFVIIa and 2 doses of aPCC. The next day, he developed jaundice and weakness, and laboratory evaluation was consistent with a diagnosis of TMA with thrombocytopenia, anemia, hyperbilirubinemia, acute renal injury, elevated LDH, and schistocytes on blood smear. He received therapeutic plasm exchange and hemodialysis as supportive care. He did not receive any further aPCC, but was given rFVIIa as needed for bleeds or procedure prophylaxis. He discontinued emicizumab, and received rFVIIa as needed as a bypassing agent. His TMA resolved by day 65.

Patient 2204 (13 year old): On study day 217, the patient developed a right ankle bleed. Over the next two and a half days, he received 5 doses of aPCC, approximately every 12 hours. On days 220-222, the patient developed emesis and abdominal pain. Laboratory evaluation on day 222 showed evidence of TMA with acute renal failure, thrombocytopenia, elevated LDH, low haptoglobin, and schistocytes on blood smear. He had normal C3, C4, and CH50 levels. His scheduled dose of emicizumab was delayed and he did not receive any additional aPCC. He did not receive plasma exchange or dialysis. His TMA resolved by study day 239, and the patient restarted emicizumab treatment. He has not had a recurrence of TMA since restarting emicizumab prophylaxis.

Patient 1301 (41 year old): The patient has a history of ileostomy placement due to a perforated bowel. On study day 237, the patient developed rectal hemorrhage. He was initially treated with more than 10 doses of rFVIIa over the next 3 days, and the bleeding continued. He became severely anemic, but declined blood transfusion. He then received more than 10 doses of aPCC over 3-4 days in an attempt to control the rectal bleeding. On study day 243, laboratory evaluation showed evidence of TMA with schistocytes on blood film, elevated LDH, anemia, low platelets, and elevated serum creatinine. ADAMTS13 level was normal. No additional doses of aPCC were given after the diagnosis of TMA. The patient received therapeutic plasma exchange against albumin. The patient continued to decline blood transfusion, and he died on day 246 from

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severe anemia due to rectal hemorrhage. At the time of his death, the TMA was improving based on laboratory evaluation.

Thromboembolic events

Thromboembolic events, or serious blood clots, occurred in two patients on emicizumab clinical trials. In both patients, the events occurred after receiving multiple doses of aPCC as a bypassing agent for a suspected bleed. A brief description of each event follows:

Patient 2171 (22 year old): On study day 131, the patient experienced a right knee joint bleed. He received 8 doses of aPCC over 4 days. On day 134, he presented with left eye swelling, blurred vision, headache, nausea, and vomiting. Brain MRI revealed a clot involving the left superior ophthalmic vein and cavernous sinus, and he was diagnosed with a cavernous sinus thrombosis. He did not have any surgical or medical interventions including no anticoagulation. The clot resolved on repeat brain imaging by study day 151. He resumed emicizumab prophylaxis on study day 162, and has not had any further thrombotic events.

Patient 1814 (42 year old): On study day 145, the patient experienced a right knee bleed. He received one dose of aPCC. The following day, he experienced a right shin bleed, and received an additional dose of aPCC. Later that day, he applied ice to his shin due to pain, and after removing the ice pack, he noted skin changes. He was diagnosed with extensive skin necrosis of his right shin and limited necrosis of his left calf. Ultrasound of the area of skin necrosis revealed a superficial thrombosis of the right saphenous vein. The investigator considered the skin necrosis was due to the thromboembolic event. He did not receive any anticoagulation. Emicizumab was permanently discontinued, and the skin necrosis and superficial thrombosis were resolving at the last report.

TMA/TE events and bypassing agent use

The TMA and TE events only occurred when patients received aPCC. The Applicant did an analysis of how much aPCC was used during each bleeding event. The labeled dose for aPCC is 50-100 U/kg q6-12 hours depending on the type of the bleed. A “high-intensity” aPCC treatment event was defined as someone who received >100 U/kg/day for >1 day, which is boxed in gray in Table 30 below. There were 78 treatment events in 20 patients at all doses. Seventy of the events were not determined to be “high-intensity” and 8 were “high-intensity”. Of the 8 “high-intensity” events, 5 lead to TMA/TE, resulting in an occurrence of 63%.

Reviewer comment: The following tables on aPCC and rFVIIa treatments are patients in HAVEN1 only who received the bypassing agents on day 8 or later after initiation of emicizumab up to 30 days after emicizumab exposure. The Sponsor states that prior to day 8 of treatment the emicizumab serum concentrations would not be high enough to cause the drug-drug interaction

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with concomitant aPCC, though there is no objective data to support this assertion. One additional patient in HAVEN2 had an aPCC treatment event and is included in the simplified table proposed for inclusion in the prescribing information. Six patients in ACE001JP/ACE002JP had aPCC treatment events and are not included in this analysis.

Table 30: aPCC Average Daily Use and Duration of Treatment, per Treatment Event

	<50 U/kg/day	50-100 U/kg/day	101-150 U/kg/day	>150 U/kg/day	Any dose
1 day	6	46	8	5	65
2 days	-	3	1 ^b	-	4
3 days	-	-	3 ^{a,a}	1 ^b	4
4 days	-	1	2	1 ^a	4
>4 days	1	-	-	-	1
All	7	50	14	7	78

^a Thrombotic microangiopathy

^b Thrombotic event

Source: Adapted from Table 9 of 90-day Safety Update, analysis not independently verified.

No events occurred when rFVIIa was used alone as a bypassing agent. However, one patient with TMA received both aPCC and rFVIIa, but he continued to receive rFVIIa and the TMA was resolving. A similar analysis of “high-intensity” rFVIIa events was performed as shown in Table 31 below. The labeled dose for rFVIIa is 90 ug/kg q2hr, so a “high-intensity” event was defined as >180 ug/kg/day for >1 day, which is boxed in gray. There were 140 treatment events in 37 patients at all doses. There were 21 “high intensity” rFVIIa events, and 119 events that were not high intensity.

Table 31: rFVIIa Average Daily Use and Duration of Treatment

	<90 ug/kg/day	90-180 ug/kg/day	181-270 ug/kg/day	>270 ug/kg/day	Any dose
1 day	23	43	33	15	114
2 days	1	3	6	6	16
3 days	-	1	2 ^a	-	3
4 days	-	-	-	-	-
>4 days	-	-	2	5	7
All	24	47	43	26	140

^a Thrombotic microangiopathy, in patient who also received high-intensity aPCC

Source: Adapted from Table t_ucmt04_r7a_il03_ip22_ip11_SAP2 of 90-day Safety Update, analysis not independently verified.

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Reviewer comment: Thrombotic microangiopathy and thromboembolic events occurred in patients who received multiple doses of aPCC as a bypassing agent while on emicizumab prophylaxis. The occurrence of TMA and thromboembolic events was uncommon, occurring in three and two patients, respectively. However, the events were serious and potentially life threatening. The symptoms of TMA and thromboembolic events can be vague and difficult to recognize by patients, caregivers, and healthcare providers. While the events in the trial only occurred in patients who received higher doses of aPCC, the clinical trial experience was small and of relatively short duration and cannot exclude the possibility of occurrence of events with lower doses of aPCC or with rFVIIa as a bypassing agent.

After occurrence of the first 4 events (2 TMA, 2 TE), the clinical trials were amended to recommended that the use of aPCC or other bypassing agents should be avoided or limited, and if needed to treat breakthrough bleeds, rFVIIa should be used if possible. The trials were temporarily halted of enrollment until iDMC review, and patients were reconsented. An exclusion criterion to exclude patients at high risk to experience thrombotic microangiopathy was added. After these changes, one patient experienced TMA. The patient was treated at a local hospital in communication with the site investigator. The investigator conveyed to the treating physician the risk of TMA with aPCC treatment; however, the patients bleed did not stop after use of rFVIIa alone which necessitated the use of aPCC.

As demonstrated by this patient, some patients may require aPCC treatment despite the recommendation to avoid aPCC if possible. A study by Astermark et al, 2007, indicated that a significant proportion of patients have better bleeding control with one bypassing agent (aPCC or rFVIIa) and not the other, referred to as “discordant pairs”, in more than 40% of patients. For the patients who were discordant, about 2/3 preferred aPCC and 1/3 preferred rFVIIa (Astermark, Donfield et al. 2007). Complete avoidance of aPCC for patients on emicizumab prophylaxis is likely not possible.

The prescribing information indicates that patients that TMA/TE events occurred in patients who received a cumulative amount of aPCC of >100 U/kg/24 hours for more than 24 hours in the clinical trials. If aPCC must be used, then patients should be monitored for TMA/TE.

The labeled dose for aPCC is 50-100 units/kg/dose with frequency depending on the type and duration of bleed. The prescribing information indicates that if patients need more than 100 units/kg, they should be treated under physician supervision. The signs and symptoms of TMA and TE are conveyed in the prescribing information and medication guide for prescribers, patients, and caregivers.

To monitor for the occurrence of TMA/TE in the post-marketing setting, the Applicant will be required to report all TMA/TE events in 15-day Alert reports for 5 years following approval. Periodic safety reports will include analyses of cumulative data on the rate of TMA/TE.

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Treatment Emergent Adverse Events and Adverse Reactions

The Table below shows a pooled analysis of 189 patients in three clinical trials (HAVEN1, HAVEN2, ACE002JP) with AEs that occurred at ≥5%.

Table 32: Pooled Safety Analysis, Common AEs in ≥5%

PT	Events	# of Subjects	% N=189
Injection site reaction^	93	35	18.51
Viral upper respiratory tract infection*	32	28	14.89
Headache	32	28	14.81
Upper respiratory tract infection*	28	22	11.7
Arthralgia	27	18	9.57
Contusion*	36	17	9.04
Influenza*	13	13	6.91
Pyrexia	15	13	6.91
Diarrhea	14	12	6.38
Dental caries*	14	11	5.85
Cough*	12	10	5.32
Myalgia	14	9	4.79

[^]Reported as High Level Term

*Removed from report of AEs in label

Source: FDA reviewer analysis

Injection site reaction reported in the label includes preferred terms of injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site pain, injection site pruritus, injection site rash, and injection site reaction. One report of injection site reaction was removed from the reported AEs because it was attributed to the alcohol wipes.

The Applicant removed nasopharyngitis, upper respiratory tract infection, contusion, influenza, cough, dental caries from the reported AEs in the label based on their assessment using a modified Bradford Hill Criteria.

Reviewer comment: The proposal to exclude AEs that are unlikely to be related to emicizumab is appropriate. The study drug was generally well tolerated with most reported AEs being low grade and reported as likely unrelated to study drug by investigators.

Injection site reactions (ISRs) lead to discontinuation of study drug in one patient in study ACE001JP; no other patients discontinued, modified dosing, or interrupted emicizumab for an ISR. No serious ISRs were reported. Six patients received treatment for ISRs, 3 patients in BH29884 and 3 patients in ACE001/002JP. Treatments included topical astringents or corticosteroids, antihistamines, or NSAIDs.

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Randomized safety analysis

To identify which AEs were more common in the emicizumab treated patients compared to no prophylaxis, an evaluation of the safety during the 24 weeks of the randomized portion of the HAVEN1 trial was performed by the Applicant. The number of patients per group is small since the randomized portion only included 34 patients treated with emicizumab prophylaxis and 18 with no prophylaxis for 24 weeks.

Table 33: Safety in Randomized Portion of HAVEN1, Arm A vs. Arm B

PT	Arm A: Emicizumab N=34	Arm B: No prophylaxis N=18
Injection site reaction	8 (23.5)	-
Upper respiratory tract infection	7 (20.6)	3 (16.7)
Fatigue	3 (8.8)	-
Hair growth abnormal	3 (8.8)	-
Headache	3 (8.8)	-
Cough	2 (5.9)	-
Folliculitis	2 (5.9)	-
Enteritis	2 (5.9)	-
Toothache	2 (5.9)	-
Arthralgia	2 (5.9)	-
Myalgia	2 (5.9)	-
Nasopharyngitis	1 (2.9)	2 (11.1)
Hemarthrosis	-	2 (11.1)

Source: Adapted from Table t_aet02_01_inc10_il04_ip21_ip11_ipae_SAP1 in Applicant's BH29884 CSR. Analysis not independently verified.

Reviewer comment: Due to the small number of patients randomized and the limited duration prior to patients on Arm B switching to emicizumab prophylaxis, this analysis is of limited utility. The study was not blinded which could lead to reporting bias and likely underreporting in the no prophylaxis arm.

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Table 34: Pooled Safety Analysis by Age Group

PT	Adults (18+ yrs) N=86	Peds (2-<18 yrs) N=55	12-<18 yrs N=36	6-<12 yrs N=15	2-<6 yrs N=4
Injection site reaction	17 (19.8)	9 (16.4)	6 (16.7)	3 (20.0)	-
Nasopharyngitis	12 (14.0)	4 (7.3)	1 (2.8)	1 (6.7)	2 (50.0)
Contusion	8 (9.3)	3 (5.5)	2 (5.6)	-	1 (25.0)
Headache	8 (9.3)	9 (16.7)	9 (25.0)	-	-
Dental caries	7 (8.1)	1 (1.8)	1 (2.8)	-	-
Upper respiratory tract infection	7 (8.1)	7 (12.7)	5 (13.9)	1 (6.7)	1 (25.0)
Arthralgia	6 (7.0)	2 (3.6)	1 (2.8)	1 (6.7)	-
Diarrhea	6 (7.0)	3 (5.5)	2 (5.6)	-	1 (25.0)
Pharyngitis	6 (7.0)	-	-	-	-
Excoriation	5 (5.8)	-	-	-	-
Fatigue	5 (5.8)	1 (1.8)	1 (2.8)	-	-
Myalgia	4 (4.7)	3 (5.5)	2 (5.6)	1 (6.7)	-
Pyrexia	4 (4.7)	4 (7.3)	2 (5.6)	1 (6.7)	1 (25.0)
Influenza	2 (2.3)	3 (5.5)	3 (8.3)	-	-
Insomnia	1 (1.6)	3 (5.5)	2 (5.6)	1 (6.7)	-

Source: FDA reviewer analysis

Reviewer comment: Analysis by age group was done with the original submission of 141 patients. The analysis was not repeated after the 90-day safety update.

Comparing adults to adolescents overall, there are only minor differences with more nasopharyngitis in adults and more headaches in children, but no notable differences. When you further break it down by age groups, then the numbers in each age group are too small for an accurate analysis of the incidence of any AE. However, there is no unexpected safety signal in any age group, and the general distribution of AEs by age group was consistent over all analysis groups. The majority of AEs were low grade and determined to be unrelated to the study drug.

Laboratory Findings

No clinically significant changes in laboratory parameters were observed during treatment with emicizumab.

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Vital Signs

No clinically significant changes in vital sign parameters were observed during treatment with emicizumab.

Electrocardiograms (ECGs) and QT

No dedicated cardiovascular safety pharmacology studies were performed. Routine ECG monitoring was performed in HAVEN1 and HAVEN2 at baseline, week 4, week 24, and at study completion/termination. No clinically significant changes from baseline were seen in any ECG parameter including QT interval.

Immunogenicity

Four (2.8%) patients with hemophilia developed anti-emicizumab antibodies. All 4 patients were in Study ACE002JP, treated in the two lower dose cohorts (3 patients in the 0.3 mg/kg cohort and 1 patient in the 1.0 mg/kg cohort) and at doses lower than HAVEN1 and HAVEN2.

None of the antibodies were neutralizing. The assay used to detect anti-drug antibodies may not be sensitive to detect low levels of anti-drug antibodies in the presence of therapeutic doses of emicizumab. See the clinical pharmacology section for a detailed analysis.

In HAVEN1, two patients had PK measurements decrease over time, indicating possible anti-drug antibodies. One patient (1002) had no changes to his dosing, and has not had any bleeds on study. He had two SAEs, but both were designated unrelated by the investigator. The other patient (1121) had declining PK measurements, and met bleeding criteria to up-titrated his dose, so increased to 3 mg/kg/week. After up-titration, his PK measurements did not increase as much as expected. He had only 1 bleed after up-titration, and no related or serious AEs. Both patients are still on emicizumab treatment.

One healthy volunteer developed a neutralizing anti-drug antibody in Study ACE001JP.

8.2.5. Analysis of Submission-Specific Safety Issues

In both HAVEN1 and HAVEN2, adverse events of special interest included suspected Hy's Law, suspected transmission of infectious agents by the study drug, systemic hypersensitivity reactions, thromboembolic events, and thrombotic microangiopathy.

Suspected Hy's Law

There were no aspartate transaminase or alanine transaminase elevations associated with bilirubin elevations that met Hy's law laboratory criteria in any of the studies.

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Suspected transmission of infectious agents by the study drug

There were no AEs of suspected transmission of an infectious agent in this study

Systemic hypersensitivity reactions

No events consistent with systemic hypersensitivity, anaphylactic, or anaphylactoid reactions were identified in this study.

Thromboembolic events and thrombotic microangiopathy

See Section 8.2.4 above.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Clinical outcome assessments were used to confirm efficacy and were included as secondary efficacy objectives in HAVEN1 and HAVEN2. See Section 8.1.2 and 8.1.4 above. COA tools were not used to inform safety or tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

A safety analysis by age group is presented in Table 34 above. Due to the small sizes of the safety population and the low rate of TEAEs, further safety analyses by demographic subgroups were not performed.

8.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies were performed.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

A formal human carcinogenicity was not conducted for emicizumab. Tumor development is not expected based on the mechanism of action of emicizumab.

MAED SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps) included 1 event of warts in a patient on emicizumab for >52 weeks.

Human Reproduction and Pregnancy

All patients enrolled in the emicizumab clinical trials have been male because hemophilia A is an X-linked disorder and the incidence of hemophilia A with FVIII inhibitors is exceedingly rare in women. As a large antibody, emicizumab is unlikely to cross the placenta.

