Official Title: A Single-Arm, Multicenter Phase IIIB Clinical Trial to Evaluate the Safety and Tolerability of Prophylactic Emicizumab in Hemophilia A Patients With Inhibitors

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PROTOCOL

TITLE:	**A SINGLE-ARM, MULTICENTER PHASE IIIB CLINICAL TRIAL TO EVALUATE THE SAFETY AND TOLERABILITY OF PROPHYLACTIC EMICIZUMAB IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
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MEDICAL MONITOR:	Dr. [redacted] MD, MBA
SPONSOR:	F. Hoffmann-La Roche Ltd
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PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	09-Mar-2018 10:00:09

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Additional safety and efficacy data are now available based on completed and ongoing emicizumab clinical trials. In addition, inconsistencies within the protocol have been corrected.

The changes and associated rationales are described below, along with the sections of the protocol which have been impacted. Similar changes have been made to the synopsis where applicable.

Change and Rationale	Sections Impacted
For consistency purposes, the study patient population of interest is now referred to as patients with congenital hemophilia A who have persistent inhibitors against FVIII	Throughout protocol
For consistency purposes, study drug, study medication and investigational medicinal product (IMP) are now referred to as "emicizumab"	Throughout protocol
Background clinical data with emicizumab has been updated as new information is now available from additional clinical trials (JP29574, BH29884, BH29992). This includes updated safety and efficacy information, an updated summary of anti-drug antibodies, and new guidance regarding peri-operative management of patients receiving emicizumab. Specific safety events (hypercoagulation, thromboembolic events and thrombotic microangiopathy) have also been updated.	1.2.2 1.3 3.3.1 5.1.1
For consistency, thromboembolic events and thrombotic microangiopathy (TMA), both adverse events of special interest, are now described as thromboembolic events, microangiopathic hemolytic anemia or TMA (e.g. hemolytic uremic syndrome).	2 (Table 7) 3.1 3.3 4.5.6.8 6.4 9.4.1

Change and Rationale	Sections Impacted
Any hemostatic medications (e.g. bypassing agents) and other medications used to treat or prevent bleeds in the 6-month period prior to starting emicizumab treatment will also be collected. The use of bypassing agents and the management of breakthrough bleeds has been made consistent throughout the protocol, as well as updated based on the risk of TMA and thrombotic events in patients treated with emicizumab. The use of activated prothrombin complex concentrate (aPCC) for breakthrough bleed treatment for patients on emicizumab should be avoided if possible, and rFVIIa should be the first option used to treat, starting with no more than 90 µg/kg as an initial dose. If aPCC needs to be used, no more than 50 IU/kg should be administered as an initial dose and doses of > 100 U/kg/24 hours or more should be avoided, as cases of TMA and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours aPCC was administered for 24 hours or more. Investigators should provide or remind patients of the exact dose and schedule of bypassing agents or FVIII required to treat any bleed. At the start of the study, Investigators shall discuss with patients the recommended doses of any additional coagulation factors used. Where possible, the use of aPCC for any reason should be avoided during the study. Factor eight inhibitor bypassing activity (FEIBA) can not be used prophylactically, and the use of anti-fibrinolytics in conjunction with aPCC or Byclot® is not permitted.	3.1 3.3.2 4.4 Appendix 1
Patients who discontinued emicizumab prior to the completion of the 2-year treatment period were required to undergo a Safety Follow-up visit 24 weeks post-emicizumab discontinuation. For patients discontinuing emicizumab at Month 18 or beyond, this meant that these patients were actually followed for longer than patients who completed the 2-year treatment period. This has now been revised such that patients who discontinue emicizumab prior to the completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first.	3.2 4.4 4.6 Appendix 1
Biomarker information will not be used to support the selection of a recommended emicizumab dose, as emicizumab dosing has already been determined.	3.3.4

Change and Rationale	Sections Impacted
It has been clarified that the interim analysis will occur when *approximately* 100 patients have received treatment with emicizumab for at least 24 weeks. A second analysis will be performed when *approximately* 100 patients have received treatment with emicizumab for at least 52 weeks. It has also been clarified that the independent Data Monitoring Committee (iDMC) will monitor the study throughout its duration, and not just at the time of the interim analyses.	3.1 3.3.9 6.9.1 9.4.1
It has been clarified that the patient-reported outcomes of Health-Related Quality of Life (HRQoL) and EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) will be obtained using an electronic patient-reported outcome (ePRO) device, whereas the patient preference data will be collected on paper forms. For HRQoL and EQ-5D-5L, paper versions are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.	3.3.10 4.1.1 4.5.9 7.3 Appendix 1
The inclusion criterion requiring patients to have a body weight ≥ 40 kg at time of screening has been removed. Data is now available in the pediatric patient population and in lower weight patients, confirming that the standard emicizumab dose can be used.	4.1.1
It has been clarified that the 3-mL glass vials of drug product contain 1 mL of emicizumab	4.3.1.1
Recommended injection sites have been added to the protocol, based on the Instructions for Use for emicizumab	4.3.2.1
Guidance regarding the vial pooling of emicizumab has been clarified. Up to two 1-mL vials of the emicizumab drug product solution can be combined into a single syringe. If the patient's dose is > 2 mL, a second injection will be required. For efficiency reasons, Sponsor approval for the pooling of drug product is no longer required.	4.3.2.1
The management of missed emicizumab doses has been updated based on the US Prescribing Information. If the patient forgets or cannot administer emicizumab on the scheduled dosing day, emicizumab should be administered as soon as possible before the day of the next scheduled dose, and then the patient should resume the usual weekly dosing schedule. Doses should not be doubled to make up for a missed dose. All four loading doses of 3 mg/kg should be taken, even if this is done over a period or more than four weeks.	4.3.2.1
The footnotes of the Schedule of Activities and the description of the procedures within the protocol have been made consistent.	4.5 Appendix 1