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Pediatrics and Assessment of Effects on Growth

Pediatric patients were included in both HAVEN1 (12-<18 years) and HAVEN2 (<12 years). Height measurements were assessed with vital signs. However, the small size of the trials and the short duration do not allow for assessment for effects on growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Four patients received doses >110% of the planned dose. No serious adverse events were reported in any patient. The risk of overdose is low for emicizumab given the wide therapeutic index.

Due to the mechanism of action for emicizumab, there is no drug abuse potential.

Withdrawal of emicizumab would return patients to their baseline absent FVIII and resulting bleeding risk. There is no expectation that the bleeding risk would be higher after discontinuation than prior to the emicizumab treatment. Few patients discontinued emicizumab treatment, so no assessment could be made regarding withdrawal or rebound bleeding events.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Emicizumab is not marketed in any country, and there is no postmarket experience.

Expectations on Safety in the Postmarket Setting

The main safety concern that could pose a significant risk in the post-marketing setting is thrombotic microangiopathy or thromboembolic events when emicizumab is given with aPCC as a bypassing agent for a bleed, especially when higher doses are used. The risk was mitigated by guidance on the appropriate use of bypassing agents, avoiding aPCC if possible, and using the lowest possible dose of aPCC if needed. The PI and Medication Guide also convey the signs and symptoms of TMA and TE to providers, patients, and caregivers.

Emicizumab is dosed with an initial 4 week loading dose followed by maintenance dosing. Medication errors are possible with the transition of dosing, but the therapeutic window is broad for emicizumab, so errors in dosing are not expected to lead to serious safety events.

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8.2.11. Integrated Assessment of Safety

The submitted evidence has provided substantial evidence for the safe use of emicizumab as prophylaxis for the prevention of bleeding in pediatric and adult patients with hemophilia A with FVIII inhibitors. Evidence of safety was provided from all patients in the pivotal phase 3 trial (HAVEN1) in adolescents and adults, the single-arm trial in pediatric patients (HAVEN2), and the phase 1b (ACE001JP/ACE002JP) in adolescents and adults. The safety is generally unremarkable except for common, but mild infusion reactions.

The risk of TMA/TE with concomitant aPCC is well described above. The risk was conveyed to prescribers in clinical amendments to both clinical trials. The events have resolved with discontinuation of aPCC use and supportive care. The risk of events is expected to be mitigated in the postmarketing setting by providing information to prescribers and patients describing the signs and symptoms and to indicate that aPCC should be avoided if possible.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

Statistical significant results are confirmed for the primary bleed endpoint (treated bleed, Arm A vs. Arm B) and all secondary bleed endpoints (Arm A vs. Arm B, intra-patient comparison in Arm A and Arm C) based on HAVEN1.

While the results for physical function from HAVEN1 appear to be robust, it lacks acceptable clinical meaningful threshold, and the interpretation of the results in the context open-label nature of the design should viewed cautiously.

The observation time in HAVEN2 (include patients who are younger than 12 years and had been receiving emicizumab for over 12 weeks) is comparably shorter than the observation time in the HAVEN1. The ABR analysis results may not be stable due to the short observation time, and the analysis result should be interpreted with caution.

8.4. Conclusions and Recommendations

The low ABR for all bleed types with emicizumab prophylaxis is consistent in all age groups across two clinical trials, HAVEN1 and HAVEN2. The safety data in the pooled analysis are favorable for all age groups. The identified risk of TMA and thromboembolic events can be decreased by recommending avoiding the use of aPCC when possible or low doses when needed. This review

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team recommends regular approval of emicizumab for the indication “for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.”

APPEARS THIS WAY ON ORIGINAL

X

X

X

Xin Gao, Ph.D.

Primary Statistical Reviewer

Susan Jin, M.S.

PRO Statistical Reviewer

Yuan Li Shen, Dr. P.H.

Statistical Team Leader

X

X

Lori Ehrlich, MD, PhD

Primary Clinical Reviewer

R. Angelo de Claro, MD

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

This Application was not presented to the Oncologic Drug Advisory Committee.

The Application was discussed with a special government employee (SGE), Christopher Templin. He is a patient representative with experience with hemophilia B with a prior FIX inhibitor and extensive involvement in advocacy for hemophilia. Mr. Templin was provided with a briefing document discussing the relevant efficacy and safety information related to the emicizumab development program. Specifically, Mr. Templin was asked to evaluate the benefit:risk profile for emicizumab in light of the unexpected TMA/TE safety signal.

The Division held a teleconference with Mr. Templin on October 31, 2017. He also provided a written response to the discussion question. In summary, Mr. Templin conveyed his opinion that emicizumab appears to be safe and effective and would be a good tool for patients with inhibitors. However, he had strong concerns regarding the serious adverse events. He emphasized that the hemophilia community has mixed education backgrounds and not all hemophilia treatment centers are equipped to adequately educate patients on the seriousness of the events and how to recognize the AEs. He felt the FDA and the Sponsor should educate the public on the risks to patients, including potentially alerting non-profit/advocacy organizations when events occur.

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10 Pediatrics

The Applicant was granted Orphan Designation for emicizumab for the treatment of patients with hemophilia A and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA).

Pediatric patients with hemophilia A with FVIII inhibitors were included in both HAVEN1 and HAVEN2. The Applicant is seeking an indication to include both adult and pediatric patients with no age limitation. See Section 8 for information regarding efficacy and safety in children and discussion regarding the indication.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Many of the changes from the proposed PI were to adequately present the risks of TMA/TE events when aPCC is used as a bypassing agent for patients treated with emicizumab.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
HIGHLIGHTS	Thrombotic microangiopathy, thromboembolism, and laboratory coagulation interference as W&P	<ol style="list-style-type: none"> Due to the seriousness and frequency of events, TMA and TE for patients receiving aPCC were moved to a boxed warning. Removed emicizumab/aPCC from drug interactions because of duplication with the W&P. Potential interaction with rFVIIa and FVIII remains.
1 INDICATIONS AND USAGE	For routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors	Added “adult and pediatric patients” to provide clarity on the intended population. Edited to read “to prevent or reduce the frequency...” for consistency with other agents used for prophylaxis in hemophilia.
(b) (4)	(b) (4)	(b) (4)
		(b) (4)
		(b) (4)

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		(b) (4)
5 WARNINGS AND PRECAUTIONS	5.1 TMA associated with HEMLIBRA and aPCC 5.2 TE associated with HEMLIBRA and aPCC 5.3 Laboratory coagulation test interference	1. Removed statement stating that (b) (4) (b) (4) (b) (4)
6 ADVERSE REACTIONS	TMA and TE information describing each event	1. TMA/TE information presented with more general presentation, treatment, and outcome in Section 5.1 and 5.2. (b) (4)
8.4 Pediatric Use	Stated number of pediatric patients enrolled with reference to 14 and 12.3.	1. Revised label to provide details on pediatric patients enrolled in pivotal trials per Pediatric Labeling Guidance.
14 CLINICAL STUDIES	Study 1 (HAVEN1) Included all primary and secondary endpoints for emicizumab prophylaxis vs. no prophylaxis Included intra-patient comparison for patients on prior prophylaxis with bypassing agent Included Haem-A-QoL (b) (4) physical health sub-score (b) (4)	Study 1 (HAVEN1) 1. Retained information on all bleed categories for emicizumab prophylaxis vs. no prophylaxis. 2. Retained information on intra-patient comparison for patients on prior prophylaxis with bypassing agent [see Section 8.1.2 for discussion of the intra-patient comparison]. 3. Displayed only the Haem-A-QoL physical health sub-score [see Section 8.1.2 for discussion of inclusion of PRO endpoints]

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	<p>Study 2 (HAVEN2) Included percent of patients with zero bleeds for [REDACTED] Information regarding use of bypassing agents for minor surgeries/procedures</p>	(b) (4)
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Medication Guide

Patient prescribing information (PPI) was included in the prescribing information by the Applicant. Due to the inclusion of a boxed warning for the interaction of emicizumab and aPCC, the format was changed to a Medication Guide. It conveys the risks and signs and symptoms of TMA and TE. The MG conveys that if more than 100 U/kg of aPCC is needed, then the patient should talk to their healthcare provider.

12 Risk Evaluation and Mitigation Strategies (REMS)

The risks of emicizumab including TMA/TE can be adequately managed in the post-marketing setting through product presentation and labeling. The package insert will also include a Medication Guide. No additional risk management strategies are assessed to be necessary beyond the recommended labeling.

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13 Postmarketing Requirements and Commitment

The Applicant agreed with postmarketing commitments related to immunogenicity assessments and other CMC issues. Refer to action letter for final wording.

APPEARS THIS WAY ON ORIGINAL

14 Division Director (DHOT)

APPEARS THIS WAY ON ORIGINAL

X

Haleh Saber, PhD, Deputy Division Director

15 Division Director (OCP)

X

Nam Atiqur Rahman, PhD

APPEARS THIS WAY ON ORIGINAL

16 Division Director (OB)

X

Thomas Gwise, PhD, Deputy Division Director

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical)

I concur with the review staff regarding the approval of this groundbreaking treatment for patients with hemophilia A with inhibitors. Hemlibra (emicizumab-kxwh) is a non-blood product and first-in-class bispecific antibody which bridges activated coagulation factor IXa and factor X to replace the function of missing activated factor VIII that is needed for effective hemostasis. The product is a weekly administered product. The results of clinical trials HAVEN 1 and HAVEN 2 demonstrated dramatic decreases in bleeding rates and bleeding rate secondary endpoints. In HAVEN1 patients 12 years of age and older were randomized between prophylaxis with Hemlibra and no prophylaxis and demonstrated an 87% reduction in annualized bleeding rates compared with no prophylaxis, and the intra-patient comparison analyses supported the primary randomized comparison reduction. HAVEN2 was a non-randomized, single arm, multicenter study which enrolled patients aged younger than 12 years with hemophilia A who have inhibitors against FVIII. HAVEN2 also demonstrated a 99% reduction in bleeding events. Additionally, the Applicant collected patient reported outcome data in adults using Haem-A-QoL and which demonstrated improvements in physical functioning and total score, and in EQ-5D-5L. Information was collected in pediatric and adolescent patients aged 8-17 in HAVEN1 and HAVEN2 using the Haemo-QoL Short Form. The major safety concern identified was the occurrence of thrombotic microangiopathy (TMA) and thromboembolism (TE) in patients. Exploratory analyses suggested that those who receive >100 units/kg/24 hours of activated prothrombin complex concentrate treatment for more than 24 hours while on emicizumab-kxwh prophylaxis may have an increased risk of TMA and TE. The labeling will have a Boxed Warning regarding this potential risk. Signs and symptoms of TMA and TE are described for prescribers, patients, and caregivers in the prescribing information and medication guide. The Applicant will have 6 PMCs to address development of antibodies, antibody binding and manufacturing issues. Additionally, we are asking the Applicant to submit for 5 years all cases of TMA and TE.

APPEARS THIS WAY ON ORIGINAL

Ann T. Farrell, MD

18 Office Director (or designated signatory authority)

Hemlibra (emicizumab) is a first-in-class bispecific antibody which bridges activated coagulation factor IXa and factor X to replace the function of missing activated factor VIII that is needed for effective hemostasis.

Emicizumab demonstrated a decreased in annualized bleeding rate (ABR) compared with no prophylaxis in Study HAVEN1. The study also included an intra-patient comparison which demonstrated a decrease in ABR for patients on emicizumab prophylaxis compared to their prior prophylaxis regimen. A single arm study, HAVEN2, showed a low occurrence of bleeds in pediatric patients, similar to the findings in adults. Based on these findings, this application will be approved for “for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.”

The risk-benefit profile was also assessed by Drs. Farrell, de Claro, and Ehrlich who also recommend approval and I concur with their recommendation.

X

APPEARS THIS WAY ON ORIGINAL

Richard Pazdur, MD

19 Appendices

19.1. References

Astermark, J., S. M. Donfield, D. M. DiMichele, A. Gringeri, S. A. Gilbert, J. Waters, E. Berntorp and F. S. Group (2007). "A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study." Blood **109**(2): 546-551.

George, J. N. and C. M. Nester (2014). "Syndromes of thrombotic microangiopathy." N Engl J Med **371**(7): 654-666.

Konkle, B. A., L. S. Ebbesen, E. Erhardtzen, R. P. Bianco, T. Lissitchkov, L. Rusen and M. A. Serban (2007). "Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors." J Thromb Haemost **5**(9): 1904-1913.

Kulkarni, R., R. J. Presley, J. M. Lusher, A. D. Shapiro, J. C. Gill, M. Manco-Johnson, M. A. Koerper, T. C. Abshire, D. DiMichele, W. K. Hoots, P. Mathew, D. J. Nugent, S. Geraghty, B. L. Evatt and J. M. Soucie (2017). "Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention Universal Data Collection System." Haemophilia **23**(2): 207-214.

Muto, A., K. Yoshihashi, M. Takeda, T. Kitazawa, T. Soeda, T. Igawa, Z. Sampei, T. Kuramochi, A. Sakamoto, K. Haraya, K. Adachi, Y. Kawabe, K. Nogami, M. Shima and K. Hattori (2014). "Anti-factor IXa/X bispecific antibody ACE910 prevents joint bleeds in a long-term primate model of acquired hemophilia A." Blood **124**(20): 3165-3171.

Soucie, J. M., B. Evatt and D. Jackson (1998). "Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators." Am J Hematol **59**(4): 288-294.

Williams, M. D., E. A. Chalmers, B. E. Gibson, Haemostasis and B. C. f. S. i. H. Thrombosis Task Force (2002). "The investigation and management of neonatal haemostasis and thrombosis." Br J Haematol **119**(2): 295-309.

(b) (4)



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19.2. Financial Disclosure**Covered Clinical Study (Name and/or Number): BH29884**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>178</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>none</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u>		
Is an attachment provided with the reason: N/A	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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Covered Clinical Study (Name and/or Number): BH29992

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>74</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u>		
Is an attachment provided with the reason: N/A	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

Refer to Section 5.5.3.

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19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

The bioanalytical assay is acceptable to measure emicizumab plasma concentrations for samples collected in the dose finding and efficacy and safety trials. The concentration of emicizumab was determined in human plasma using a validated ELISA method. A high-binding plate was coated overnight with rAJ540-rbtIgG (capture antibody). After a wash, rAQ8-mIgG2b (detector antibody) was added to the plate and incubated. The bound detector antibody was detected by using a peroxidase labeled goat anti-mouse IgG. After a wash to remove unbound reagent, ABTS solution was added and incubated. The absorbance is proportional with the emicizumab concentration in the sample (wavelength at 405 nm and 490 nm as reference). The calibration curve standards range from concentrations of 100 ng/mL to 6400 ng/mL. The performance of sample analysis was monitored by quality control samples (QC) in human plasma spiked with three different concentrations. Long term storage stability at the appropriate storage conditions was demonstrated. The assay precision ranged from 9.5% to 13.3% and accuracy ranged from 97.6% to 103.2%. **Table 35** shows the method validation results.

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Table 35: Bioanalytical Method Validation Results

Validation parameter	Validation result
Minimum dilution of sample	50-fold with assay buffer
Calibration range	100 ng/mL to 6400 ng/mL in neat plasma
Calibration model	4 PL with $1/y^2$ weighting
Lower limit of quantification	100 ng/mL
Upper limit of quantification	6400 ng/mL
Intra-run precision	6.9% to 9.9%
Inter-run precision	5.7% to 10.0%
Intra-run accuracy	97.3% to 120.2%
Inter-run accuracy	97.8% to 103.0%
Prozone effect	No Prozone effect was observed up to a concentration of 1,000,000 ng/mL.
Dilution linearity	Samples can be diluted up to 6561-fold with plasma. As the samples are diluted 50-fold with assay buffer prior to analysis, the overall maximum dilution factor is 328050-fold
Microplate homogeneity	No positional effect was observed. The back-calculated concentrations of the LLOQ samples were between 96.6% and 124.0 % of their nominal value with an overall CV of 5.9%.
Selectivity	The method was selective for the determination of Emicizumab at 100 ng/mL (LLOQ) and at 3200 ng/mL (QC high). All unspiked samples were below the LLOQ. Selectivity has been demonstrated in hemolysis or a high lipid content samples.
Specificity	The assay tolerates concentrations up to 50000 ng/mL of Factor IX and X at the LLOQ and QC high level.
Freezing and thawing stability	Stability of samples has been demonstrated after 4 F/T cycles. Emicizumab in human plasma showed no notable deterioration during a maximum of four freezing and thawing cycles.
Bench top stability	Stability of samples has been demonstrated at ambient temperature up to 24 hours.
Stability at 2-8 °C	Stability of samples has been demonstrated at 2-8 °C up to 24 hours.
Long term stability	Stability of samples has been demonstrated at -20 °C and -70 °C up to 7 months.

Source: REPORT NO. 1070310, Validation Report

The assay method validation report and bioanalytical report for the immunogenicity assay were submitted. The drug tolerance of assay is 40 mcg/mL. Since the Geometric mean of Css,trough of emicizumab in the safety and efficacy trials was 52.7 mcg/mL, the assay was inadequate to detect anti-emicizumab antibodies at the proposed dose. Since the assay has limited sensitivity with the observed Css,trough, the following PMC will be issued to request a evaluation of the incidence of anti-emicizumab antibodies following the development of new validated assays for binding and neutralizing antibodies.