Change and Rationale	Sections Impacted
As a result of a Regulatory Authority request, it has been clarified that medical history includes information on prior surgery. In addition, relevant data will be collected on any surgery or procedures performed during the study, type of surgery / procedure, other associated treatments, outcomes, etc.	3.1 4.5.2 4.5.8 Appendix 1
Protocol text has been clarified, and Table 9 added, to help distinguish which laboratory tests are assessed by the central laboratory vs the local laboratory	4.5 Appendix 1
It has been clarified that central labs are part of the non-electronic case report form (eCRF) data which will be sent to the Sponsor directly by the central lab vendor	4.5.6 Appendix 1
It has been clarified that the specific tests utilized for hepatitis and human immunodeficiency virus (HIV) testing are per local standard of care. As this patient population is at high risk for HIV, hepatitis A, B and C, sites should consider testing for these. While the specific serological tests used is at the discretion of the Investigator, this is with the understanding that the status of that participants' hepatitis or HIV is confidently known at time at enrollment.	4.5.6.3 Appendix 1
It has been clarified that safety biomarker assessments may include, but are not limited to, D-dimer. Additional analyses may occur over the duration of the study as relevant biomarkers are identified.	4.5.6.7 Appendix 1 Appendix 2
It has been clarified that safety biomarkers, safety coagulation system biomarkers and pharmacodynamic (PD) biomarkers require citrate plasma samples.	4.5.6.7 Appendix 1 Appendix 2
Residual samples from biomarker assessments will be stored and used not later than 5 years after the clinical study report (CSR) has been written. It has been clarified that additional testing may include other future exploratory research, as all relevant biomarkers are not currently known.	4.5.6.9 4.5.6.12
It has been clarified that patients will use an ePRO device to record bleeds and hemophilia medication use, where possible.	3.1 3.3.7 4.5.7 Appendix 1
For clarification, the versions/language of the specific HRQoL assessments being used have been added to the body of the protocol, and copies of the questionnaires have been removed from the appendices.	4.5.9.1 Appendix 3 Appendix 4 Appendix 5

Change and Rationale	Sections Impacted
Additional reasons which require the patient to permanently discontinue emicizumab have been added, to comply with the Roche protocol template. These reasons include any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive emicizumab, the Investigator or Sponsor determines it is in the best interest of the patient, and any requirement of another medication not permitted per protocol.	4.6.2
Although the clinical development of emicizumab is still ongoing, information regarding the safety profile of the drug is now relatively well understood. Therefore, the statement that 'the complete safety profile is not known at this time' has been removed.	5.1
In the event of a breakthrough bleed that is treated with bypassing agents, additional laboratory tests are recommended. Ideally, samples for these tests should be analysed at the central laboratory. Exceptionally in urgent situations where results are required quickly, local laboratory testing can be used, with results recorded in the eCRF. All laboratory results which are required as part of the patient's safety assessment should be recorded in the unscheduled visit eCRFs.	4.5.6.8 Appendix 1
The wording regarding the interpretation of coagulation assays for patients receiving emicizumab has been updated for clarification, and Table 11 has been added to describe coagulation test results which are affected or unaffected by emicizumab.	5.1.3
It has been clarified that a pre-existing medical condition is one that is present during the study Screening Period	5.3.5.9
To avoid frequent protocol updates, specific details (name / phone numbers) for the emergency medical contacts have been removed. Instead, sites may call the Emergency Medical Call Center Help Desk to access the Roche Medical Emergency List	5.4.1
For clarification, protocol "violations" have been re-worded as protocol "deviations". Major protocol deviations and the number of patients with at least one major protocol deviation will be summarized.	6.2
Statistical wording referring to comparison between groups has been removed, as this is a single-arm study.	6.5
It has been clarified that the data from the ePRO device will be transmitted electronically to the eCRF in real time.	7.3

Change and Rationale	Sections Impacted
Consenting patients may be asked about their study experience via a short study-specific survey at the end of the study. Completion of this survey is optional. Survey questions will ask the patient to rate their study experience on topics that include information provided prior to the study, the consent and enrolment process, study participation, study results and feeling appreciated as a study patient. The goal of this survey is to identify areas where Roche is performing well and areas where improvement may be required.	9.7
Unused references have been deleted, and new references added based on new information added to the protocol.	10
Anti-FVIII antibodies will be collected at the Day 1, Week 1 visit (not during Screening). In addition, the ePRO bleed / medication recording does not require collection during Screening. These changes are corrections of an error. Additional revisions have been made to ensure consistency between the Schedule of Activities and the body of the protocol.	Appendix 1
After informed consent has been obtained but prior to initiation of emicizumab, serious adverse events caused by a protocol-mandated intervention should be reported.	Appendix 1
It has been clarified that in the Schedule of Activities, the time point reference to “month” is referring to calendar months.	Appendix 1
For clarification, additional details have been added to the schedule of biomarker samples, including study visits, time windows and details on the assays.	Appendix 2

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 3:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

TITLE PAGE:

VERSION NUMBER: ~~2~~*3*

…

DATE FINAL: *Version 3: See electronic date stamp below*

DATES AMENDED: *Version 1: 31 January 2017*

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Emicizumab—F. Hoffmann-La Roche Ltd
Protocol MO39129, Version ~~2~~*3*

PROTOCOL AMENDMENT ACCEPTANCE FORM

VERSION NUMBER: ~~2~~*3*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

CTX	*C-terminal telopeptide of collagen 1*
ECL	*electrochemiluminescence*
EDTA	*ethylenediaminetetraacetic acid*
NIS	*non-interventional study*
OPG	*osteoprotegerin*
P1NP	*procollagen type 1 amino-terminal propeptide*
RANK-L	*receptor activator of nuclear factor kappa-B ligand*
SMT	*Study Management Team*

1.2.2 Clinical Experience

Available experience with emicizumab in humans includes data from one completed Phase I study (ACE001JP – Last Patient Last Visit on 17 April 2015) and its ongoing Phase I/II extension study (ACE002JP). *Currently available experience with emicizumab in humans includes data from two completed Phase I studies (ACE001JP and JP29574), one ongoing Phase I/II study (ACE002JP) extension in hemophilia A patients, and two ongoing Phase III studies in hemophilia A patients with inhibitors (adult patients - BH29884; pediatric patients – BH29992).*

The clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) is ongoing for emicizumab. Refer to the emicizumab Investigator's Brochure for details on the preclinical and clinical studies.

1.2.2.1 Studies ACE001JP and ACE002JP

ACE001JP was a single study conducted in three parts, which included both healthy subjects (Part A and Part B) and patients with hemophilia A (Part C). The objective of Parts A and B in healthy subjects was to investigate the tolerability, safety, PK, and PD response of SC-administered emicizumab in adult Japanese and Caucasian men and to evaluate for racial differences, if any, in their PK and PD response. ~~Healthy male volunteers aged 20–44 were eligible for enrollment.~~ A total of 64 healthy *male* volunteers were enrolled in Parts A and B ~~from August 2012 to April 2013~~. In Part C, the objective was to investigate the tolerability, safety, PK, and PD response of SC-administered emicizumab in patients *12–59 years of age* with *congenital* hemophilia A *who* ~~. Patients were eligible for enrollment if they were 12–59 years of age, ≥ 40 kg in weight, had a diagnosis of congenital hemophilia A, and~~ had previous documentation of bleeds and/or coagulation factor treatment in the last 6 months. ~~For those with inhibitors, patients must have had ≥ 6 bleeds in the 6 months prior to enrollment, and for those without inhibitors, patients were required to have received ≥150 lifetime doses of FVIII replacement, including in the last 6 months.~~ A total of 18 patients ~~with hemophilia A~~ were enrolled *in Part C* ~~from May 2013 to June 2014~~.

Parts A and B of Study ACE001JP (completed) consisted of a randomized, placebo-controlled, single ascending dose (SAD) study, which was conducted in Japanese (n=40; Part A) and Caucasian (n=24; Part B) healthy men. In total, 48 subjects received a single SC injection of 0.001 mg/kg to 1 mg/kg emicizumab and 16 subjects received a single SC injection of placebo. Part C of Study ACE001JP was an open-label, multiple ascending dose (MAD) study in 18 Japanese patients with hemophilia A, both with and without inhibitors. Of note, patients received concurrent coagulation factor products to control breakthrough bleeds. Of the 18 patients in Part C of Study ACE001JP, six patients were dosed with 0.3 mg/kg/week SC following a single loading dose of 1 mg/kg SC, six patients were dosed with 1 mg/kg/week SC following a single loading dose of 3 mg/kg SC, and six patients received 3 mg/kg/week emicizumab SC without a loading dose.

Patients who participated in Part C of Study ACE001JP were offered the opportunity to continue in the extension study (ACE002JP). In order to be eligible for the extension study, patients must have completed 12 weeks of assigned treatment in Study ACE001JP and had bleeds prior to study entry. ~~Seventeen of 18 patients in Part C of Study ACE001JP~~

~~completed the 12 week treatment period. One patient discontinued the treatment and moved to the post discontinuation follow up period. A total of 16 of the 17 patients who completed the 12 week treatment period subsequently enrolled into extension Study ACE002JP, and one patient moved to the post treatment observation period of Study ACE001JP. Thus, , which includes six patients from the 0.3 mg/kg/week group, five patients from the 1 mg/kg/week group, and five patients from the 3 mg/kg/week group of Study ACE001JP~~

The duration of follow-up for the patients in the 0.3, 1, and 3 mg/kg/week cohorts who enrolled in Study ACE002JP ranges from 140 to 145, 116 to 124, and 89 to 98 weeks, respectively (cut-off date 15th February 2016).For Studies ACE001JP and ACE002JP, the efficacy parameter of annualized bleeding rate (ABR) has been calculated by annualizing the number of bleeds that required treatment with coagulation factor products during the 6 months prior to study enrollment and during the treatment period after the first emicizumab administration. During the 6 months before study enrollment, the patients without inhibitors received FVIII prophylactic replacement therapy, while the patients with inhibitors received episodic therapy and/or prophylactic therapy with bypassing agents.

After administration of emicizumab to patients with hemophilia A, annualized bleeding rates (ABRs) decreased in all patients in Studies ACE001JP and ACE002JP compared with the pre-treatment period, regardless of whether or not they had FVIII inhibitors, with the exception of one patient in the 3 mg/kg/week group who was previously treated with FVIII prophylaxis and had a baseline ABR of 0 (in this patient, the ABR was maintained at 0 while receiving emicizumab). Among all patients, percentage reduction in ABR ranged from 22.8% to 100% in the 0.3 mg/kg/week group, from 57.5% to 100% in the 1 mg/kg/week group, and from 90.1% to 100% in the 3 mg/kg/week group.

The safety data from completed studies of healthy male volunteers (Japanese and Caucasian) in ACE001JP Parts A and B (n=48) showed that emicizumab was well tolerated and the incidence of adverse events was similar in the emicizumab dosing groups and the placebo group. Moreover, no racial differences or dose-dependent increases in the incidence of adverse events were observed. There were no serious adverse events, adverse events leading to discontinuation, or deaths in either study. From ACE001JP Part C and its ongoing extension ACE002JP (as of the cut-off date 15 February 2016), most adverse events were of mild or moderate intensity, except for 2 severe adverse events (appendicitis and mesenteric hematoma). The majority of the adverse events were not considered related to emicizumab (see the Emicizumab Investigator's Brochure).

1.2.2.2 JP29574

Completed Study JP29574 included 5 groups of 12 healthy Japanese volunteers. This study investigated the relative bioavailability between Phase I/II 80 mg/mL formulation and Phase III 150 mg/mL formulation materials and among three different sites of injection, as well as the absolute bioavailability. Results showed no significant difference in the incidence of adverse events observed by formulation, injection site, or administration route.

Emicizumab has been well tolerated in patients in the Phase I/II studies (cut-off date 15th February 2016; see the emicizumab Investigator's Brochure). The majority of adverse events have been mild in intensity, except for five moderate adverse events (upper respiratory tract

infection, bipolar I disorder, hemophilia [left hip joint bleeding due to hemophilia], headache, and asthma) and two severe adverse events (appendicitis and mesenteric hematoma). Both severe events were considered to be serious adverse events and not related to emicizumab administration. A total of seven patients have reported injection-site reactions (including erythema, hematoma, rash, pain, discomfort, and pruritus). All injection-site reactions were mild in intensity. Besides injection-site reactions, the most frequently reported adverse events (at least four patients) have been nasopharyngitis, pharyngitis, dental caries, excoriation, and headache. There have not been any dose-dependent increases in adverse events, and the majority of the adverse events have not been considered to be related to emicizumab. Treatment was discontinued for one patient with injection-site erythema in the 1 mg/kg weekly group; the event was mild in intensity and resolved. The same patient also reported one non-related serious adverse event (hemophilia [left hip joint bleeding due to hemophilia]) approximately 24 weeks after the last dose of study drug. In the Phase I/II studies, no thromboembolic adverse events have been reported when emicizumab has been administered alone or concomitantly with FVIII products or bypassing agents as episodic therapy.

1.2.2.3 Studies BH29884 and BH29992

~~The ongoing Phase III study (BH29884) is enrolling patients with hemophilia A aged 12 years or older who have inhibitors against FVIII and have received episodic or prophylactic treatment with bypassing agents prior to study entry.~~

As of October 2016, thrombotic microangiopathy (TMA) has been observed in two patients receiving emicizumab and bypassing agents see Section 5.1.1.3) and two cases of thromboembolic events have been observed in two patients receiving the same regimen (see Section 5.1.1.2).

The HAVEN 1 study (BH29884; NCT02622321) was a randomized, multicenter, open-label, clinical trial in 109 adult and adolescent males (aged 12 to 75 years and > 40 kg) with hemophilia A with FVIII inhibitors who previously received either episodic (on-demand) or prophylactic treatment with bypassing agents. Patients received weekly emicizumab prophylaxis (Arms A, C, and D), 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter, or no prophylaxis (Arm B). Dose up-titration to 3 mg/kg once weekly was allowed after 24 weeks on emicizumab prophylaxis in case of suboptimal efficacy (i.e., ≥ 2 spontaneous and clinically significant bleeds). During the study, two patients underwent up-titration of their maintenance dose to 3 mg/kg once weekly.