PMC: Assess binding and neutralizing anti-product antibody (APA) responses with a validated assay capable of sensitively detecting APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The APA response will

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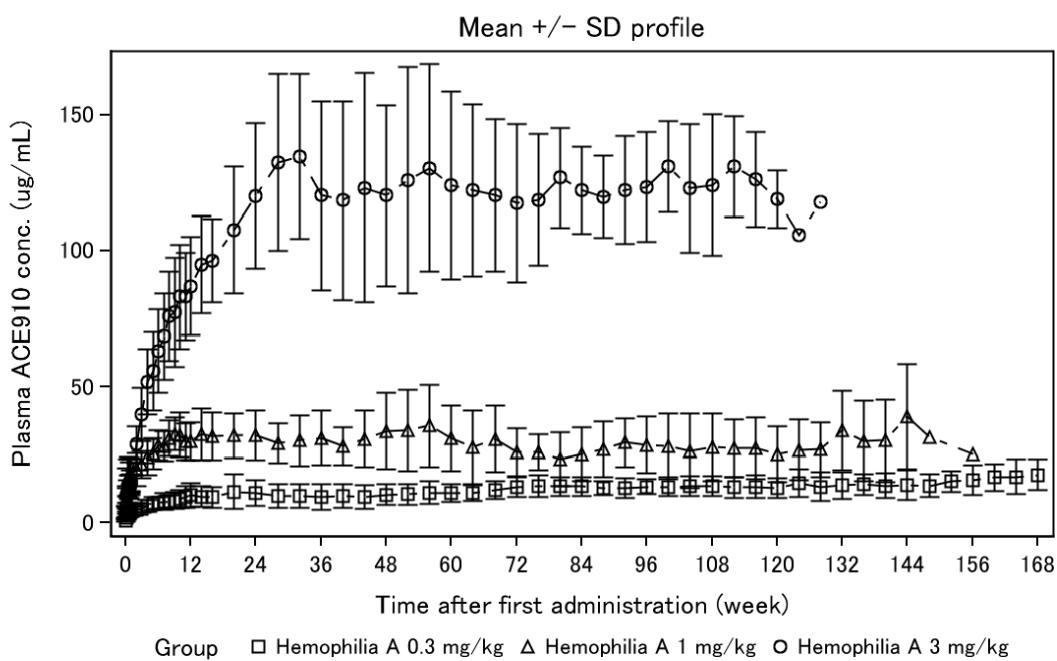
be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient's test sample at each sampling point.

19.4.2. Clinical PK and PD Assessments

Trial ACE001JP Part C and extension ACE002JP

A single arm, open label, multicenter, first in human, dose finding trial was conducted to evaluate the safety, tolerability, PK, immunogenicity, and the inhibitory effect of emicizumab on bleeding during long-term treatment in patients with hemophilia A. Patients received emicizumab at doses 0.3 mg/kg/week, 1 mg/kg/week or 3 mg/kg/week as a SC injection. An initial loading dose was given for 4 weeks at approximately 3-fold the proposed maintenance dose for patients enrolled into the 0.3 mg/kg/week and 1 mg/kg/week dose levels. Following weekly SC administration, plasma emicizumab concentration increased over time in all the dosing groups (**Figure 15**). The time to reach steady state was approximately 12 weeks for dose groups of 0.3 mg/kg/week and 1 mg/kg/week with a loading dose, and approximately 24 weeks for dose group of 3 mg/kg/week without a loading dose. Css,trough increased in a dose proportional manner with mean \pm SD of 10.3 ± 4.5 mcg/mL, 29.9 ± 6.9 mcg/mL, and 120 ± 26.8 mcg/mL for the 0.3, 1, and 3 mg/kg/week doses, respectively (**Table 36**).

Figure 15: Mean Time Course of Plasma Emicizumab Concentration Following Weekly Subcutaneous Injections in Patients with Hemophilia A



Datetime: November 16, 2016 19:02:00 / Cutoff: September 30, 2016

Source: CSR ACE002JP, Figure 11.4.1.1-1

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Table 36: Summary Statistics of Pharmacokinetic Parameters of Emicizumab Following Weekly Subcutaneous Administration

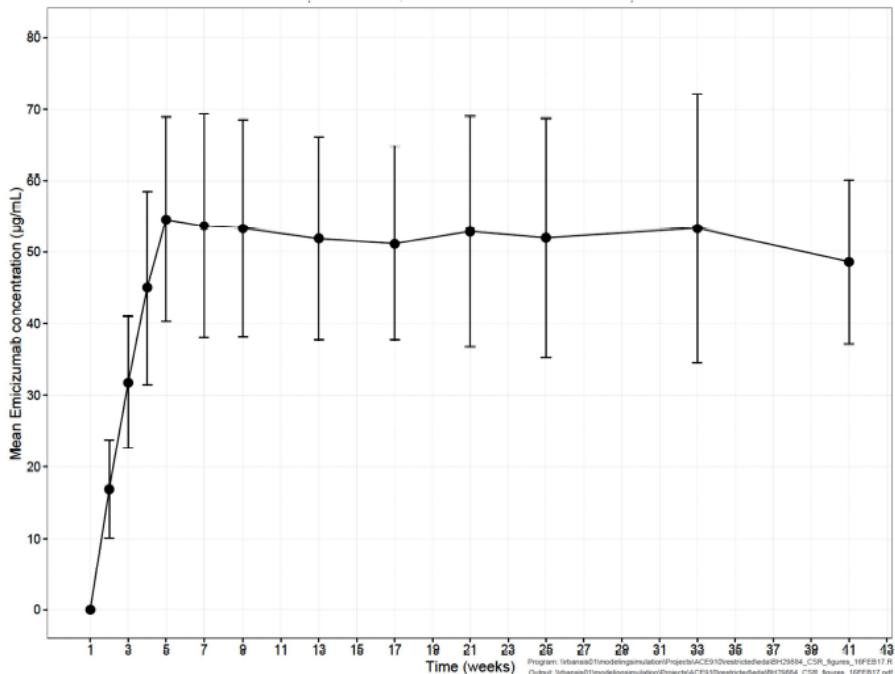
PK parameter	Unit	Dose (mg/kg)	N	n	Mean	SD	CV (%)	Median	Minimum	Maximum	Geomet. mean	Geomet. CV (%)
t _{1/2}	day	–	3	3	24.3	3.49	14.3	26.0	20.3	26.7	24.2	15.1
kel	1/day	–	3	3	0.0289	0.00450	15.6	0.0267	0.0259	0.0341	0.0287	15.1
C _{trough, ss}	ug/mL	0.3	6	6	10.3	4.54	44.1	8.90	4.75	15.9	9.45	48.9
	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

Source: CSR ACE002JP, Table 11.4.1.2-1

Trial BH29884

The applicant conducted a randomized, multicenter, open-label, clinical trial in patients age 12 years or older with hemophilia A with FVIII inhibitors to evaluate efficacy and safety. The study evaluated prophylactic treatment with emicizumab at a dose of 3 mg/kg/week for 4 weeks (loading dose), followed by 1.5 mg/kg/week thereafter (maintenance dose). The mean Css,trough of 54.6 mcg/mL was achieved at Week 5. After 24 weeks of treatment, mean Css,trough was 52 mcg/mL as shown in **Figure 16** and **Table 37**.

Figure 16: Mean Time Course of Plasma Emicizumab Concentration Following Multiple Weekly Subcutaneous Injections of Emicizumab in Patients with Hemophilia A



Source: CSR BH29884, Figure 17

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Table 37: Plasma Trough Concentration (mcg/mL) by Scheduled Time and Descriptive Statistics

Scheduled Day	Week 1	Week 2	Week 3	Week 4	Week 5	Week 7	Week 9	Week 13	Week 17	Week 21	Week 25	Week 33	Week 41	Week 49
N	101	99	102	99	98	93	82	70	60	54	49	23	7	1
Mean	.	16.9	31.8	45.0	54.6	53.7	53.3	51.9	51.2	52.9	52.0	53.3	48.6	32.5
SD	.	6.8	9.2	13.6	14.3	15.7	15.2	14.3	13.6	16.1	16.7	18.8	11.5	.
Min	.	5.4	2.5	16.0	23.4	19.0	16.1	18.4	24.0	22.2	21.1	26.3	25.6	32.5
Median	.	15.5	32.5	44.1	53.1	52.6	51.4	51.4	50.9	50.4	46.6	46.8	48.8	32.5
Max	.	44.9	51.2	97.8	89.9	98.4	97.7	82.7	83.8	92.3	99.6	89.3	61.5	32.5
Geom mean	.	15.7	30.0	43.0	52.7	51.4	51.0	49.7	49.3	50.4	49.5	50.2	47.1	32.5
CV of geom mean	.	40.6	40.9	31.5	27.6	31.1	31.2	31.8	28.4	32.2	32.9	36.8	29.4	.

Source: CSR BH29884, Table 36.

Trial BH29992

The applicant is conducting a single-arm, multicenter, open-label, clinical trial to evaluate the efficacy, safety and PK of emicizumab in patients <12 years of age (with allowance for patients 12 years to 17 years who weigh < 40 kg) with hemophilia A and FVIII inhibitors. The study is evaluating prophylactic treatment with emicizumab at a dose of 3 mg/kg/week for 4 weeks (loading dose), followed by 1.5 mg/kg/week thereafter (maintenance dose). The mean Css,trough of emicizumab increased with a weekly dose of 3 mg/kg to reach a mean Ctrough of 53.6 mcg/mL at Week 5 (**Table 38** and **Figure 17**). No effects of age on emicizumab exposure were identified in this population (**Figure 18**).

Table 38: Summary Statistics of Emicizumab Plasma Concentration (mcg/mL) in Trial BH29992

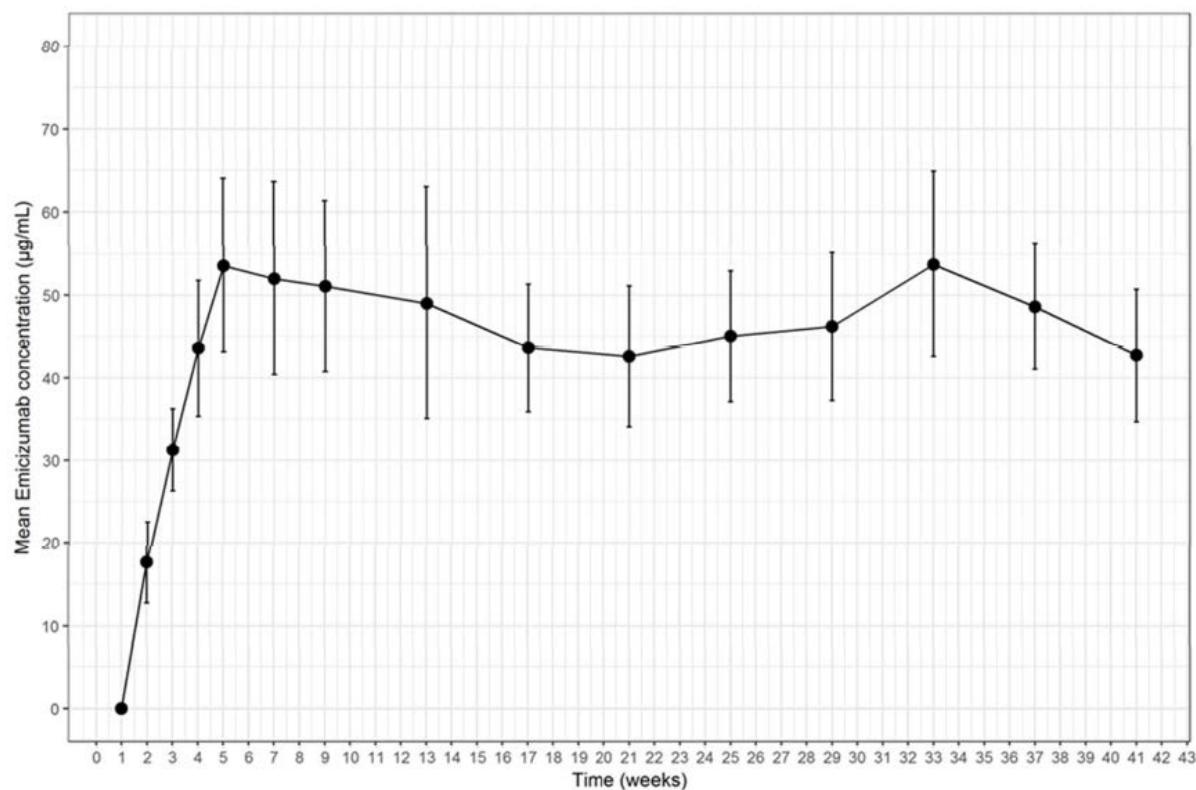
Scheduled day	WEEK 1 WEEK 2 WEEK 3 WEEK 4 WEEK 5 WEEK 7 WEEK 9							WEEK 13	WEEK 17	WEEK 21	WEEK 25	WEEK 29	WEEK 33	WEEK 37	WEEK 41
	1	8	15	22	29	43	57	85	113	141	169	197	225	253	281
N*	59	59	49	43	41	36	30	22	20	20	20	20	19	16	5
Mean	.	17.6	31.3	43.6	53.6	52.0	51.1	49.0	43.6	42.6	45.0	46.2	53.7	48.6	42.7
SD	.	4.9	5.0	8.2	10.4	11.6	10.3	14.0	7.7	8.5	7.9	9.0	11.1	7.6	8.0
Min	.	8.2	22.4	28.5	35.8	31.2	29.1	33.9	30.0	29.2	34.7	29.4	35.0	34.1	30.9
Median	.	17.2	30.0	42.9	53.0	51.3	49.8	43.4	44.2	43.7	45.7	46.8	52.2	48.0	43.2
Max	.	33.3	43.1	64.5	87.4	80.0	75.8	83.9	57.6	58.5	60.9	62.6	72.7	61.8	52.2
Geom mean	.	17.0	30.9	42.8	52.6	50.7	50.0	47.4	42.9	41.8	44.4	45.4	52.6	48.0	42.1
CV of geom mean	.	27.1	15.9	18.8	19.4	23.1	21.1	26.2	18.5	20.5	17.4	20.3	21.2	16.3	20.1

Source: Study BH29992. 90-day safety update, Table 10

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Figure 17: Trial BH29992: Mean Time Course of Plasma Emicizumab Concentration Following Multiple Weekly Subcutaneous Injections of Emicizumab in Patients < 12 Years Old with Hemophilia A

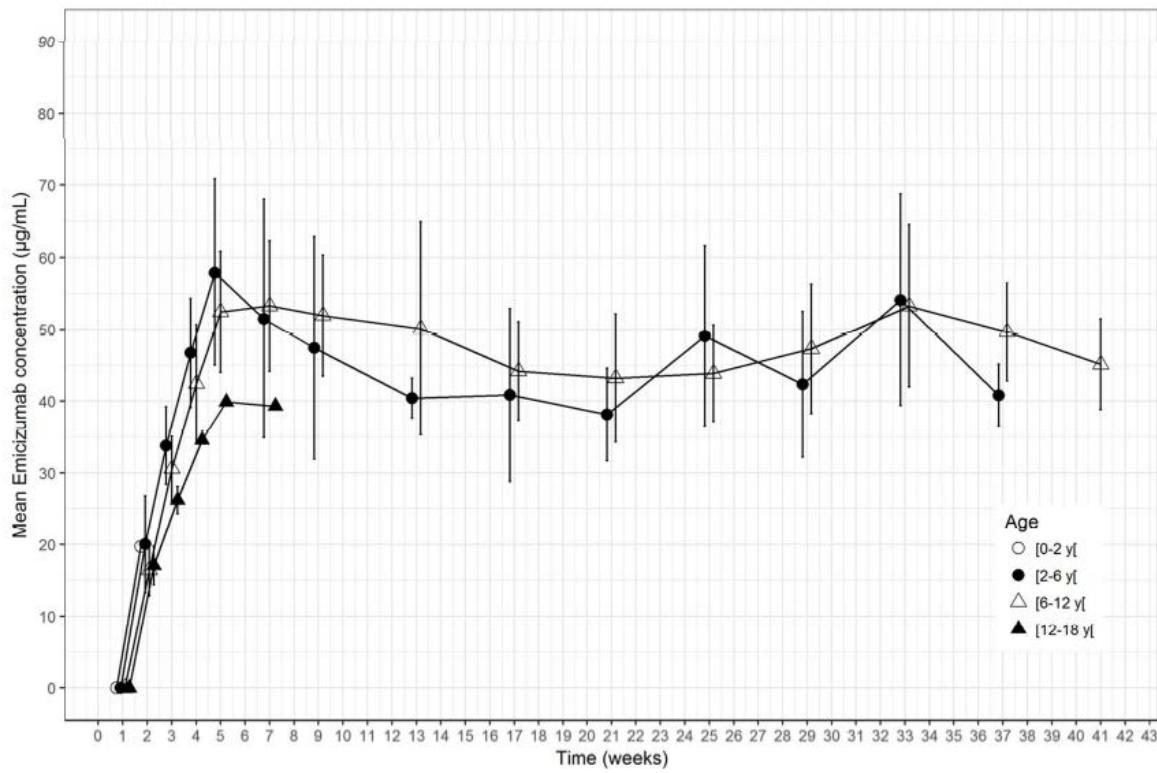


Source: Trial BH29992. 90-day safety update, Figure 4

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Figure 18: Trial BH29992: Mean Time Course of Plasma Emicizumab Concentration Following Multiple Weekly Subcutaneous Injections of Emicizumab in Patients < 12 Years Old with Hemophilia A by Age Group



Source: Trial BH29992. 90-day safety update, Figure 5

19.4.3. Population PK Analyses

Summary of Applicant's Population PK Analyses

Objectives:

The objectives of the population PK analysis were to:

- Describe the PK profile of emicizumab in hemophilia A patients with or without FVIII inhibitors
- Explore and quantify the contribution of selected covariates in explaining the between-patient variability in PK parameters of emicizumab
- Determine individual estimates of PK parameters (to be used for exposure-efficacy and safety analyses)

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Data:

Data from trial ACE001JP(Part C)/ACE002JP and trials BH29884 and BH29992 were included in the analysis.

Methods:

Models with one and two compartments were tested. For the absorption phase, a first-order model, with or without a lag time, was tested. The compartmental models were parameterized in terms of clearance(s) and volume(s) of distribution. First Order Conditional Estimation (FOCE) with interaction was used as it is the preferred method in the case of rich data per patient, or large between-patient variability.

The association between patient covariates and PK parameters were evaluated in a stepwise fashion.

The ability of the population model to describe the data was assessed by graphical analysis including goodness-of-fit plots.

The predictive performance of the population PK model was evaluated by conducting a visual predictive check (VPC).

Results:

A total of 1814 emicizumab plasma concentrations measured in 141 patients from trials BH29884, BH29992 and ACE001JP/ACE002JP were available for the the population PK analysis. The population PK model analysis was done in two main steps. In the first step, the PK data from the data cut-off of 25 October 2016, 28 October 2016 and 15 February 2016 for trials BH29884, BH29992 and ACE001JP/ACE002JP respectively were used to build an Interim_PK_database and to conduct the population PK model development. In the second step, a Final_PK_database was built from the same data cut off dates for trial BH29884 and trial BH29992 and from a data cut-off of 30 September 2016 for trial ACE001JP/ACE002JP and was used to provide the final population parameter estimates from the Interim Final PK model of the first step.

The number of emicizumab plasma concentrations per study is provided in Table 39.

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Table 39: Number of Emicizumab Plasma Concentrations by Study Available in the Interim and Final Population PK Databases

Study no.	No. plasma concentration /No. Patients		
	Interim_PK_database		Final_PK_database
	Base model ^{a,b}	Interim model ^{a,b,c}	Final model ^{a,d}
BH29884	863 / 103	863 / 103	863 / 103
BH29992	127 / 20	120 / 19	120 / 19
ACE001JP Part C	321 / 16	321 / 16	321 / 16
ACE002JP	388 / 14	388 / 14	485 / 14
Total	1699 / 139	1692 / 138	1789 / 138

^a BLQ concentrations (n=15), PK concentrations following plasma exchange (n=2 – ID=360) were not included

^b Two inconsistent patient PK profiles in ACE001JP/ACE002JP (ID=266 and ID=276) (n=98) were not included

^c PK concentrations from ID=501 in BH29992 with low baseline albumin were not included

^d Two inconsistent patient PK profiles in ACE001JP/ACE002JP (ID=266 and ID=276) (n=112) and PK concentrations from ID=501 in BH29992 with low baseline albumin were not included.

Source: Applicant's Population PK and PK/PD report Table 7 on page 54

The different covariates used in the population PK analyses are summarized in Table 40.

Table 40: Summary of Covariates

Covariate	All Patients (N=141)	BH29884 (N=103)	BH29992 (N=20)	ACE001JP / ACE002JP (N=18)
	Mean (SD) Median (Min/Max)	Mean (SD) Median (Min/Max)	Mean (SD) Median (Min/Max)	Mean (SD) Median (Min/Max)
Albumin (g/L)	44.7(4.34) 45(16.8/54.93)	45.0(3.86) 45(34/54.9)	41.8(6.56) 43(16.8/50)	45.9(2.29) 46(42/52)
Total Bilirubin (μmol/L)	10.6(6.73) 8.89(3.25/46)	10.6(6.51) 8.89(3.42/46)	6.89(3.17) 6.41(3.25/13.68)	14.1(8.84) 12.0(3.42/35.91)
Prothrombin time (sec)	13.0(1.08) 13.2(10/15.3)	13.0(1.09) 13.2(10/15.3)	13.5(0.73) 13.5(11.9/14.7)	12.2(1.05) 12.3(10.4/14.5)
Alanine Amino Transferase(U/L)	25.8(24.0) 20(5/210)	25.58(18.98) 22(5/130)	19(11.5) 16(8/61)	34.5(48.1) 16(7/210)
Aspartate Amino Transferase(U/L)	25.8(13.1) 21(11/89)	24.7(10.1) 21(12/67)	30.2(19.5) 25(11/88)	27.6(18.3) 20(14/89)
Platelet (10 ⁹ /L)	259(66.6) 257(117/457)	258(63.0) 253(117/416)	306(69.2) 298(157/457)	214(51.7) 207(131/304)

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Covariate	Categories	All Patients (N=141)	BH29884 (N=103)	BH29992 (N=20)	ACE001JP / ACE002JP (N=18)
		n (%)	n (%)	n (%)	n (%)
Race2	1: White / Caucasian	76 (54)	66 (64.1)	10 (50.0)	0 (0)
	2: Black or African American	12 (8.5)	11 (10.7)	1 (5.0)	0 (0)
	3: Asian	43 (30.5)	20 (19.4)	5 (25.0)	18 (100)
	9: Other or Unknown	10 (7.1)	6 (5.8)	4 (20)	0 (0)
Patient Status	1: Non-Inhibitor	11 (7.8)	0 (0)	0 (0)	11 (61.1)
	2: Inhibitor	130 (92.2)	103 (100)	20 (100)	7 (38.9)
NCI hepatic impairment criteria	Normal	114 (80.9)	87 (84.5)	17 (85.0)	10 (55.6)
	Mild GB1	13 (9.2)	5 (4.9)	3 (15.0)	5 (27.8)
	Mild GB2	4 (2.8)	1 (1)	0 (0)	3 (16.7)
	Moderate	4 (2.8)	4 (3.9)	0 (0)	0 (0)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)
Site of injection (First dose)	Unknown	6 (4.3)	6 (5.8)	0 (0)	0 (0)
	1: lower abdomen / abdomen	89 (63.1)	58 (56.3)	13 (65.0)	18 (100)
	2: thigh	13 (9.2)	9 (8.7)	4 (20.0)	0 (0)
	3: upper arm	35 (24.8)	32 (31.1)	3 (15.0)	0 (0)
	4: upper arm & lower abdomen	2 (1.4)	2 (1.9)	0 (0)	0 (0)
	5: upper arm & thigh	1 (0.7)	1 (1)	0 (0)	0 (0)
	6: lower abdomen & thigh	0 (0)	0 (0)	0 (0)	0 (0)
Anti-therapeutic antibody	9: unknown	1 (0.7)	1 (1)	0 (0)	0 (0)
	0: Negative	137 (97.2)	103 (100)	20 (100)	14 (77.8)
	1: Positive	4 (2.8)	0 (0)	0 (0)	4 (22.2)

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Covariate	All Patients (N=141)	BH29884 (N=103)	BH29992 (N=20)	ACE001JP / ACE002JP (N=18)
	Mean (SD) Median (Min/Max)	Mean (SD) Median (Min/Max)	Mean (SD) Median (Min/Max)	Mean (SD) Median (Min/Max)
Age (years)	27.8 (16.4) 23.0 (3.2/75.0)	30.6 (15.8) 27.0 (12.0/75.0)	8.1 (2.8) 8.6 (3.2/12.2)	33.8 (13.7) 34.5 (12.0/58.0)
Body Mass Index (kg/m ²)	23.3 (5.63) 22.8 (13.2/47.2)	24.5 (5.5) 23.6 (15.1/47.2)	18.0(4.5) 16.5(13.2/27.0)	22.3 (4.2) 21.7 (14.4/30.0)
Body Surface Area (m ²)	1.69 (0.36) 1.74 (0.61/2.38)	1.82 (0.24) 1.82 (1.31/2.38)	1.05 (0.30) 1.00 (0.61/1.69)	1.70 (0.19) 1.67 (1.40/1.98)
Height (cm)	164 (17.8) 168 (97.3/194)	170 (9.56) 170 (147/194)	130 (18.9) 129 (97.3/164)	167 (6.83) 168(153.5/177)
Body Weight (kg)	64.7 (21.9) 64.2(14.2/131)	71.4(18.2) 69 (40.1/131)	31.7 (14.5) 26.9 (14.2/63.0)	62.8 (13.8) 60.3 (40.8/81.7)

Source: Applicant's Population PK and PK/PD report Table 8-10 on page 55-57

The results showed that a one-compartment model with first-order absorption and first-order elimination could adequately describe the emicizumab concentration-time data. Between-subject variability was incorporated on apparent clearance (CL/F), apparent volume of distribution (V/F) and absorption rate constant (KA). The residual variability was modeled as a combination of an additive and a multiplicative-error model.

After the covariate model building process, the following covariate-PK relationships were found to be statistically significant and were incorporated in the final model: body weight on CL/F, age on CL/F, ALB (albumin) on CL/F, body weight on V/F, ALB on CL/F, and black race on V/F.

PK parameter estimates from the final model are summarized in Table 41 and diagnostic plots are presented in Figure 19. Figure 20 shows the visual predictive check (VPC) results for trials BH29884 and BH29992.

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Table 41: Summary of PK Parameter Estimates form the Final Model

Parameter	Unit	Estimate	RSE (%)	95% CI (lower, upper)	Shrinkage (%)
Fixed Effects					
CL/F	L/day	0.244	4.1	(0.225, 0.263)	
V/F	L	11.4	3.3	(10.6, 12.1)	
KA	1/day	0.494	12.9	(0.369, 0.619)	
Random Effects					
BPV					
CL/F	CV%	25.0	14.7 ^a		8.7
V/F	CV%	29.1	15.4 ^a		7.3
KA	CV%	65.1	20.5 ^a		37.5
Correlation	-	0.358	34.9 ^b		
CL/F–V/F					
Covariate Effects					
Effect of WT on CL/F	-	0.965	5.9	(0.852, 1.08)	
Effect of AGE on CL/F	-	6.62×10^{-3}	37.2	$(1.72 \times 10^{-3}, 11.5 \times 10^{-3})$	
Effect of ALB on CL/F	-	4.81×10^{-2}	31.2	$(1.87 \times 10^{-2}, 7.75 \times 10^{-2})$	
Effect of WT on V/F	-	1.02	6.3	(0.895, 1.14)	
Effect of ALB on V/F	-	1.49×10^{-2}	47.1	$(1.18 \times 10^{-3}, 2.86 \times 10^{-2})$	
Effect of Black or African American on V/F	-	-0.360	21.6	(-0.513, -0.207)	
Error Model					
σ_1 (additive)	µg/mL	0.025 F	-		
σ_2 (proportional)	%	13.7	4.1	(12.6, 14.8)	
RUNID: RUN5736, OFV: 7937.939					

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

^a RSE computed for the corresponding variance.

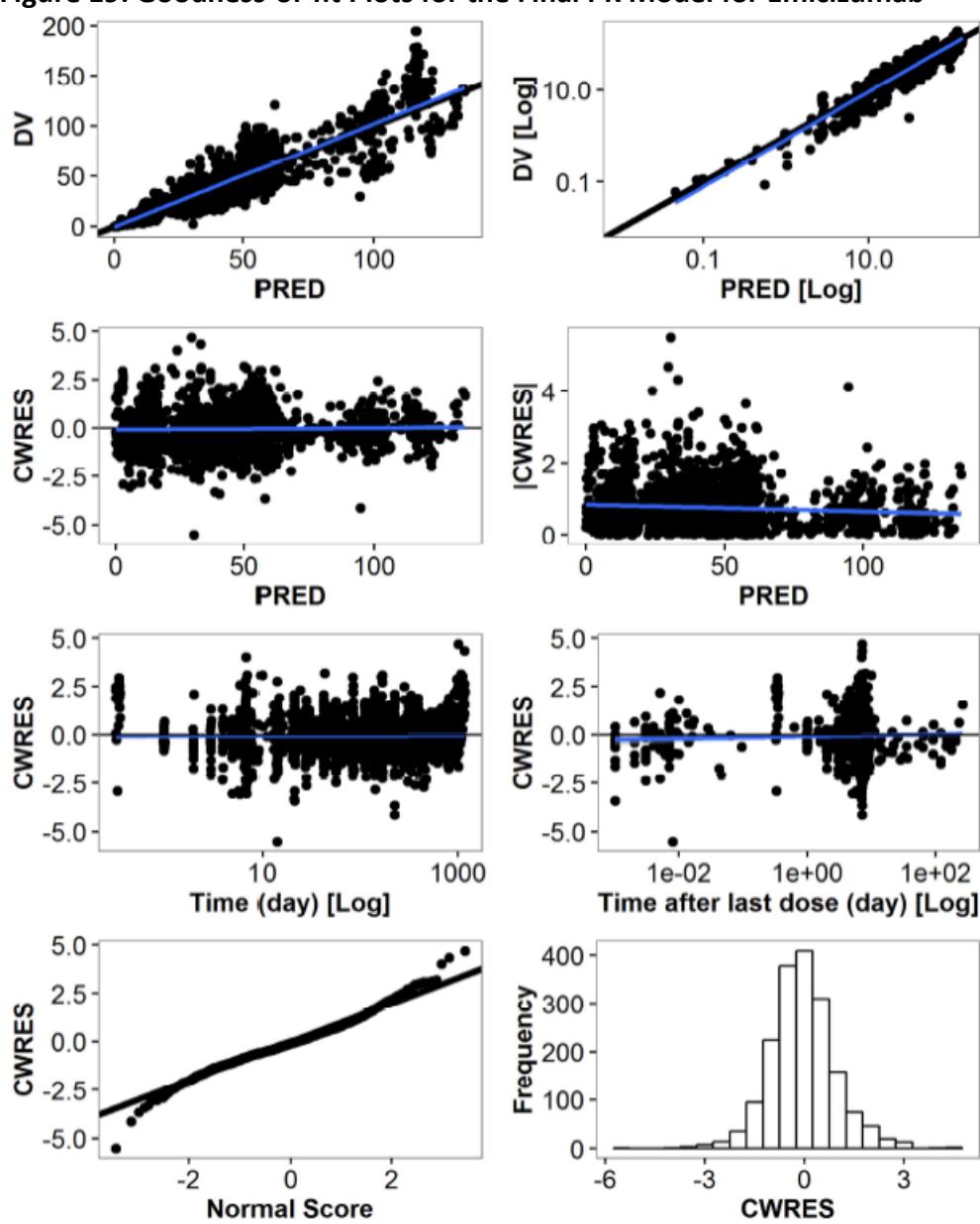
^b RSE computed for the corresponding covariance.

Source: Applicant's Population PK and PK/PD report Table 16 on page 72

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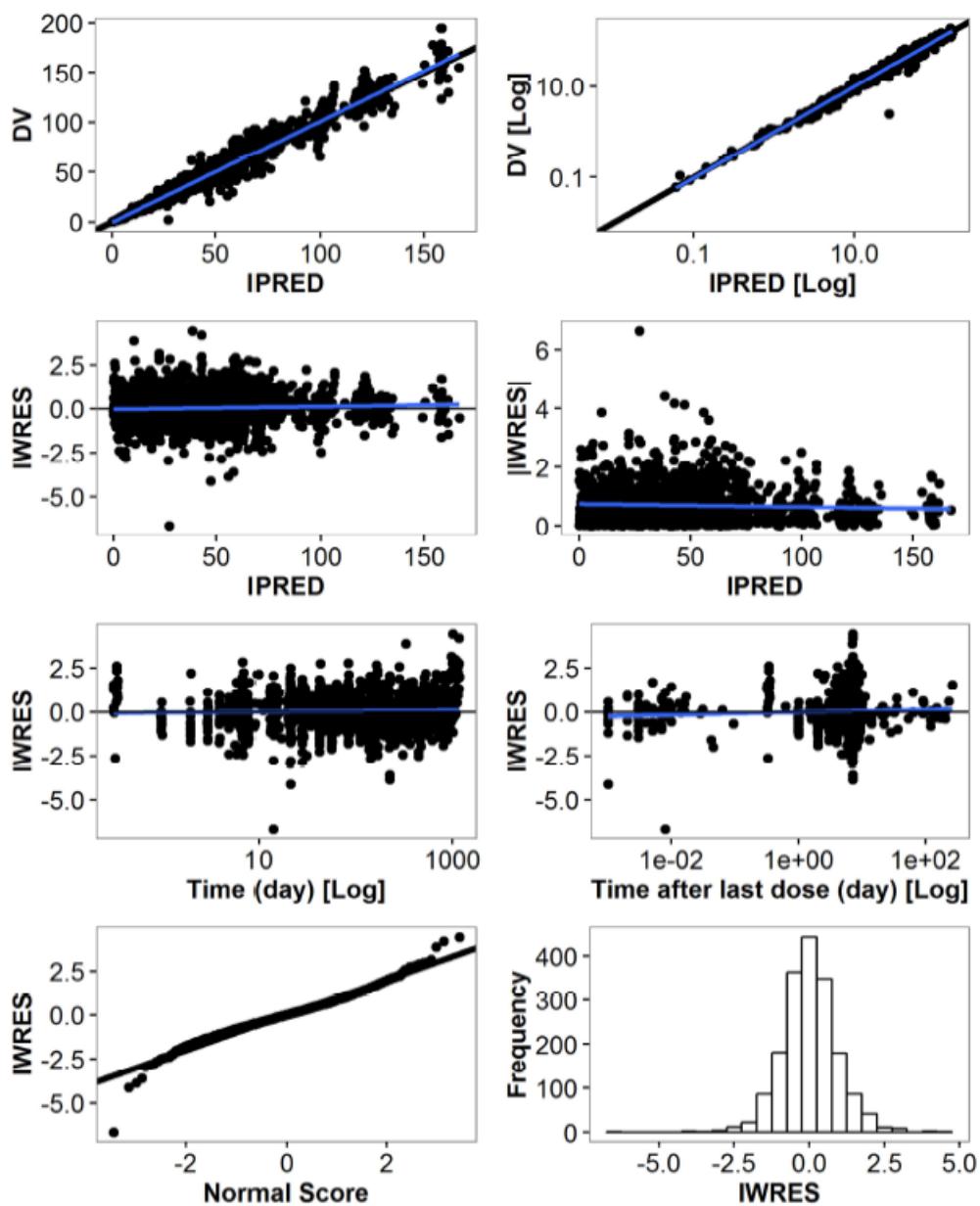
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Figure 19: Goodness-of-fit Plots for the Final PK Model for Emicizumab



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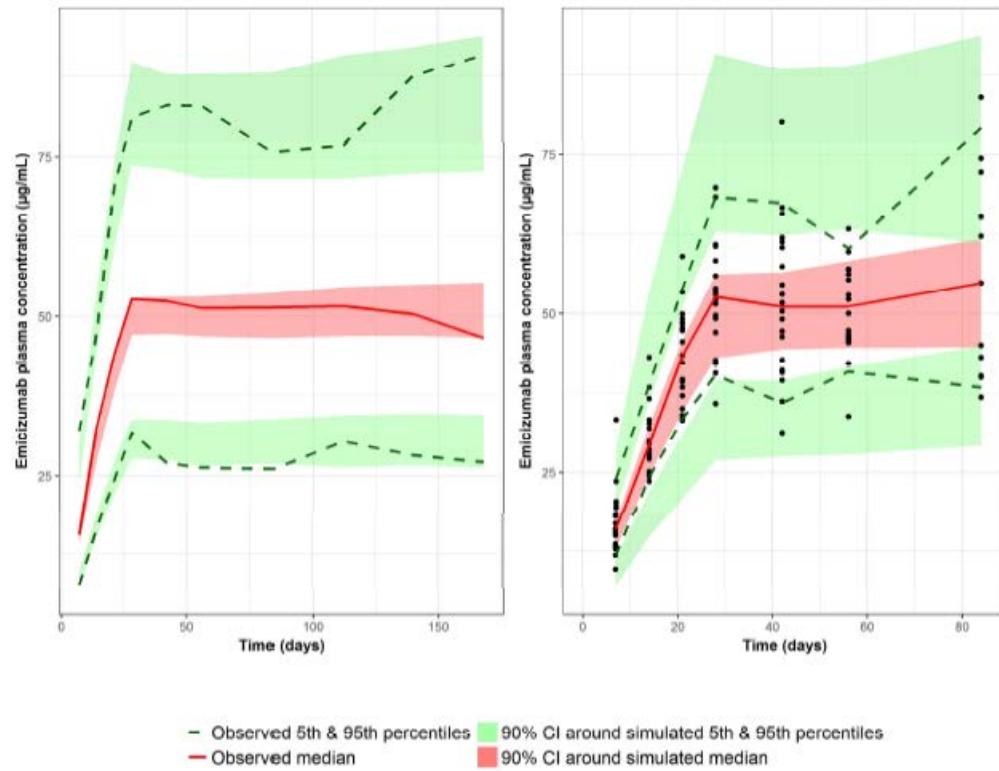
DV – Observed emicizumab concentrations [$\mu\text{g/mL}$], PRED (IPRED) – NONMEM predicted emicizumab concentrations [$\mu\text{g/mL}$] based on population (individual) PK parameters, TIME – time after first drug intake [days], CWRES (IWRES) – Conditional (Individual) weighted residual values.