Fifty-three patients previously treated with episodic (on-demand) bypassing agents were randomized in a 2:1 ratio to receive emicizumab prophylaxis (Arm A) or no prophylaxis (Arm B), with stratification by prior 24-week bleed rate (< 9 or ≥ 9). Patients randomized to Arm B could switch to emicizumab prophylaxis after completing at least 24 weeks without prophylaxis.

Forty-nine patients previously treated with prophylactic bypassing agents were enrolled into Arm C to receive emicizumab prophylaxis. Seven patients previously treated with episodic (on-demand) bypassing agents who had participated in a non-interventional study (NIS) prior to enrollment, but

were unable to enroll into HAVEN 1 prior to the closure of Arms A and B, were enrolled into Arm D to receive emicizumab prophylaxis.

Efficacy was evaluated based on the ABR requiring treatment with coagulation factors (minimum of 24 weeks or date of discontinuation) among patients previously treated with episodic bypassing agents who were randomized to emicizumab prophylaxis (Arm A) compared with those receiving no prophylaxis (Arm B). The trial also evaluated the randomized comparison of Arms A and B for the efficacy of weekly emicizumab prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds, as well as patient-reported symptoms and physical functioning.

The study also evaluated the efficacy of weekly emicizumab prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agents in patients who had participated in the NIS prior to enrollment (Arms A and C, respectively). Only patients from the NIS were included in this comparison, because bleed and treatment data were collected with the same level of granularity in both periods.

The efficacy results of emicizumab prophylaxis compared with no prophylaxis in bleed rate for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds are shown in Table 1.

Table 1 ***Annualized Bleed Rate with Emicizumab Prophylaxis Arm versus No Prophylaxis Arm in Patients ≥ 12 Years of Age***

Endpoint	*Emicizumab Prophylaxis (N = 35)*	*No Prophylaxis (N = 18)*
Treated Bleeds		
ABR (95% CI) [a]	*2.9 (1.7, 5.0)*	*23.3 (12.3, 43.9)*
% reduction (95% CI) *p-value*	*87% (72.3%, 94.3%)* *< 0.0001*	
% patients with 0 bleeds (95% CI)	*62.9 (44.9, 78.5)*	*5.6 (0.1, 27.3)*
Median ABR (IQR)	*0 (0, 3.7)*	*18.8 (13.0, 35.1)*
All Bleeds		
ABR (95% CI) [a]	*5.5 (3.6, 8.6)*	*28.3 (16.8, 47.8)*
% reduction (95% CI) *p-value*	*80% (62.5%, 89.8%)* *< 0.0001*	
% patients with 0 bleeds (95% CI)	*37.1 (21.5, 55.1)*	*5.6 (0.1, 27.3)*
Treated Spontaneous Bleeds		
ABR (95% CI) [a]	*1.3 (0.7, 2.2)*	*16.8 (9.9, 28.3)*
% reduction (95% CI) *p-value*	*92% (84.6%, 96.3%)* *< 0.0001*	
% patients with 0 bleeds (95% CI)	*68.6 (50.7, 83.1)*	*11.1 (1.4, 34.7)*
Treated Joint Bleeds		
ABR (95% CI) [a]	*0.8 (0.3, 2.2)*	*6.7 (2.0, 22.4)*

Endpoint	*Emicizumab Prophylaxis (N = 35)*	*No Prophylaxis (N = 18)*
% reduction (95% CI) *p-value*	*89% (48%, 97.5%)* *0.0050*	
% patients with 0 bleeds (95% CI)	*85.7 (69.7, 95.2)*	*50.0 (26.0, 74.0)*
Treated Target Joint Bleeds		
ABR (95% CI) [a]	*0.1 (0.03, 0.6)*	*3.0 (1.0, 9.1)*
% reduction (95% CI) *p-value*	*95% (77.3%, 99.1%)* *0.0002*	
% patients with 0 bleeds (95% CI)	*94.3 (80.8, 99.3)*	*50.0 (26.0, 74.0)*

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

a. Based on negative binomial regression.

In the intra-patient analysis, emicizumab prophylaxis resulted in a statistically significant (p = 0.0003) reduction (79%) in bleed rate for treated bleeds compared with previous bypassing agent prophylaxis collected in the NIS prior to enrollment (Table 2).

Table 2 Intra-Patient Comparison of Annualized Bleed Rate with Emicizumab Prophylaxis versus Previous Bypassing Agent Prophylaxis

Endpoint	Emicizumab Prophylaxis (N = 24)	Previous Bypassing Agent Prophylaxis (N = 24)
Treated Bleeds		
ABR (95% CI) [a]	*3.3 (1.3, 8.1)*	*15.7 (11.1, 22.3)*
% reduction (95% CI) *p-value*	*79% (51.4%, 91.1%)* *0.0003*	
% patients with 0 bleeds (95% CI)	*70.8 (48.9, 87.4)*	*12.5 (2.7, 32.4)*
Median ABR (IQR)	*0 (0, 2.2)*	*12 (5.7, 24.2)*

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

a. Based on negative binomial regression.

The study evaluated patient-reported hemophilia-related symptoms (painful swellings and presence of joint pain) and physical functioning (pain with movement and difficulty walking far) using the Physical Health Score of the Haemophilia Adult Quality of Life Questionnaire (Haem-A-QoL) for patients aged ≥ 18 years. The weekly emicizumab prophylaxis arm (Arm A) showed an improvement compared with the no prophylaxis arm (Arm B) in the Haem-A-QoL Physical Health Subscale score at the Week 25 assessment (Table 3). The improvement in the Physical Health Score was further supported by the Total Score as measured by the Haem-A-QoL at Week 25.

Table 3 *Change in Haem-A-QoL Physical Health Score in Patients (≥ 18 Years of Age) with No Prophylaxis versus Emicizumab Prophylaxis at Week 25*

Haem-A-QoL Scores at week 25	*Emicizumab Prophylaxis (N = 25 [a])*	*No Prophylaxis (N = 14 [a])*
Physical Health Score (Score range 0 to 100) [b]		
Adjusted mean [c]	*32.6*	*54.2*
Difference in adjusted means (95% CI)	*21.6 (7.9, 35.2)*	
p-value	*0.0029*	

a. *Number of patients ≥ 18 years who completed the Haem-A-QoL questionnaire.*
b. *Lower scores are reflective of better functioning.*
c. *Adjusted for baseline, and baseline by treatment group interaction.*

The HAVEN 2 study (BH29992; NCT02795767) was a single-arm, multicenter, open-label, clinical study in pediatric males (age < 12 years, or 12–17 years who weigh < 40 kg) with hemophilia A with FVIII inhibitors. Patients received emicizumab prophylaxis at 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter.

The study evaluated the efficacy of weekly emicizumab prophylaxis, including the efficacy of weekly emicizumab prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agent treatment in patients who had participated in a NIS prior to enrollment (intra-patient analysis).

At the time of the interim analysis, efficacy was evaluated in 23 pediatric patients who were < 12 years old and had been receiving weekly emicizumab prophylaxis for at least 12 weeks, including 19 patients age 6 to < 12 years and 4 patients age 2 to < 6 years.

ABR and percent of patients with zero bleeds were calculated for 23 patients (Table 4). The median observation time for these patients was 38.1 weeks (12.7–41.6 weeks).

Table 4 *Annualized Bleed Rate with Emicizumab Prophylaxis in Pediatric Patients < 12 Years of Age (Interim Analysis)*

Endpoint	*ABR [a] (95% CI) N = 23*	*Median ABR (IQR) N = 23*	*% Zero Bleeds (95% CI) N = 23*
Treated Bleeds	*0.2 (0.1, 0.6)*	*0 (0, 0)*	*87 (66.4, 97.2)*
All Bleeds	*2.9 (1.8, 4.9)*	*1.5 (0, 4.5)*	*34.8 (16.4, 57.3)*
Treated Spontaneous Bleeds	*0.1 (0, 0.5)*	*0 (0, 0)*	*95.7 (78.1, 99.9)*
Treated Joint Bleeds	*0.1 (0, 0.5)*	*0 (0, 0)*	*95.7 (78.1, 99.9)*
Treated Target Joint Bleeds	*Not Estimable [b]*	*0 (0, 0)*	*100 (85.2, 100)*

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

a. *Based on negative binomial regression*
b. *No treated target joint bleeds reported*

In the intra-patient analysis, 13 pediatric patients who had participated in the NIS had an ABR of 17.2 (95% CI [12.4, 23.8]) on previous bypassing agent treatment (prophylactic treatment in 12 patients and on-demand treatment for one patient). Weekly emicizumab prophylaxis resulted in an ABR for treated bleeds of 0.2 (95% CI [0.1, 0.8]) based on negative binomial regression,

corresponding to a 99% reduction in bleed rate. On emicizumab prophylaxis, 11 patients (84.6%) had zero treated bleeds.

Safety

The following adverse reactions are based on pooled data from a randomized trial (HAVEN 1), single-arm trial (HAVEN 2), and a dose-finding trial, in which a total of 189 male patients with hemophilia A received at least one dose of emicizumab as routine prophylaxis. Ninety-four patients (50%) were adults (18 years and older), 38 (20%) were adolescents (12 years up to less than 18 years), 55 (29%) were children (2 years up to less than 12 years), and two (1%) were infants (1 month up to less than 2 years). Seven of the 189 patients (4%) included in the safety population were patients without FVIII inhibitors from the dose-finding trial. The median duration of exposure across the studies was 38 weeks (0.8 to 177.2 weeks).

The most frequently reported adverse reactions observed in ≥ 10% of patients treated with at least one dose of emicizumab were injection-site reactions (ISRs), headache, and arthralgia.

Four patients (2.1%) in the clinical trials receiving emicizumab prophylaxis withdrew from treatment due to adverse reactions, which were thrombotic microangiopathy (TMA), skin necrosis and superficial thrombophlebitis, and ISR.

Adverse reactions observed in patients who received emicizumab are shown in Table 5.

Table 5 Adverse Reactions Reported in ≥ 5% of Patients from Pooled Clinical Trials with Emicizumab

Body System	*Adverse Reaction*	*Number of Patients n (%) (N = 189)*
General Disorders and Administration Site Conditions	*Injection site reaction [a]*	*35 (19%)*
	Pyrexia	*13 (7%)*
Nervous System Disorders	*Headache*	*28 (15%)*
Gastrointestinal Disorders	*Diarrhea*	*12 (6%)*
Musculoskeletal and Connective Tissue Disorders	*Arthralgia*	*18 (10%)*
	Myalgia	*9 (5%)*

a. *Includes injection site bruising, injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticarial, and injection site warmth.*

Characterization of aPCC Treatment in Pooled Clinical Trials

There were 125 instances of aPCC treatment in 36 patients, of which 13 instances (10.4%) consisted of on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more; two of the 13 were associated with thrombotic events and three of the 13 were associated with TMA (Table 6). No TMA or thrombotic events were associated with the remaining instances of aPCC treatment.

Table 6 Characterization of aPCC Treatment in Pooled Clinical Trials

Duration of aPCC treatment	Average cumulative amount of aPCC over 24 hours (U/kg/24 hours)		
	< 50	50 – 100	> 100
< 24 hours	7	76	18
24 – 48 hours	0	6	3 [b]
> 48 hours	1	4	10 [a,a,a,b]

* *An instance of aPCC treatment is defined as all doses of aPCC received by a patient, for any reason, until there was a 36-hour treatment-free break.*

a. *Thrombotic microangiopathy*

b. *Thrombotic event*

Injection Site Reactions

In total, 35 patients (19%) reported ISRs. All ISRs observed in emicizumab clinical trials were reported as mild to moderate intensity and 88% resolved without treatment. The commonly reported ISR symptoms were injection site erythema (7.4%), injection site pruritus (5.3%), and injection site pain (5.3%).

1.2.2.4 Pharmacokinetics

Emicizumab exhibited linear PK in healthy adult male volunteers in Study ACE001JP. Following a single SC injection, the elimination $t_{1/2}$ (4–5 weeks) of emicizumab was similar to that of other human IgG antibodies. ~~Furthermore, comparison of PK profiles between Japanese and Caucasian healthy volunteers did not reveal racial differences.~~

…

Based on data from Study JP29574 in healthy Japanese subjects, comparison of PK profiles between Japanese and Caucasian healthy volunteers did not reveal racial differences. Also, similar PK profiles were observed following SC injections in abdomen, upper arm, and thigh, which suggests that emicizumab can be interchangeably injected in these three locations.

1.2.2.5 Anti-drug Antibodies

~~Up until April 2015, emicizumab has been administered to 48 healthy subjects and 18 patients with hemophilia A. A total of six subjects/patients tested positive for anti-drug antibodies (ADAs) on at least one occasion. The presence or absence of ADAs had no impact on the efficacy of emicizumab in patients with hemophilia A. Further information can be found in the emicizumab Investigator's Brochure.~~

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to emicizumab-kxwh in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of emicizumab was evaluated using an enzyme-linked immunosorbent assay (ELISA) or an electrochemiluminescence (ECL) assay. No patients tested positive for anti-emicizumab antibodies in HAVEN 1 and HAVEN 2 (n = 171). Four patients tested positive for anti-emicizumab antibodies in the dose-finding trial (n = 18). The anti-emicizumab antibody positive rate may be under-reported due to the limitation of the assay (US Prescribing Information).