Source: Applicant's Population PK and PK/PD report Figure 5-6 on page 73-74

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Figure 20: VPC Results for Trials BH29884 (left) and BH29992 (right)



Source: Applicant's Population PK and PK/PD report Figure 10 on page 79

The relationship between the covariates included in the final model are reported in **Table 42** together with the impact of minimum and maximum covariate values on the typical parameters, for the range of covariates observed in the PK.

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Table 42: Effect of Retained Covariates in the Final Population PK Model

Statistically Significant Effect	Relationship	Covariate Range [min, max]	% Change in PK Parameters from Typical Value [min, max]
BW (kg) on CL/F	$CL/F = 0.244 \times (BW / 70)^{0.965}$	[14, 131]	[-79, +83]
AGE (y) on CL/F	IF (AGE ≤ 22) $CL/F = 0.244$	[3, 22]	[0, 0]
	IF (AGE > 22) $CL/F = 0.244 \times (1 + 0.00662 \times (AGE - 22))$	[22, 75]	[0, +35]
ALB (g/L) on CL/F	IF (ALB < 45) $CL/F = 0.244 \times (1 - 0.0481 \times (ALB - 45))$	[34, 45[[+53, 0[
	IF (ALB ≥ 45) $CL/F = 0.244$	[45, 55]	[0, 0]
BW (kg) on V/F	$V/F = 11.4 \times (BW / 70)^{1.02}$	[14, 131]	[-81, +90]
ALB (g/L) on V/F	$V/F = 11.4 \times (1 - 0.0149 \times (ALB - 45))$	[34, 55]	[+16, -15]
BLACK on V/F	$V/F = 11.4 \times (1 - 0.360 \times BLACK)$	Non Black / Black	0 / -36

Source: Applicant's Population PK and PK/PD report Table 17 on page 75

Reviewer's Comments:

Overall, the applicant's population PK analysis is acceptable. The population PK model could adequately describe the emicizumab concentration-time data. CL/F and V/F were well correlated with body weight powers of 0.965 and 1.02 respectively. Since a weight-based dosing was studied and proposed, negligible impact of body weight on emicizumab steady-state exposure is expected. The impact of age on CL/F was only modeled for patients above 22 years old, since no effect of age on PK parameter were found in patients below 22 years old. Older patients (≥ 22 years) had slightly increased CL/F with age and decreased steady state exposure. No dose adjustment was proposed for older patients with hemophilia A. CL/F decreased with increased albumin levels which is consistent with other monoclonal antibodies. No dose adjustment for albumin levels was proposed. Although black race was a statistically significant covariate for V/F, it had no clinically relevant effect on emicizumab exposure. No patients with moderate or severe renal impairment were enrolled in clinical studies. Impairment of renal function was not expected to affect the PK of a monoclonal antibody. Limited number of patients with mild or moderate hepatic impairment was included in the analysis and no trend in PK change was observed across different hepatic function categories. Therefore, no adjustment is proposed for mild or moderate hepatic impairment.

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19.4.4. Exposure-Response Analyses

Summary of Applicant's Exposure-Response Analyses

Exposure-efficacy analyses

Graphical analyses were conducted to assess if the variability in emicizumab PK exposure at the dose of 3 mg/kg/week SC during 4 weeks followed by 1.5 mg/kg/week SC was a source of variability in response measured by ABRT (annualized treated bleeding rate) estimates. The PK and efficacy data from trials BH29884 and BH29992 were used. Since patients in these studies were not treated for the same duration at the time of the data cut-off, two different categories of patients were defined for these graphical exposure-efficacy analyses: those treated for at least 12 weeks of treatment ($N = 83$) and those treated for at least 24 weeks of treatment ($N = 52$). Although the second category included fewer patients, this longer duration of treatment was expected to provide more robust investigation of the drug effect on ABR. The PK exposure was defined either as the estimated Cav over the treatment duration or the estimated Css,trough.

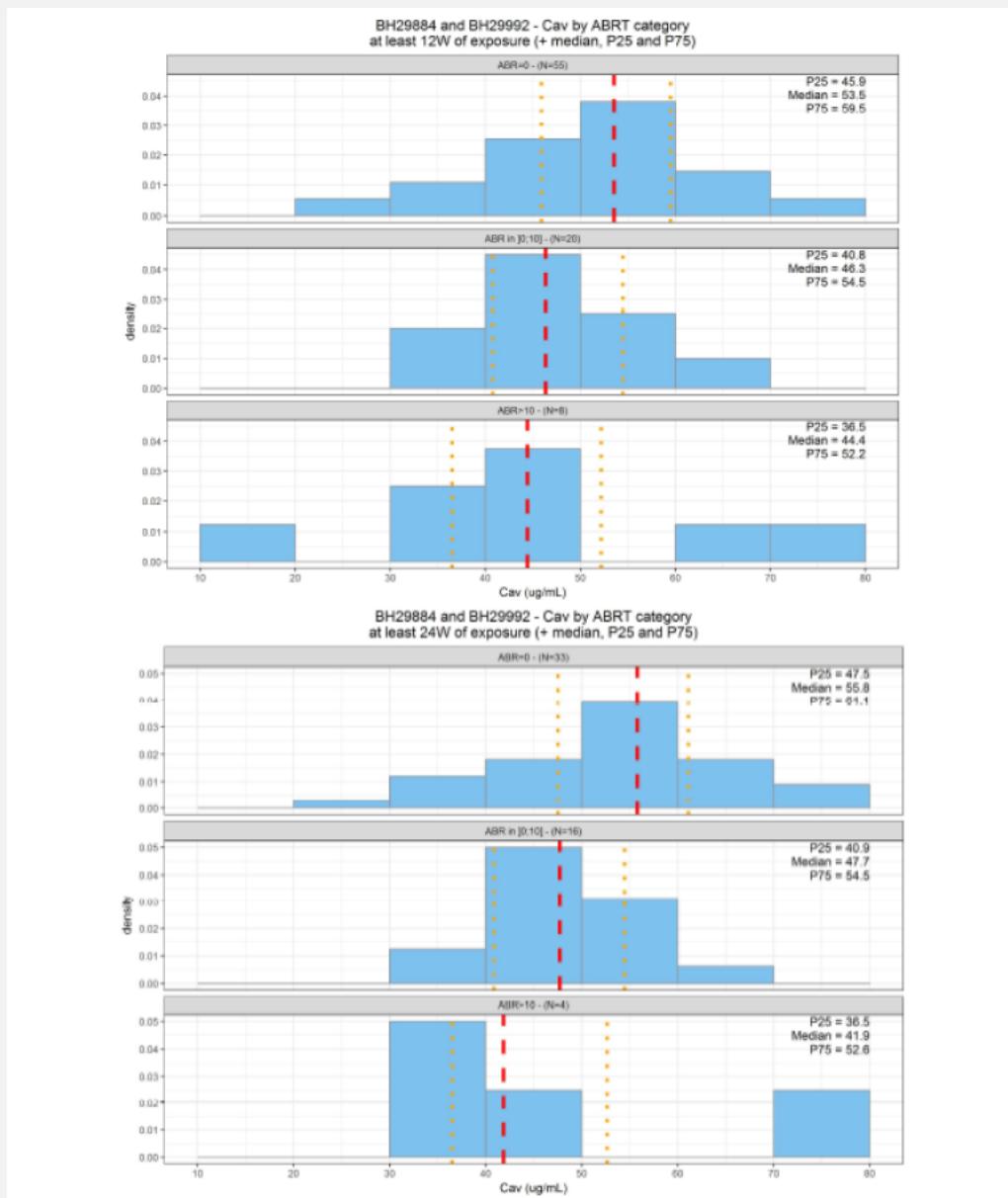
At the dose of 3 mg/kg/week SC during 4 weeks followed by 1.5 mg/kg/week SC, a large proportion of the patients had zero bleeds, both in the category of patients who completed at least 12 weeks of emicizumab treatment (66.3%) and in that who completed at least 24 weeks (62.3%). There were a limited number of patients with ABR greater than 10, 9.6% and 7.6% in the respective categories of patients.

Figure 21 and **Figure 22** display, by category of ABR, the distribution of estimated average concentrations and trough concentrations at steady state, respectively. The summary statistics are given in Table 43. The patients who have an ABR equal to zero have the highest median emicizumab Cav and Css,trough, in the 2 patient categories; however, there is a large overlap of the PK exposure distributions by ABR category and no clear ER relationship can be observed. Similar overlaps are observed when considering different categories of ABR: ABR = 0; ABR in [0; 4]; ABR > 4.

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Figure 21: Distribution of Estimated Concentration Averages (C_{av}) by Category of ABR for Patients Who Received at Least 12 Weeks of Emicizumab Treatment in Trials BH29992 and BH29884 (Top) and for Patients Who Received at Least 24 Weeks of Emicizumab Treatment (Bottom)



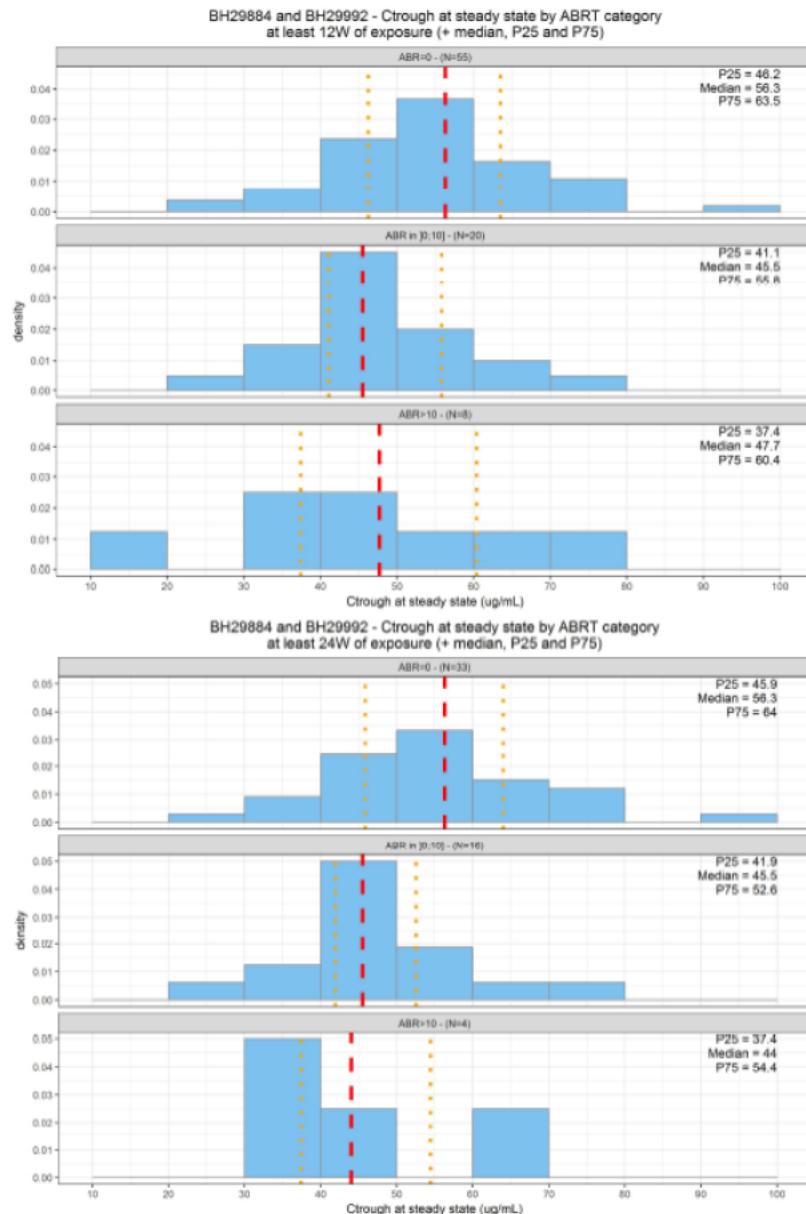
Dotted red line represents the median of the C_{av} and the orange dotted lines the 25th (P25) and 75th (P75) percentiles of observation respectively. Distributions are represented as density histograms so that the area of each rectangle equals the relative frequency of the corresponding class, and the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

Source: Applicant's Population PK and PK/PD report Figure 14 on page 88

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Figure 22: Distribution of Estimated Trough Concentrations at Steady State ($C_{ss,trough}$) by Category of ABR for Patients Who Received at Least 12 Weeks (Top) or Least 24 Weeks (Bottom) of Emicizumab Treatment in Trials BH29992 and BH29884



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

Source: Applicant's Population PK and PK/PD report Figure 15 on page 89

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Table 43: Summary Statistics of Average Concentrations and Estimated Steady State Trough Concentrations per Patient Category and per ABR Category

Patient Category	ABRT	C_{av} ($\mu\text{g}/\text{mL}$)			$C_{ss,\text{trough}}$ ($\mu\text{g}/\text{mL}$)		
		Median	P25	P75	Median	P25	P75
Completed at least 12 weeks of treatment	0	53.5	45.9	59.5	56.3	46.2	63.5
] $0 - 10]$	46.3	40.8	54.5	45.5	41.1	55.8
	>10	44.4	36.5	52.2	47.7	37.4	60.4
Completed at least 24 weeks of treatment	0	55.8	47.5	61.1	56.3	45.9	64.0
] $0 - 10]$	47.7	40.9	54.5	45.5	41.9	52.6
	>10	41.9	36.5	52.6	44.0	37.4	54.4

P25 and P75: 25th and 75th percentiles

Source: Applicant's Population PK and PK/PD report Table 24 on page 87

Reviewer's Comments:

Numerical trend of exposure-response relationship between emicizumab C_{av} and $C_{ss,\text{trough}}$ and ABR was observed from the applicant's exploratory graphical analyses. The reviewer confirmed the positive exposure-efficacy relationship by conducting independent ER analysis. Refer to reviewer's analysis section for details.

Exposure-safety analyses

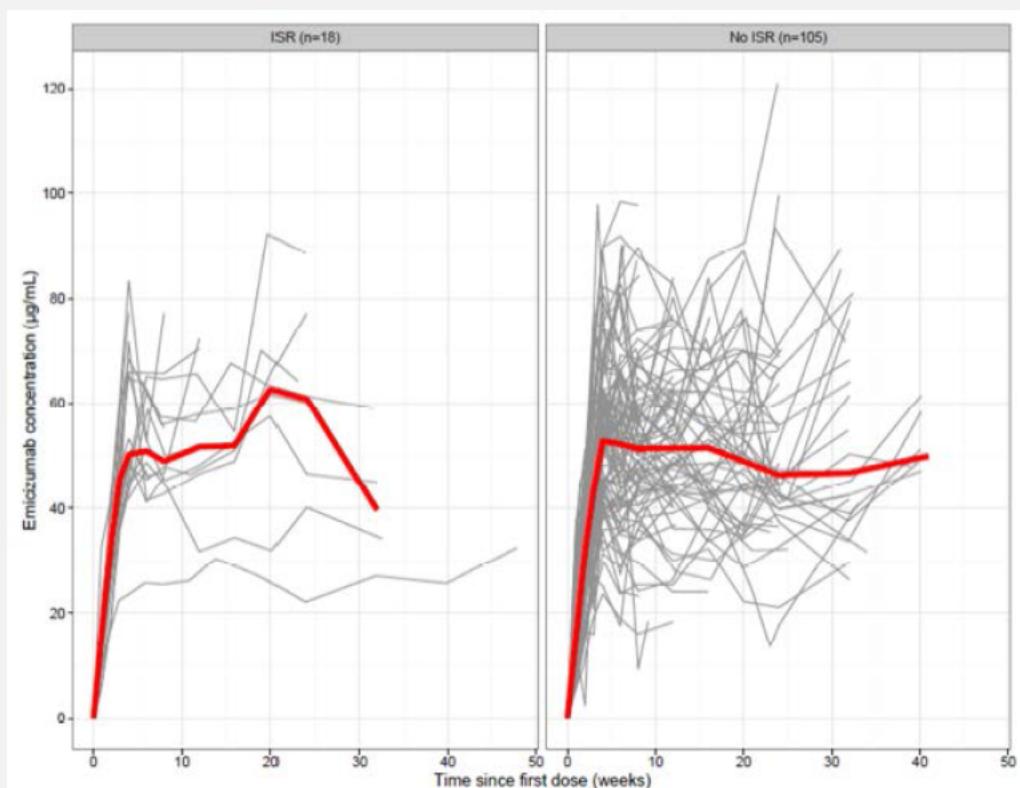
The exposure-safety database was composed of 123 patients (103 from trial BH29884) and 20 from trial BH29992).