1.2.2.6 Peri-Operative Management of Patients on Emicizumab

The safety and efficacy of emicizumab has not been specifically tested in patients undergoing procedures or surgeries. Limited data are available from pivotal clinical trials, where hemophilia A patients with inhibitors receiving emicizumab prophylaxis underwent procedures and surgeries, either with or without the additional use of bypassing agents. The use of bypassing agents was at the investigator's discretion.

Procedures/surgeries that were performed without peri-operative bypassing agent use and did not result in a bleed included skin biopsy, tooth extraction or restoration, esophagogastroduodenoscopy with biopsy, ultrasound fluid aspiration, and port or central line removal. Other procedures/surgeries which were performed with peri-operative bypassing agent use (preventive and/or treatment for bleeds) included central line catheter placement, tooth extractions and appendectomy. One hip replacement was performed with peri-operative bypassing agent (rFVIIa) and FVIII use (preventive and treatment for bleed) as well as tranexamic acid.

No emicizumab dose adjustments are recommended for patients undergoing procedures or surgeries. Thorough documentation of surgeries will be requested.

The available data are insufficient to provide specific dosing guidance for the use of bypassing agents or FVIII in peri-operative settings. If bypassing agents or FVIII are required in the peri-operative period, please refer to the dosing guidance for those concomitant medications in Section 4.4 and in the emicizumab Investigator's Brochure.

~~Based on the Phase I/II data described above, a clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) has been developed for emicizumab. Refer to the emicizumab Investigator's Brochure for details on the preclinical and clinical studies.~~

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

…

Emicizumab has been well tolerated in patients in the Phase I/II studies (cut-off date 15th February 2016). The majority of adverse events have been mild in intensity, with the most common being ~~injection site reactions~~ *ISRs*. The majority of the adverse events have not been considered to be related to emicizumab. In these studies, no thromboembolic or systemic hypersensitivity adverse events have been observed. However, as of *April 2017* ~~October 2016~~, ~~two~~ *three* cases of TMA, and ~~two~~ *three* thromboembolic events *in two patients,* have been observed in the ongoing Phase III Study BH29884 in patients who received

emicizumab as well as bypassing agents for the treatment of breakthrough bleeds. ~~Three~~ *Four* of these patients have fully recovered and the *fifth patient died (death due to serious adverse event of rectal haemorrhage unrelated to emicizumab, with the TMA related to emicizumab and aPCC)* ~~fourth patient's condition has improved~~ (see Sections 5.1.1.2 and 5.1.1.3).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety and tolerability of emicizumab in patients with *congenital* hemophilia A who have *persistent* inhibitors against FVIII at enrollment. Specific objectives and corresponding endpoints for the study are outlined below (Table 7).

Table 7 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Objective:	
• To evaluate the overall safety and tolerability of prophylactic administration of emicizumab	• Incidence and severity of *all* adverse events, including thromboembolic *events, microangiopathic hemolytic anemia or* TMA *(e.g. hemolytic uremic syndrome),* systemic hypersensitivity, anaphylaxis, and anaphylactoid events • Changes in physical examination findings, vital signs, and laboratory parameters

3.1 DESCRIPTION OF THE STUDY

This single-arm, multicenter, open label Phase IIIb clinical study will enroll patients aged 12 years or older with *congenital* hemophilia A who have persistent inhibitors against FVIII at enrollment. Approximately 200 patients with inhibitors will be enrolled globally. Patients will receive prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period (Figure 1).

…

The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A who have persistent inhibitors against FVIII at enrollment. In order to achieve this objective, all adverse events, including adverse events of special interest, will be captured on an ongoing basis, as they occur during the study. Physical examinations, vital signs, and laboratory values will be assessed as per the Schedule of Activities (Appendix 1
Schedule of Activities
).

…

The final analysis will be conducted when all patients have completed 2 years of treatment or have withdrawn, whichever occurs sooner. Patients, or their legally authorized representative, will be asked to report bleed information *on an electronic patient-reported outcome (ePRO) device where possible*, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. HRQoL will be assessed

and the EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) will be completed prior to the first emicizumab administration *(Week 1)*, at the *Month* 3, 6, 12, and 18 ~~month~~ assessments, and at study completion as outlined in the Schedule of Activities (Appendix 1

Schedule of Activities

). Additional secondary endpoints include assessing patient preference for the emicizumab regimen compared with the previous regimen using a questionnaire (EmiPref).

…

For the assessment of anti-FVIII antibodies, functional assays for FVIII inhibitors that utilize a clotting readout (classic Bethesda or Nijmegen assay) cannot be used for patients on emicizumab therapy as emicizumab drives clotting even in the presence of FVIII inhibitors, causing a false-negative test result. After the first dose, local measurement of FVIII inhibitors, if indicated, requires use of an enzyme linked immunosorbent assay- (ELISA-) based test or a chromogenic Bethesda assay. At the discretion of the local investigator, any additional urgent request to assess FVIII inhibitors will need to be sent to a central laboratory (see Appendix 2

Schedule of Biomarker Samples

for additional information).

~~An independent Data Monitoring Committee (iDMC) composed of, at minimum, hemostasis/thrombosis experts and a statistician will be in place throughout the duration of the study and will monitor the study data at pre specified intervals and ad hoc as needed throughout the study.~~

The use of aPCC is to be avoided throughout the study. If bypassing agents are needed to treat breakthrough bleeds or additional treatment to prevent or treat bleeding during surgeries, recombinant activated human Factor VII (rFVIIa) should be used at the lowest dose expected to achieve hemostasis. If rVIIa is not available or not an option for medical reasons, activated prothrombin complex concentrate (aPCC, including Factor eight inhibitor bypassing activity [FEIBA]) may be used. If aPCC is used, 50 units/kg of aPCC should be administered as an initial dose and it is critical that the dose administered does not exceed the recommended dose (see the local prescribing information for the marketed bypassing agent in question).

Drugs intended to control breakthrough bleeds (e.g. rFVII, FVIII, aPCC) or bleeds during surgeries should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase the patient's coagulation potential, the doses required to achieve hemostasis may be lower than doses used prior to starting emicizumab. Investigators shall discuss at the start of the study with patients recommended doses of any additional coagulation factors used, following the guidance below.