A comparison of the observed individual PK profiles between patients who experienced ISRs (injection site reactions) during their treatment and patients who did not is displayed in Figure 23. The medians and inter-quartile ranges of observation periods were similar in both groups (84 days [55.9, 168] for the patients group without ISR and 105 days [56.9,168] for patients group with ISR). No obvious difference in the median profiles was observed between the two groups showing no evidence of relationship between emicizumab exposure and the occurrence of injection site reactions.

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Figure 23: Emicizumab Concentration Time Course per Group of Patients with at Least One Injection Site Reaction (N = 18, Left) or without any Injection Site Reaction (N = 105, Right) Over the Entire Profile of Administration (Trials BH29884 and BH29992)



Grey lines represent the individual emicizumab concentration-time profiles. Red lines represent the median Emicizumab concentration-time profiles

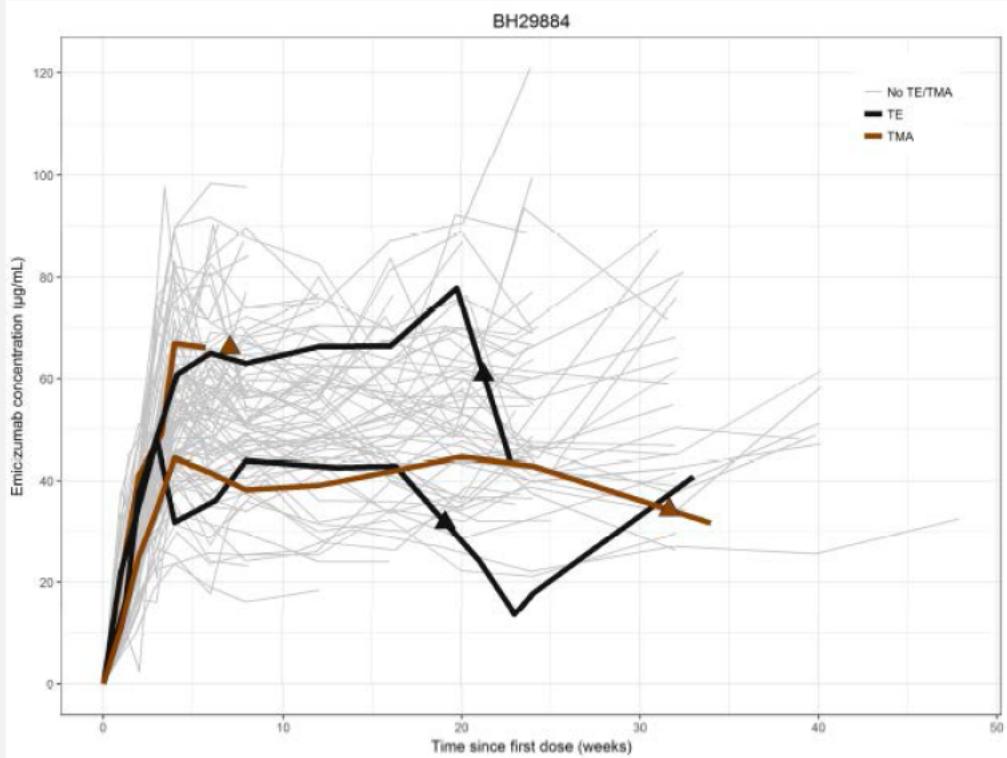
Source: Applicant's Population PK and PK/PD report Figure 29 on page 104

Figure 24 displays the individual PK concentrations observed in trial BH29884 with the 4 patients who experienced TMA (thrombotic microangiopathy) or TE (thromboembolic events) highlighted with different colors. Those 4 profiles lie within the between patient variability of the PK time course profiles, and no evidence of relationship between emicizumab exposure and the occurrence of those TMA or TE can be derived.

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Figure 24: Individual Observed Emicizumab Concentration Time Courses (trial BH29884) Overlaid by Emicizumab Concentration Time Courses for Patients with TMA (Brown) or with TE (Black) Events



Source: Applicant's Population PK and PK/PD report Figure 30 on page 105

Reviewer's Comments:

The relationship between emicizumab exposure and ISR and TMA/TE were explored by comparing the emicizumab exposure in patients with or without the events of interest. Results showed that no apparent relationship between emicizumab exposure and the occurrence of ISR or TMA/TE was identified.

Reviewer's Analysis

Introduction:

Numerical trend of positive exposure-efficacy relationship was observed from the applicant's exploratory graphical E-R analysis. The reviewer conducted independent analysis to confirm the observed positive exposure-efficacy relationship.

Objective:

- To evaluate the relationship between emicizumab exposure and efficacy endpoint, i.e. ABR (annualized bleeding rate).

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Data:

PK and efficacy data from trials BH29884 and BH29992 were used in this analysis.

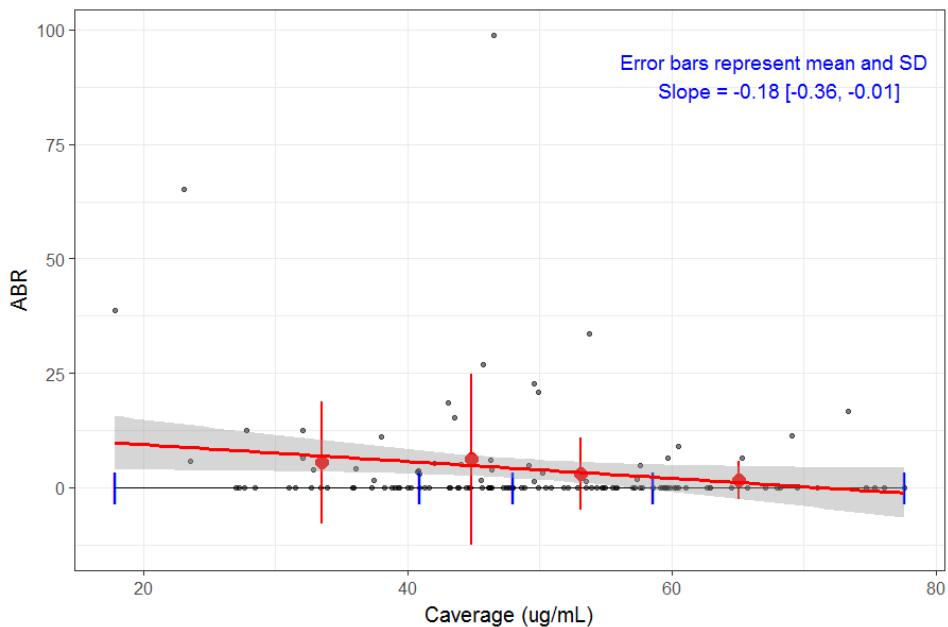
Methods:

Liner regression analysis was conducted to assess the relationship between absolute ABR values and emicizumab average concentration. In addition, logistic regression was performed to evaluate the relationship between the probability for achieving ABR of 0 and emicizumab average concentration.

Results:

All patient with PK and efficacy data from trials BH29884 and BH29992 were included in the analysis. Positive exposure-efficacy relationship at the dose of 3 mg/kg/week SC during the first 4 weeks followed by 1.5 mg/kg/week SC was identified from both linear regression for absolute ABR values (Figure 25) and logistic regression analyses for achieving ABR of 0 (Figure 26). Sensitivity analyses were conducted for patients who received at least 12 weeks of emicizumab treatment or for patients who received at least 24 weeks of emicizumab treatment. And, steady-state emicizumab concentration was also evaluated in the sensitivity analysis. Results from sensitivity analyses (not shown here) are consistent with reviewer's analysis results in this report.

Figure 25: Linear Regression of Absolute ABR Values against Average Emicizumab Concentration

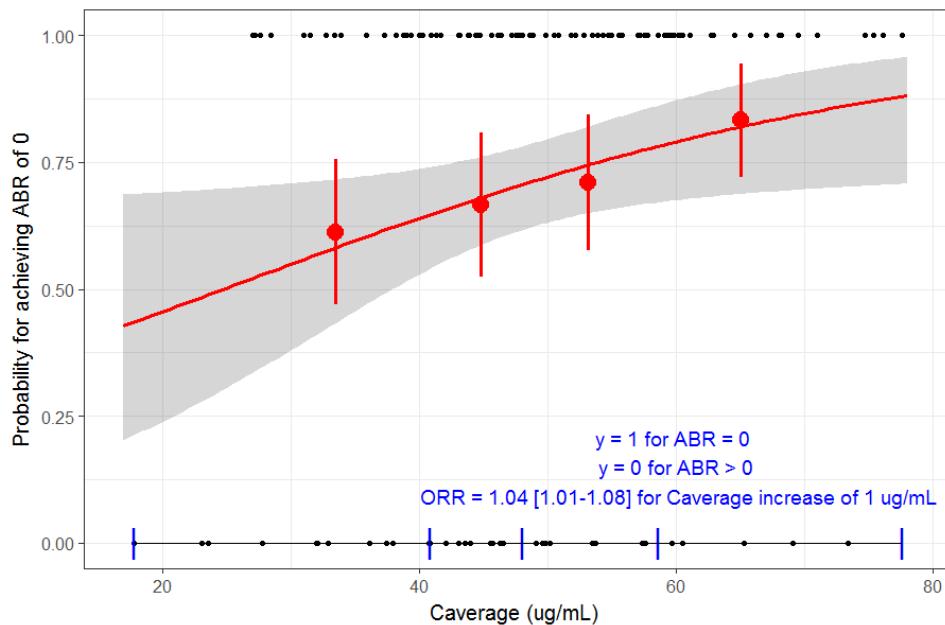


Note: Red solid line is the linear regression line. Grey shaded area is the 90% CI for the regression line. Horizontal black line at bottom with blue vertical bars represents the emicizumab exposure quantiles. Red dots with red vertical bars represent mean \pm SD of ABR within each exposure quantile. Black dots represent observed data.

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Figure 26: Logistic Regression of Probability of Achieving ABR of 0 against Average Emicizumab Concentration



Note: Red solid line represents the logistic regression line. Grey shaded area is the 90% CI for the regression line. Horizontal black line at bottom with blue vertical bars represents the emicizumab exposure quantiles. Red dots with red vertical bars represent mean and 90% CI of probability of achieving ABR of 0 within each exposure quantile. Black dots represent observed data.

Listing of Datasets and Analyses Codes

File Name	Description	Location in \\cdsnas\\pharmacometrics\\
EXPEFF.csv	PK and efficacy data set for studies BH29884 and BH29992	\\cdsnas\\pharmacometrics\\Reviews\\Ongoing PM Reviews\\Emicizumab_BLA761083_XW\\E-R Analysis
Linear regression.r	R code for linear regression analysis	
Logistic regression.r	R code for logistic regression analysis	

19.5. Additional Clinical Outcome Assessment Analyses

Clinical Outcome Assessment (COA) analyses for patients ≥ 18 years old in HAVEN1 using Haem-A-QoL are included in Section 8.1.2. EQ-5D-5L was also used in patients ≥ 18 years old in HAVEN1.

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The analyses were not included in the prescribing information because the tool is primarily used for health economics, and the relevant information regarding physical functioning is better captured in the Physical Health Score of Haem-A-QoL.

COA information was collected in pediatric and adolescent patients aged 8-17 in HAVEN1 and HAVEN2 using the Haemo-QoL Short Form. Results of the COA assessments in pediatric patients were not included in the prescribing information because the non-randomized, single-arm design of the assessments leads to significant reporter bias without comparison to patients who did not receive emicizumab prophylaxis.

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/s/

LAURA C WALL
11/14/2017

LORI A EHRLICH
11/14/2017

CHRISTOPHER M SHETH on behalf of SHWU LUAN LEE
11/14/2017

CHRISTOPHER M SHETH
11/14/2017

HALEH SABER
11/14/2017

XIAOFENG WANG
11/14/2017

JIANG LIU
11/14/2017

STACY S SHORD
11/14/2017

NAM ATIQUR RAHMAN
11/14/2017

I agree with the Recommendation of the review team.

YUAN L SHEN on behalf of XIN GAO
11/14/2017

Note: Susan Jin is the stat. reviewer for PRO analysis, but is not available to sign the review today.

YUAN L SHEN
11/14/2017

THOMAS E GWISE

11/14/2017

(acting for Dr. Sridhara)

ROMEO A DE CLARO

11/14/2017

ANN T FARRELL

11/14/2017

RICHARD PAZDUR

11/16/2017

MEMORANDUM

Date: November 13, 2017

To: File for BLA 761083

Re: Executive carcinogenicity assessment committee (ECAC's) concurrence with the Division on the adequacy of the carcinogenicity assessment for emicizumab.

From: Christopher Sheth, PhD
Pharmacology-Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)

Drug: Hemlibra (emicizumab)

During the development of emicizumab under IND, the Sponsor submitted a question in a meeting request asking if the Agency agreed that the completed nonclinical studies supported the product's registration. The Agency responded to the question with: In general, we agree with your development program. However, the carcinogenic potential of the product should be addressed as product development continues. The Sponsor subsequently submitted the requested carcinogenicity assessment to the IND on July 9, 2015, and upon our review the Division agreed that the carcinogenicity assessment was sufficient to waive the requirement for additional nonclinical carcinogenicity studies. The Division summarized the Sponsor's assessment and forwarded that and our recommendation to the ECAC as an FYI as there was no formal ECAC meetings regarding emicizumab. The ECAC agreed with the Division that there was no need for additional nonclinical carcinogenicity studies for emicizumab on August 7, 2015.

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/s/

CHRISTOPHER M SHETH

11/13/2017

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Full Review Template version: June 27, 2017

COA ID	C2017202
BLA #	761083
Referenced IND for NDA/BLA	122954
Established Name/Trade Name	Hemlibra®
Applicant	Genentech/Roche
Indication	Prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency)
Meeting Type/Deliverable	BLA labeling
SDN#	1
Date of Consult Request	June 28, 2017
Review Completion Date	September 29, 2017
Review Division	Division of Hematology Products (DHP)
Clinical Reviewer	Lori Ehrlich, MD
Review Division PM	Laura Wall
COA Reviewer	Nikunj B. Patel, PharmD
COA TL	Selena Daniels, PharmD, MS
COA Associate Director	Elektra J. Papadopoulos, MD, MPH
Instrument 1	Haem-A-QoL(Adults)
Instrument 2	EQ-5D-5L
COA Type 1 and Endpoint Concepts	Physical health; HRQL
COA Type 2 and Endpoint Concepts	Health status
Intended Population	Pediatric, adolescent, and adult patients with hemophilia A (congenital factor VIII deficiency)
Internal Meeting	Not applicable
Sponsor Meeting/WRO	Not applicable

Please check all that apply:

- Rare Disease/Orphan Designation
- Pediatric

Clinical Outcome Assessment Review

Nikunj B. Patel, PharmD

BLA 761083

Emicizumab (HEMLIBRA®)

Haem-A-QoL (physical health; HRQL); EQ-5D-5L (health status)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Hematology Products (DHP) regarding BLA 761083. The Applicant (Genentech) is seeking an approval for the new molecular entity, emicizumab (HEMLIBRA®), for the treatment of hemophilia A. The proposed indication is prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. The Applicant implemented the following patient-reported outcome (PRO) instruments in their pivotal, phase 3, open-label, multicenter, global, randomized study BH29884 (or hereafter referred as HAVEN1) as secondary efficacy measures in adult patients with hemophilia A:

- Haemophilia-specific Quality of Life (Haem-A-QoL for Adults), which assesses health-related quality of life (HRQL), including physical health (Appendix A)
- EuroQoL Five-Dimension-Five-Levels Questionnaire (EQ-5D-5L), which assesses health status (Appendix B)

Because all primary and secondary efficacy endpoints were met, the Applicant has proposed PRO-related labeling claims (see Section C 1.4). The Division requested COA input on the validity and reliability of the above-mentioned PRO instruments to support relevant labeling claims in the Package Insert (PI) Section 14.

The review concludes that the Haem-A-QoL Physical Health domain appears fit-for-purpose to assess physical health in the target patient population; however, there are some limitations of (b) (4) which are described in Section C5 of this review. Despite these limitations, the Physical Health domain score appears to be adequate to support potential claims related to physical health (swellings, joint pain, and physical function) as many items appear clinically relevant and meaningful to patients¹, and showed improvement. The threshold for meaningful change is unknown; however based on the Haem-A-QoL Physical Health cumulative distribution function (CDF) plot there appears to be a clear separation between the two arms across the entire distribution of responses.²

(b) (4)



¹ FDA Voice of the Patient Report for the Patient-Focused Drug Development Meeting on Hemophilia A, September 22, 2014; <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM513311.pdf>

² BLA 761083 Response to FDA Information Request (Received on September 25, 2017)

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Haem-A-QoL (physical health; HRQL); EQ-5D-5L (health status)

(b) (4)



(b) (4)



Generally, the open-label trial design limits interpretability of PRO data because patient's knowledge of treatment assignment may lead to systematic overestimation of treatment effect; however, larger effect size can overcome this limitation. Please refer to relevant Clinical and Statistical reviews for additional PRO data analyses.

Future Clinical Trials in Hemophilia A: We recommend further improvement to the Haem-A-QoL instrument to ensure the content of all domains is clinically relevant and meaningful to patients. Generally, we recommend the use of well-defined and reliable instruments that measure clinically meaningful outcomes, such as disease-specific signs/symptoms and functional impacts (e.g., physical function). Patient input should be obtained to inform instrument development.

If a HRQL claim is sought, we recommend that the instrument measure the patient's general perception of the effect of both illness and treatment on physical, psychological, and social aspects of life. Further, we recommend separate measurement of treatment-related symptoms using an unbiased selection of symptom concepts from an item library (e.g., PRO-CTCAE).

B. BACKGROUND

Materials reviewed:

- Clinical Study Report (CSR) for Study BH29884 (HAVEN1)
- Information Request for additional PRO data analyses (DARRTS Reference ID 4147598) and Applicant's responses submitted on September 7, 2017 and September 25, 2017

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Haem-A-QoL (physical health; HRQL); EQ-5D-5L (health status)

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

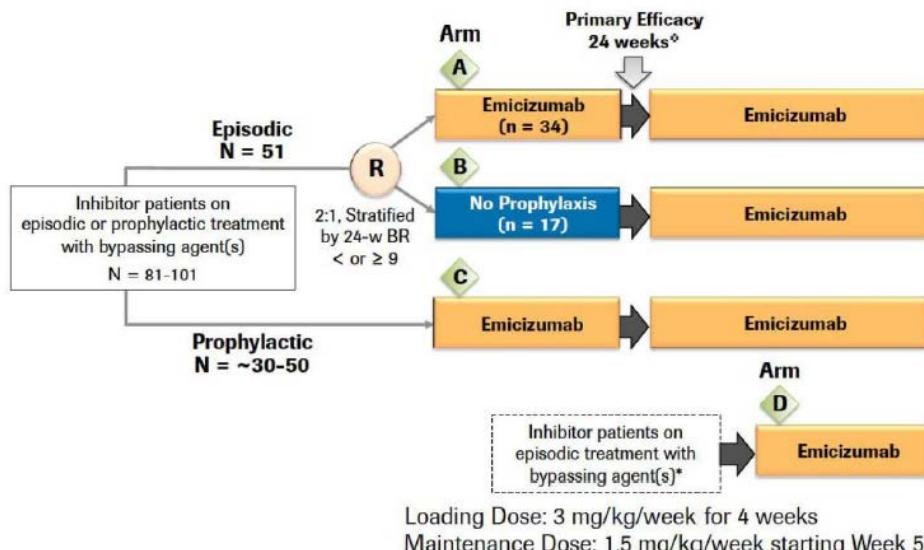
1.1 Clinical Trial Population

HAVEN1 clinical trial population consisted of patients (≥ 12 years of age) with hemophilia A and factor VIII inhibitors who were previously receiving treatment with either episodic or prophylactic bypassing agents. The key inclusion criterion included patients with diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e. ≥ 50 BU). Refer to the Clinical review for additional background.

1.2 Clinical Trial Design

HAVEN1 was an open-label, multicenter, global, randomized study in adult and adolescent patients ≥ 12 years of age. Fifty-three (n=53) patients were randomized in a 2:1 ratio to receive either emicizumab prophylaxis (Arm A; n=35) or no prophylaxis in the control arm (Arm B; n=18). All patients were male adolescents and adults. Emicizumab was administered by the patient or caregiver subcutaneously at a weekly loading dose of 3mg/kg for the first 4 weeks followed by a maintenance dose of 1.5mg/kg/week. Refer to the Clinical and Statistical reviews for additional background. Figure 1 provides an overview of the study design.

Figure 1 Overview of Study Design



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

(Source: HAVEN1 CSR, Page 50)

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Reviewer Comments: The open label clinical trial design is a limitation to the interpretability of PRO data. Patient's knowledge of treatment assignment may lead to systematic overestimation of the treatment effect.

1.3 Endpoint Hierarchy and Definition

Table A (below) provides an overview of the primary and secondary endpoints.

Table A: Overview of the Primary and Secondary Endpoints

Endpoint	Definition	Arms Compared and Analysis Population	Statistical Model
Primary Endpoint			
Treated bleeds	Treated bleeds that met 72HR	A vs B, ITT	NBR
Secondary Endpoints			
All bleeds	Treated and non-treated bleeds that met 72HR	A vs B, ITT	NBR
Treated joint bleeds	Treated bleeds that met 72HR where type = "joint" and unusual sensation (e.g., tingling) has been observed in combination with ≥ 1 following symptoms: unusual sensation, swelling/warmth, pain/decreased RoM, difficulty moving the joint	A vs B, ITT	NBR
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)	A vs B, ITT	NBR
Treated spontaneous bleeds	Treated bleeds with no known contributing factor (e.g., trauma, surgery) that met 72HR	A vs B, ITT	NBR
Intra-patient comparisons	Treated bleeds (as above) and All bleeds (as above)	Intra-patient NIS (Arm A and Arm C)	NBR
EQ-5D-5L	IUS and VAS at 24 weeks	A vs B, ITT	ANCOVA
Haem-A-QoL ^a	Total Score and Physical Health Scale at 24 weeks	A vs B, ITT	ANCOVA

72HR = 72-hour rule; ANCOVA = analysis of covariance; ITT = intent-to-treat; NBR = negative binomial regression; NIS = Non-Interventional Study; RoM = range of motion; VAS = visual analog scale.

^a patients ≥ 18 years of age

(Source: HAVEN1 CSR, Page 72)

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Note: The PRO endpoints assessments were conducted at Week 25, and not Week 24, as shown in the table above.

Reviewer Comment: The Applicant pre-specified PRO endpoints and controlled for type I error.

The Applicant performed additional post-hoc exploratory PRO analyses as follows (Source: HAVEN1 CSR, Page 73):

(b) (4)



See Section C4 for PRO instrument scoring algorithms.

Refer to the Clinical and Statistical reviews for additional background on the endpoints.

Reviewer Comments: There is insufficient evidence to support the proposed thresholds of meaningful change for either PRO instrument. Refer to Section C7 for additional comments.

1.4 Labeling or promotional claim(s) based on the COA

The Applicant proposed the following PRO labeling in the Section 14 of the USPI:

(b) (4)



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(b) (4)



Reviewer Comment: The Haem-A-QoL Physical Health domain appears to be adequate to support potential claims, however modifications may be warranted to the proposed claims. Refer to Section C5 for additional background on the PRO instruments.

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2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

This reviewer created the following table to illustrate the conceptual frameworks for the Haem-A-QoL and EQ-5D-5L:

Table B: Conceptual frameworks for Haem-A-QoL and EQ-5D 5L

Items/domains	General Concept
<ul style="list-style-type: none">• Physical health (5 items)• Feeling (4 items)• View of yourself (5 items)• Sports and leisure (5 items)• Work and school (4 items)• Dealing with hemophilia (3 items)• Treatment (8 items)• Future (5 items)• Family planning (4 items)• Partnership and sexuality (3 items)	<i>Health related quality of life as assessed by Haem-A-QoL(Adults)</i>
<ul style="list-style-type: none">• Mobility• Self-care• Usual activities• Pain/discomfort• Anxiety/depression	<i>Health status as assessed by EQ-5D-5L</i>

Refer to the Appendices A and B for copies of the PRO instruments.

***Reviewer Comments:** In general, the concepts assessed under the Haem-A-QoL Physical Health domain appear reasonable (e.g., joint pain, painful swelling, impaired mobility, reduced physical functioning).*

3 CLINICAL OUTCOME ASSESSMENT(S)

Instruments:

- **Haemophilia-specific Quality of Life (Haem-A-QoL for Adults):** This PRO instrument is designed to assess health-related quality of life (HRQL) in adult patients (aged 18 and above) with hemophilia A. It consists of 46 items comprising 10 dimensions (physical health, feelings, view of yourself, sports and leisure time, work and school, dealing, treatment, future, family planning, and relationships/partners) and a scale representing total score. Items are rated with five respective response options: never, rarely, sometimes, often, and all the time. The recall period is “in the past month” for physical health, feeling, view of yourself, sports and leisure, work and school, dealing with hemophilia, and treatment domains. The recall period is “recently” for future, family planning, and partnership and sexuality domains. See Appendix A for a copy of the instrument.

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- **EuroQoL-Five-Dimension-Five Levels Questionnaire (EQ-5D-5L):** The EQ-5D-5L is a 5-item generic patient-reported preference-based instrument designed to assess health status in adults and in adolescents aged 12 to 18 years across five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Patients rate each of the items as “no problem,” “some problem,” or “extreme problem.” The second section of the instrument measures self-rated (global) health status utilizing a vertically oriented visual analog scale where 100 represents the “best possible health state” and 0 represents the “worst possible health state.” Patients are asked to rate their current health by placing a mark along this continuum. The recall period is “today” for the entire instrument. See Appendix B for a copy of the instrument.

Prior versions: Not applicable

User manual(s): The Applicant did not provide corresponding user manuals.

Timing, data collection method, and mode of administration: The PRO instruments were self-administered using an electronic handheld device (ePRO). Because of electronic administration, patients were not able to skip any questions. The Haem-A-QoL and EQ-5D-5L instruments were administered at baseline (Week 1), Week 5 and every four weeks thereafter until completion of the study. Additionally, patients were prompted to complete the EQ-5D-5L instruments on days when patients reported having a new bleed in addition to regular administration schedule as described above. (Source: HAVEN1 CSR, pp2415-2420)

Training method/materials: The Applicant provided training materials for review upon information request.

4 SCORING ALGORITHM

Haem-A-QoL (Adults): Items (i.e. individual questions in the questionnaire, e.g. My swellings hurts is one of the five items of the scale: physical health) are rated along five response options: never (1), rarely (2), sometimes (3), often (4), all the time (5), with some items having a ‘Not applicable’ option that is scored as a (0). The transformed score ranges from 0 to 100. Higher scores are reflective of greater impairment or poorer HRQL.

Before calculating the scale score some items need to be reverse scored (See Table C below). The reverse scoring for those items is as follows: (1=>5), (2=>4), (3=>3), (4=>2), and (5=>1). Any (0) will be recoded as missing data for the purposes of scale scoring.

For reporting purposes, the individual items are combined to scales (e.g. physical health) and the scales can be combined to form an overall total score. There are 3 steps in the process of deriving the transformed scale score which is used for all the analyses:

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1. Raw Scale Score: Derived as the sum of all items in a scale, e.g. the raw score for physical health is the sum of the 5 items from this scale. A total score is calculated by summing up all of the raw and reverse coded items in the available scales.
2. Standardized Scale Score: To get the standardized scale score, the raw scale score is divided by the number of items in the scale. That way a comparison of scores across scales per patient is possible.
3. Transformed Scale Score: The scores for each scale can be standardized onto a 100-point scale. This is done with the following formula:

$$\begin{aligned} \text{TSC} &= 100 \times \frac{(\text{raw scale score} - \text{minimal possible raw score})}{\text{possible range of raw scale scores}} \\ &= 100 \times \frac{(\text{standardized scale score} - 1)}{4} \end{aligned}$$

The transformed Scale Score is the score used for all analyses in the CSR and referred as domain score or total score (i.e., global score of all the domains for a questionnaire) on the outputs.

Table C: The questions from Haem-A-QoL whose items need re coding are :

Category	Question
View of yourself	I felt comfortable with my body
	I was able not to think all the time about my hemophilia
Dealing with hemophilia	I tried to recognize early on when a bleed developed
	I was able to tell whether or not I was bleeding
	I was able to control my bleeds
Treatment	I was satisfied with the hemophilia center
Future	I have been expecting that things will get better in the future
Sports and leisure	I played sports just as much as others
Work and school	I was able to go to work/school regularly in spite of my hemophilia
	I was able to work/study like healthy colleagues

Table D: Example on how to derive the transformed score from the raw data:

Domain score: Physical health (subscale)

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(Items)	never (=1)	rarely (=2)	sometimes (=3)	often (=4)	all the time (=5)
<i>In the past month...</i>					
1. my swellings hurt				X	
2.I had pain in my joints			X		
3.it was painful for me to move	X				
4. I had difficulty walking as far as I wanted to					X
5.I needed more time to get ready because of my condition		X			

- Raw Physical health Score: $\text{Sum of all items} = 4 + 3 + 1 + 5 + 2 = 15$
- Standardized Physical health Score: $= \frac{\text{Raw physical health score}}{\text{Number of item}} = \frac{15}{5} = 3$
- Transformed Physical health Score: $= 100 \times \frac{(\text{standardized physical health score}-1)}{4} = 100 \times \frac{(3-1)}{4} = 50$

In this example, the transformed Physical Health domain score for this particular patient is 50.

Example on how to derive the total score from the domain scores:

For the total score, the raw scale scores correspond to the sum of all the items for a patient. Let's say that for a patient, the raw total score is 107.

For the standardized total score, it is $= (\text{raw total score}) / (\text{number of item responded}) = 107/46 = 2.32$

Note, the maximum number of items that a patient can respond is 46. For the transformed total score, it is $= 100 \times (2.32-1)/4 = 33$

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Missing data for Haem-A-QoL:

In general, a domain score can be calculated if $\geq 50\%$ of the Haem-A-QoL items have been answered otherwise it is set to missing even if even 1 item have been answered. However, in HAVEN1 study a the questionnaire is being administered electronically and patients are not able to skip items and therefore the data is complete.

Of note, patients can answer “Not applicable” in the Haem-A-QoL to questions in the sports and leisure, work and school, and family planning scales. In this case, the minimum number of items that needs to be completed and not responded to as “Not applicable” is:

- Sports and leisure: 3
- Work and school: 2
- Family planning: 2

The total score takes into account the individual item of the domain even if $<50\%$ of the items for a domain have been answered.

A complete questionnaire can be missing if a patient did not complete the whole questionnaire. Compliance is discussed in HAVEN1 CSR section 4.5.2 (page 92).

EQ-5D-5L: The EQ-5D-5L questionnaire is a health utility measure to assess patients' health status.

1. Utility Score: The part of EQ-5D-5L classifies the health state in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Every dimension consists of five levels, which are coded as follows: 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. All five dimensions can be combined in a five-digit number which then describes the patient's health state. This descriptive number is converted to a single summary index utility score by using published weights; in this study the UK crosswalk value set was used. It ranges from -0.594 to 1 where values less than zero report a utility worse than death and 1 reflects the best health possible.
2. VAS (Visual Analog Scale): Additionally, in a second part, the current health status is measured by the visual analog scale (VAS) with values ranging from 0 to 100 (higher values mean better health) directly filled by the patients.

5 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- Literature review and/or publications
 Documentation of expert input

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Emicizumab (HEMLIBRA®)

Haem-A-QoL (physical health; HRQL); EQ-5D-5L (health status)

- Qualitative study protocols and interview guides for focus group or patient interviews
- Chronology of events for item generation, modification, and finalization (item tracking matrix)
- Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
- Qualitative support for meaningful change
- Quantitative study summary with evidence to support item retention and scoring
- Transcripts (if available)

Upon an information request, the Applicant provided primarily literature to help support content validity of the PRO instruments. The Haem-A-QoL and EQ-5D-5L instruments were selected after a review of the literature and existing instruments to assess physical health, HRQL, and health status.

The Applicant stated the Haem-A-QoL was developed with input from patients and clinicians, where patients reported that issues related to physical health were the most important, with social interactions, dependence, future, and work issues being additionally important; however, the Applicant did not provide any supportive documentation. The Applicant appears to rely on literature references by von Mackensen et al (von Mackensen & Bullinger, 2004) and Pollack et al (Pollak, Muhlan, S, & Bullinger, 2006) to provide additional qualitative evidence, however, these references discuss a similar instrument (possibly an earlier version of the Haem-A-QoL) titled “Haemo-QoL” intended to assess HRQL in pediatric patients. While there is some overlapping content, the Haem-A-QoL (Adults) and Haemo-QoL are two different instruments intended for two different patient groups.

The Applicant stated that EQ-5D-5L was chosen based on its face validity as an additional measure of health status and areas impacted by hemophilia (Herdman et al., 2011).

Reviewer Comments:

Haem-A-QoL: The Haem-A-QoL is a multi-domain instrument designed to assess HRQL in the target patient population. HRQL is a multi-domain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life. While the Applicant referenced supportive literature, which can provide some information about the development work but does not allow for a detailed FDA review of the research. On face validity, the Haem-A-QoL may appear to measure disease related impacts on physical, psychological, and social aspects of life generally, however, there are some important limitations. This reviewer describes some of the strengths and limitations of using the Haem-A-QoL in the target patient population below for the purposes of use in clinical trials to support labeling claims.

- *Strengths:*
 - *The “Physical Health” domain appears to assess the most clinically relevant symptoms and impacts for the most part in the target patient population (e.g., joint pain, painful swelling, impaired mobility, reduced physical functioning).*

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For example, questions asking patients to describe frequency of painful swellings, painful joints, and impaired mobility appear clinically important and meaningful to patients. According to the FDA's Voice of the Patient (VOP) Report³ on hemophilia A, patients with hemophilia A cited joint damage and/or pain as having the most significant impact on their or their loved one's daily life causing problems with mobility and physical functioning. Item #5 (asking patients about time needed to get ready) may be problematic due to possibility of ambiguous interpretation by patients.