The use of aPCC for breakthrough bleed treatment for patients on emicizumab should be avoided if possible, and rFVIIa should be the first option used to treat, starting with no more than 90 µg/kg as an initial dose. If aPCC needs to be used, no more than 50 IU/kg should be administered as an initial dose and doses of > 100 U/kg/24 hours or more should be avoided, as cases of TMA and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours aPCC was

administered for 24 hours or more. Investigators should provide or remind patients of the exact dose and schedule of bypassing agents or FVIII required to treat any bleed.

When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information *on an ePRO device where possible*, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed (e.g., other than emicizumab in case of breakthrough bleeds). The reason for the use of rFVIIa will be documented (e.g., bleeding, preventative dose before activity). Thorough documentation of the treatments for bleeds *and/or surgeries* will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. Local and central laboratory assessments are required to monitor the risk for thromboembolic events or *microangiopathic hemolytic anemia or* TMA, as per the Schedule of Activities (Appendix 1
Schedule of Activities
), if bypassing agents are used to treat a breakthrough bleed.

…

An independent Data Monitoring Committee (iDMC) will be responsible for monitoring safety the duration of the study.

3.2 END OF STUDY AND LENGTH OF STUDY

The approximate length of the entire study from the first patient enrolled to the last patient, last visit (LPLV; see below) is approximately 3 years. For each individual patient, the study is expected to last approximately 2 years (patients will receive 3 mg/kg/week emicizumab for the first 4 weeks followed by 1.5 mg/kg/week emicizumab for the remainder of the 2-year treatment period). *Patients who discontinue emicizumab prior to the completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first.*

…

Completed the ~~24 week~~ Safety Follow-up Visit 24 weeks after discontinuing emicizumab

3.3 RATIONALE FOR STUDY DESIGN

The primary *objective* ~~endpoint~~ of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A *who have persistent inhibitors against FVIII*. This study is being conducted to build on the safety data that have been obtained as part of the clinical program. The results from this study will be used to substantiate the safety database and provide long-term additional data in patients with hemophilia A who have inhibitors against FVIII. The specific focus will be to characterize any thromboembolic events, *microangiopathic hemolytic anemia or* TMA, ~~and~~ *systemic* hypersensitivity reactions*, anaphylaxis and anaphylactoid events* that may occur in patients with hemophilia A treated with emicizumab.

3.3.1 Rationale for Emicizumab Dose and Schedule

…

The safety results from studies ACE001JP/ACE002JP and BH29884 have ~~showed~~ *shown* that emicizumab has been well tolerated in patients with hemophilia A. The maximum clinical dose of 3 mg/kg weekly is associated with a 10.3-fold and 11.2-fold safety margin based on C_{max} and area under the curve during the dosage interval (AUC_T) results, respectively. No clear differences in the plasma concentrations of emicizumab have been observed between adolescent and adult patients.

…

In study BH29884, the ABR was 2.9 events (95% CI, 1.7 to 5.0) among participants who were randomly assigned to emicizumab prophylaxis (Group A, 35 participants) versus 23.3 events (95% CI, 12.3 to 43.9) among those assigned to no prophylaxis (Group B, 18 participants), representing a significant difference of 87% in favor of emicizumab prophylaxis (p<0.001). A total of 22 participants in Group A (63%) had zero bleeding events, as compared with 1 participant (6%) in Group B. Among 24 participants in Group C who had participated in a NIS, emicizumab prophylaxis resulted in a bleeding rate that was significantly lower by 79% than the rate with previous bypassing-agent prophylaxis (p<0.001) (Oldenburg et al. 2017).

3.3.2 Rationale for Patient Population

Patients with congenital hemophilia A *who have persistent* ~~and documented~~ inhibitors against FVIII at enrollment will comprise the primary population for this Phase IIIb study investigating the safety, *tolerability,* efficacy, immunogenicity, and PK of prophylactic administration of emicizumab.

…

Based on current treatment algorithms for patients with hemophilia A with inhibitors (Kempton and White II 2009; Srivastava et al. 2013), it is anticipated that the majority of adults and adolescents treated with emicizumab will have previously undergone ITI without success or are not candidates for ITI. As clinical safety data relating to the concomitant use of prophylactic emicizumab during ITI are not available at this time, patients currently receiving ITI will not be eligible for this study. *Patients receiving ITI therapy will be eligible following the completion of a 72-hour washout period prior to the first emicizumab administration.* Owing to the fact that the presence or amount of FVIII inhibitors in their plasma does not impact the efficacy of emicizumab, patients' inhibitor titers at the time of study entry will not influence their study eligibility.

3.3.3 Rationale for Control Group

This study involves the use of a single-arm study design and therefore a control group will not be used. The primary endpoint of this study is to evaluate the overall safety and

tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A *who have persistent inhibitors against FVIII*. As hemophilia A is a rare disease (Acharya 2013) and the study is designed to investigate the broad safety profile of emicizumab, approximately 200 patients will be enrolled. Given the size of the patient population, a single-arm study design without a control group is considered an appropriate method to capture the safety data that will be observed following the use of emicizumab. This type of study design has been used extensively in previous clinical studies involving patients with rare diseases (Bell and Tudur Smith 2014).

3.3.4 Rationale for Biomarker Assessments

The identity of effective PD, safety, and bone and joint biomarkers has not been fully elucidated and further testing is required to determine which assays and technical conditions are most suitable for use with emicizumab treatment. Plasma and serum samples will be collected for PD, safety, and bone and joint biomarker assessments at specific clinic visits in order to obtain evidence of the biologic activity of emicizumab in patients ~~and to support the selection of a recommended dose~~ (see Appendix 2
Schedule of Biomarker Samples
).

The PD biomarkers include, but are not limited to, coagulation assays such as aPTT and FVIII activity assays. The results of the Phase I/II study have ~~showed~~ *shown* that a dose-response relationship was apparent between aPTT and emicizumab concentration (for more information, see the Investigator's Brochure). The aPTT assay will be run in a modified form to ensure that the assay range covers all levels of emicizumab exposure. In addition, clot waveform analysis (CWA) may be run as an exploratory PD coagulation assay.

…

Residual blood and/or, plasma, and serum from collected *biomarker* samples may be stored for *up to* 5 years after the *final Clinical Study Report has been completed* ~~development of the final CSR~~ and may be used for additional exploratory emicizumab-related research, to guide development of potential *in vitro* diagnostic assay(s) related to emicizumab plasma concentration, FVIII inhibitor titre and/or coagulation activity. ~~, or for the potential evaluation of germline genomic variation, including, but not limited to, genetic loci coding for FIX and FX.~~

3.3.5 Rationale for Pharmacokinetic Sample Collection Schedule

PK samples will be collected throughout the *2-year* study *period* in order to further investigate the PK of emicizumab ~~over the 2-year study period~~ (see the Schedule of Activities; Appendix 1
Schedule of Activities
).