- *The "Work and School" domain appears particularly relevant in the target patient population because patients may have to miss school/work because of bleeding events and associated joint pain and swelling in addition to time needed for treatment according to the clinical reviewer. The FDA's VOP report on hemophilia A further accentuated this concern.*
- *One-month recall period may be reasonable for assessment of HRQL in chronic diseases such as hemophilia A. (Note: The recall period is "in the past month" for "Physical health," "Feeling," "View of Yourself," "Sports and Leisure," "Work and School," "Dealing with Hemophilia," and "Treatment" domains)*
- *Limitations:*
 - *The inclusion of certain items within the "Feeling," "View of Yourself," "Dealing with Hemophilia," "Future," "Family Planning," and "Partnership and Sexuality" domains do not appear to be sensitive to change because of treatment (e.g., "I have been finding it difficult to date because of my hemophilia"). Additionally, some questions under the family planning may be irrelevant in the HAVEN1 study because the clinical trial only included male patients (e.g., "I have had difficulties having children," "I have been afraid that I cannot have children"). However, this reviewer acknowledges that concerns about family planning may be appropriate for female patients because of postpartum bleeding, which was expressed by some patients in the FDA's VOP report on hemophilia A. It is possible that family planning could be an issue for male patients; however, the content of this domain did not appear entirely relevant for male patients. Refer to the copy of the instrument in Appendix A for additional examples.*
 - *While the "Sports and Leisure" domain appears relevant on face value, hemophilia patients are generally advised by their healthcare providers to avoid/limit contact sports such as football to reduce bleeding risk. Consequently, questions regarding contact sports such as football may not be most sensitive to change because most patients may have adjusted to recommended lifestyle prior to and during the clinical trial to prevent or minimize physical injuries. Based on input from the clinical reviewer, it is unlikely that patients would change their behavior because of an investigational prophylactic treatment, as they should be exercising caution to minimize risk of bleeding.*

³ <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM513311.pdf>

Clinical Outcome Assessment Review

Nikunj B. Patel, PharmD

BLA 761083

Emicizumab (HEMLIBRA®)

Haem-A-QoL (physical health; HRQL); EQ-5D-5L (health status)

- *The content of the “Treatment” domain may be relevant for clinical practice; however, for clinical trials it might be problematic and possibly irrelevant because it includes questions asking patients to rate health care delivery services such as availability of physician to answer questions and satisfaction with the hemophilia center, which does not measure the effect of the treatment on patients’ health. Additionally, after discussion with the clinical reviewer it appears the question asking patients about their experience using “factor concentrate” (a type of treatment in hemophilia) may be inappropriate because “factor concentrate” was not studied in the clinical trial.*
- *The questionnaire appears quite lengthy (i.e. 46 items) and could be streamlined.*
- *The recall period of “recently” for the “Future,” “Family Planning,” and “Partnership and Sexuality” domains appears ambiguous.*

According to the PRO Guidance (2009), claiming a statistical and meaningful improvement in HRQL implies: (1) that all HRQL domains that are important to interpreting change in how the clinical trial’s population feels or functions because of the targeted disease and its treatment were measured; (2) that a general improvement was demonstrated; and (3) that no decrement was demonstrated in any domain. In the HAVEN1 study, we observed statistically significant improvement in the pre-specified and alpha controlled secondary endpoints supported by Haem-A-QoL (Group adjusted mean difference favoring treatment arm at week 25: Physical Health domain = 21.55, p=0.0029; Total score =14.01, p=0.0019). Further, we observed numerical improvement in domains such as “feeling,” “sports and leisure,” “treatment,” “work and school,” “future,” and “view of yourself” in the treatment arm compared to placebo throughout the study. However, no improvement or decrement was observed in the “partnership/sexuality” and “dealing with hemophilia” domains in the treatment arm compared to placebo. These results are reflective of inherent strengths and limitations of the instrument. For example, we observed improvement in the “Physical Health” domain with greater magnitude compared to other domains, which is likely because this domain included items that are clinically relevant, meaningful to patients, and sensitive to change because of treatment. On the other hand, domains such as “partnership/sexuality” are unlikely to change because of the investigational treatment alone. Additionally, most patients responded at the lowest option (i.e. “rarely”) or “Not Applicable” on such items, suggesting patients were not experiencing these problems at baseline and therefore unlikely to show any improvement.

In sum, an improvement or deterioration in each of the Haem-A-QoL domains may inform how patients are feeling or functioning because of disease and/or treatment; however, some domains/items might not be sensitive to change, influenced by factors other than treatment/disease, and/or possibly inappropriate/irrelevant in the context of the clinical trial. Therefore, this reviewer does not agree the Haem-A-QoL instrument in totality is content valid. As such, one should exercise caution when interpreting Haem-A-QoL total score. Despite many limitations of the instrument’s total score as illustrated above, the “Physical Health” domain appears fit-for-purpose in the target patient population to assess the most relevant symptoms and impacts.

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EQ-5D-5L: The EQ-5D-5L instrument is a generic preference-based measure commonly used to provide a single health utility index value for use in economic analyses (b) (4)

However, this reviewer acknowledges that the EQ-5D-5L may be necessary for other regulatory authorities and/or payers.

6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant did not conduct psychometric evaluation of the PRO instruments, however, provided relevant literature references to help support other measurement properties (von Mackensen et al., 2017) (Varaklioti, Kontodimopoulos, Katsarou, & Niakas, 2014).

Reviewer Comments: Generally, when content validity of an instrument is not established, testing other measurement properties (reliability, construct validity, and ability to detect change) will not replace or rectify problems related to content validity of the Haem-A-QoL instrument.

7 INTERPRETATION OF SCORES

The Applicant pre-specified group comparison (change from baseline) for the Haem-A-QoL Physical Health domain and total score at 25 weeks between treatment arms as the trial endpoint. (b) (4)

Reviewer Comments: (b) (4)

As part of the post-hoc exploratory efficacy analyses, the clinical significance of Haem-A-QoL was evaluated (b) (4)

support meaningful change analyses. to

Reviewer Comments: This reviewer does not agree with the methodologies used to derive the threshold of meaningful change in the Haem-A-QoL. The general recommendation is to use anchor-based methods as the primary approach supplemented with CDF and probability density function (PDF) plots to help derive the threshold for meaningful within-patient change to help

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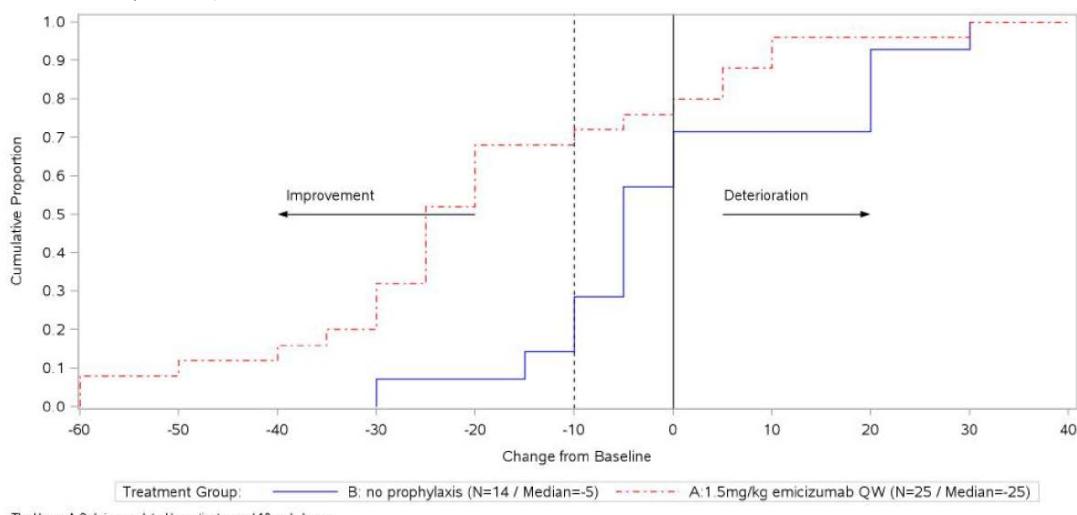
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interpret Haem-A-QoL scores. Therefore, the optimal threshold for meaningful within patient change is unclear.

This reviewer requested additional PRO analyses (DARRTS Reference ID 4147598) to understand score interpretation of the Haem-A-QoL Physical Health domain in the HAVEN1 study. Figure 2 below shows a CDF plot for the Haem-A-QoL Physical Health domain.

Figure 2: CDF Plot of Haem-A-QoL Transformed Physical Health Domain Change Scores from Baseline to Week 25, Adults, ITT (Source: FDA Information Request Response, September 25, 2017)



Reviewer Comments: While we do not know any specific meaningful within-patient change for the Haem-A-QoL Physical Health score, Figure 2 shows a clear separation between the treatment and no prophylactic arms, suggesting improvement favoring the treatment arm. Because of content validity issues (See Section C5), we did not go further with analyses related to total score.

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The Haem-A-QoL and EQ-5D-5L are available in multiple languages. The Haem-A-QoL and EQ-5D-5L are available in multiple languages, which appear to comply with best practices for translation and cultural adaptation.

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable

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10 REVIEW USER MANUAL

The Applicant did not provide a user manual for the Haem-A-QoL instrument upon request, however submitted relevant administration/training information. The EQ-5D-5L user guide is publically available (<https://euroqol.org/>) and was provided upon information request.

11 KEY REFERENCES FOR COA

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., . . . Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*, 20(10), 1727-1736. doi: 10.1007/s11136-011-9903-x

(b) (4)



Pollak, E., Muhlan, H., S, V. O. N. M., & Bullinger, M. (2006). The Haemo-QoL Index: developing a short measure for health-related quality of life assessment in children and adolescents with haemophilia. *Haemophilia*, 12(4), 384-392. doi: 10.1111/j.1365-2516.2006.01292.x

(b) (4)



Varaklioti, A., Kontodimopoulos, N., Katsarou, O., & Niakas, D. (2014). Psychometric properties of the Greek Haem-A-QoL for measuring quality of life in Greek haemophilia patients. *Biomed Res Int*, 2014, 968081. doi: 10.1155/2014/968081

von Mackensen, S., & Bullinger, M. (2004). Development and testing of an instrument to assess the Quality of Life of Children with Haemophilia in Europe (Haemo-QoL). *Haemophilia*, 10 Suppl 1, 17-25.

von Mackensen, S., Eldar-Lissai, A., Auguste, P., Krishnan, S., von Maltzahn, R., Yu, R., & Wyrwich, K. W. (2017). Measurement properties of the Haem-A-QoL in haemophilia clinical trials. *Haemophilia*, 23(3), 383-391. doi: 10.1111/hae.13140

(b) (4)



(b) (4)

D. APPENDICES

Appendix A: Haem-A-QoL (Adults)

Appendix B: EQ-5D-5L

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Appendix A: Haem-A-QoL (Adults)

(Source: HAVEN1 CSR, pp2425-2431)

Appendix 4 Haem-A-QoL (United States/English)

Trial ID:	Page 1/7
VISIT X	
Centre ID/No.:	[] [] []
Subject No.:	[] [] [] [] []
Visit Date:	[] [] [] [] [] [] D D M M M Y Y Y Y

HAEM-A- QOL

Questionnaire for Adults

Dear Patient,

We would like to find out how you have been feeling during the past weeks. Please be so kind as to answer the following questions in this questionnaire, designed specifically for people with hemophilia.

Please follow the instructions below when answering the questions:

- ⇒ Please read each question carefully.
- ⇒ Think about how things have been for you over the past weeks.
- ⇒ Put an "X" in the box corresponding to the answer that fits you best.
- ⇒ Only mark one box for each question.
- ⇒ There are no right or wrong answers.
- ⇒ It's what you think that matters.
- ⇒ There are some aspects that might not concern you (Sports & Leisure, Family Planning, Work & School, e.g., if you don't work or don't go to school). In such a case, please mark the answer category "not applicable."

All your answers will be treated with the strictest confidence!

Date of completion: __ / __ / __ (month/ day/ year)

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	Page 2/7
VISIT X	
Subject No.:	[REDACTED]

1. Here we would like to find out about hemophilia and your PHYSICAL HEALTH

<i>In the past month...</i>	never	rarely	sometimes	often	all the time
1. ... my swellings hurt	<input type="checkbox"/>				
2. ... I had pain in my joints	<input type="checkbox"/>				
3. ... it was painful for me to move	<input type="checkbox"/>				
4. ... I had difficulty walking as far as I wanted to	<input type="checkbox"/>				
5. ... I needed more time to get ready because of my condition	<input type="checkbox"/>				

2. and now about how you have been FEELING because of your hemophilia

<i>In the past month...</i>	never	rarely	sometimes	often	all the time
1. ... my hemophilia was a burden for me	<input type="checkbox"/>				
2. ... my hemophilia made me angry	<input type="checkbox"/>				
3. ... I was worried because of my hemophilia	<input type="checkbox"/>				
4. ... I felt excluded	<input type="checkbox"/>				

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	Page 3/7
VISIT X	
Subject No.:	[REDACTED]

3. How does hemophilia affect your VIEW OF YOURSELF?

<i>In the past month...</i>	never	rarely	sometimes	often	all the time
1. ... I envied healthy people my age	<input type="checkbox"/>				
2. ... I felt comfortable with my body	<input type="checkbox"/>				
3. ... hemophilia made my life more difficult	<input type="checkbox"/>				
4. ... I felt different from others because of my hemophilia	<input type="checkbox"/>				
5. ... I was able not to think all the time about my hemophilia	<input type="checkbox"/>				

4. These questions are about SPORTS AND LEISURE

<i>In the past month...</i>	never	rarely	sometimes	often	all the time	not applicable
1. ... I had to avoid sports that I like because of my hemophilia	<input type="checkbox"/>					
2. ... I had to avoid sports like football	<input type="checkbox"/>					
3. ... I played sports just as much as others	<input type="checkbox"/>					
4. ... I didn't have the freedom to travel where I wanted	<input type="checkbox"/>					
5. ... it was necessary for me to plan everything in advance	<input type="checkbox"/>					

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	Page 4/7
VISIT X	
Subject No.:	[REDACTED]

5. These questions are about WORK AND SCHOOL

<i>In the past month...</i>	never	rarely	sometimes	often	all the time	not applicable
1. ... I was able to go to work/school regularly in spite of my hemophilia	<input type="checkbox"/>					
2. ... I was able to work/study like healthy colleagues	<input type="checkbox"/>					
3. ... my everyday work/school activities were jeopardized by my hemophilia	<input type="checkbox"/>					
4. ... I found it difficult to pay attention at work/school because I was in pain	<input type="checkbox"/>					

6. The next questions are about DEALING WITH HEMOPHILIA

<i>In the past month...</i>	never	rarely	sometimes	often	all the time
1. ... I tried to recognize early on when a bleed developed	<input type="checkbox"/>				
2. ... I was able to tell whether or not I was bleeding	<input type="checkbox"/>				
3. ... I was able to control my bleeds	<input type="checkbox"/>				

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	Page 5/7
VISIT X	
Subject No.:	<input type="text"/> 1 2 3 4 5 6 7

7. and what about your TREATMENT?

<i>In the past month...</i>	never	rarely	sometimes	often	all the time
1. I was dependent on the factor concentrate because of my hemophilia	<input type="checkbox"/>				
2. I was dependent on physicians for the treatment of my hemophilia	<input type="checkbox"/>				
3. I was annoyed about the amount of time spent having the injections	<input type="checkbox"/>				
4. I felt the injections interrupted my daily activities	<input type="checkbox"/>				
5. I was afraid of complications	<input type="checkbox"/>				
6. I had problems with how my treatment was administered	<input type="checkbox"/>				
7. I was afraid that in case of emergency, other doctors wouldn't know how to treat hemophilia	<input type="checkbox"/>				
8. I was satisfied with the hemophilia center	<input type="checkbox"/>				

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	Page 6/7
VISIT X	
Subject No.:	<input type="text"/>

8. What do you think about the FUTURE?

Recently...	never	rarely	sometimes	often	all the time
1. ... I have been thinking that it will be difficult for me to lead a normal life	<input type="checkbox"/>				
2. ... I have been expecting that things will get better in the future	<input type="checkbox"/>				
3. ... I have been worrying that my condition is worsening	<input type="checkbox"/>				
4. ... my life plans have been influenced by my hemophilia	<input type="checkbox"/>				
5. ... I have been afraid that I will need a wheelchair	<input type="checkbox"/>				

9. The next questions are about hemophilia and your FAMILY PLANNING

Recently...	never	rarely	sometimes	often	all of the time	not applicable
1. ... I have had difficulties having children	<input type="checkbox"/>					
2. ... I have been afraid that I cannot have children	<input type="checkbox"/>					
3. ... I have been afraid that I will not be able to take care of my children	<input type="checkbox"/>					
4. ... I have been worrying about not being able to raise a family	<input type="checkbox"/>					

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	Page 7/7
VISIT X	
Subject No.:	<input type="text"/> / <input type="text"/>

10. What about PARTNERSHIP AND SEXUALITY?

Recently...	never	rarely	sometimes	often	all the time
1. ... I have been finding it difficult to date because of my hemophilia	<input type="checkbox"/>				
2. ... I have been insecure in my relationships with women because of my hemophilia	<input type="checkbox"/>				
3. ... I haven't been able to have a normal relationship because of my hemophilia	<input type="checkbox"/>				

THANK YOU FOR YOUR ASSISTANCE!

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Appendix B: EQ-5D-5L

(Source: HAVEN1 CSR, pp2432-2433)

Appendix 5 EQ-5D-5L (United Kingdom/English)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

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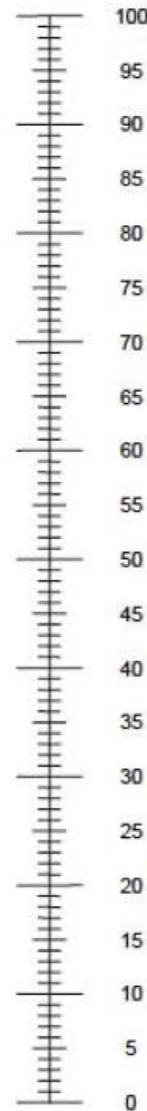
Haem-A-QoL (physical health; HRQL); EQ-5D-5L (health status)

Appendix 5 EQ-5D-5L (United Kingdom/English) (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

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/s/

NIKUNJ B PATEL

10/13/2017

SELENA R DANIELS

10/13/2017

ELEKTRA J PAPADOPOULOS

10/13/2017