3.3.6 Rationale for Immunogenicity Sample Collection

Immunogenicity will be monitored by investigating the incidence and clinical significance of antibodies to emicizumab at specified time points (see the Schedule of Activities; Appendix 1

Schedule of Activities

). The emergence of *anti-drug antibodies (*ADAs*)* has been previously observed in clinical studies involving monoclonal antibodies of the IgG4 class (Lundkvist et al. 2012; Vennegoor et al. 2013).

3.3.7 Rationale for Disease Response–based Endpoints

The secondary objective of this study is to evaluate the efficacy of prophylactic administration of emicizumab. This objective will be achieved by investigating the number of bleeds over time under emicizumab treatment, ~~and~~ *assessing* HRQoL, *and* ~~assessments~~ *evaluating health status according to EQ-5D-5L and patient preference for the emicizumab regimen compared with the previous regimen*. As mentioned in Section 3.1, this analysis will occur when all patients have completed 2 years of treatment or have withdrawn, whichever occurs sooner. In order to obtain comprehensive data on each bleed, patients will be asked to report bleed information *on an ePRO device where possible*, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed.

3.3.8 Rationale for Primary Endpoint Selection

As stated in Section 3.1, the primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab. In order to achieve this objective, *the incidence and severity of* all adverse events, including adverse events of special interest, will be captured on an ongoing basis, as they occur during the study. Physical examinations, vital signs, and laboratory values will be assessed as per the Schedule of Activities (Appendix 1

Schedule of Activities

).

3.3.9 Rationale for Interim Analyses

Owing to the long-term nature of this study, interim analyses will be conducted in order to obtain accurate information on the safety, efficacy, immunogenicity, and PK of prophylactic emicizumab at specific points throughout the study. The first interim analysis will be performed once *approximately* 100 patients have received treatment with emicizumab for at least 24 weeks. A second *interim* analysis will be performed when *approximately* 100 patients have received treatment with emicizumab for at least 52 weeks. ~~Owing to the long-term nature of this study, the interim analyses will be conducted in order to obtain accurate information on the safety, efficacy, immunogenicity, and PK of prophylactic emicizumab at specific points throughout~~

~~the study.~~ The data from these analyses will subsequently be presented to the iDMC in order to enable them to effectively monitor the study.

3.3.10 Rationale for Patient-reported Outcome (PRO) Assessments

During the study, electronic capture of HRQoL, health status (EQ-5D-5L~~), and preference data (EmiPref)~~ will be obtained using an ~~electronic patient reported outcome (~~ePRO~~)~~ device. *Patient preference data (EmiPref) will be collected on paper forms.*

…

The goal of measuring HRQoL is to quantify any treatment benefits from the patient perspective. Previous studies that have used the *Hemophilia Quality of Life questionnaire (*Haemo-QoL), a measure of HRQoL parameters affected by hemophilia in children and adolescents, have reported improvements in physical health, feelings, view of self, family relations, friend relations, perceived support, relation with others, participation in sports, dealing with hemophilia, views of treatment, views of the future, and relationships (Santagostino et al. 2014). Improvements in physical health, feelings, view of self, and participation in work have also been observed on the adult version of the measure, the Haem-A-QoL (Stasyshyn et al. 2014).

…

The EQ-5D-5L is a standardized, preference-based measure of generic health status that is applicable to a wide range of health conditions and treatments. It measures five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain */*~~and~~ discomfort, and anxiety */*~~ and~~ depression. The EQ-5D-5L also assesses current overall health. The goal of measuring EQ-5D-5L is to assess the impact of treatment with emicizumab over time on overall health and the different health dimensions. Data from the EQ-5D-5L can also be used to inform pharmacoeconomic evaluations.

4.1 PATIENTS

This global study will enroll approximately 200 patients with congenital hemophilia A *who have* ~~and documented~~ *persistent* inhibitors against FVIII at enrollment. The patients are expected to be enrolled at approximately 85 sites globally.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

…

2. *As per the investigator's judgement, a w*~~W~~illingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the PRO questionnaires and bleed diaries through the use of an electronic device *or paper*~~, as per the investigator's judgment~~

…

~~4. Body weight ≥ 40 kg at the time of screening~~

4.1.2 Exclusion Criteria

…

13. Positive serum pregnancy test result within 7 days prior to initiation of *emicizumab* ~~study drug~~ (females only)

4.3.1.1 Emicizumab

Emicizumab drug product will be supplied by the Sponsor as a sterile colourless to pale yellow liquid for SC injection in *a* single-dose 3-mL glass vial~~s~~ *containing 1 mL of emicizumab*. The recommended storage condition for emicizumab drug product is between 2°C and 8°C (36°F to 46°F), and protected from light. Vials should not be frozen or shaken.

Each single-use vial contains ~~approximately~~ 150 mg/mL emicizumab in a histidine-aspartic acid buffered solution (approximately pH 6.0), which contains arginine and Poloxamer 188. For information on the formulation and handling of emicizumab, see the Investigator's Brochure.

4.3.2.1 Emicizumab

~~As discussed in Section 3.3.1,~~ *E*~~e~~micizumab will be administered at a dose of 3 mg/kg/week subcutaneously for 4 weeks when initiating treatment, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period. There will be an option to increase the dose to 3 mg/kg/week in cases of insufficient control of bleeds on the 1.5 mg/kg/week emicizumab dose. If the investigator believes that a specific patient warrants dose up-titration following the occurrence of, for example, at least two spontaneous bleeds, significant bleeds, or a traumatic bleed out of proportion to the degree of injury, they must discuss the case with the Medical Monitor for consideration and potential approval.

Recommended injection sites include the front of middle of the patient's thighs, or the lower part of the patient's abdomen below the navel. Avoid injecting within a 2" radius around the navel. If a caregiver is giving the injection, the outer area of the upper arms may also be used. For additional information re the administration of emicizumab, refer to the Instructions for Use (IFU) document.

…

Study site HCPs will be initially trained on how to properly prepare *emicizumab* ~~the study medication~~ and administer the correct calculated dose subcutaneously as described in the ~~instructions for use (~~IFU~~)~~ document.

…

In order to minimize the number of injections for patients in certain weight categories, the administration of a single injection of up to 2 mL drug product solution may be permitted~~,~~

~~pending approval from the Sponsor, individual countries, and participating sites~~. This administration will require the combination of emicizumab drug product solution from *up to two 1-mL vials* ~~more than one vial~~ (i.e., vial pooling) *aseptically* into a single syringe, using a new transfer needle for each vial. ~~Upon Sponsor approval, T~~the detailed procedure for vial pooling will be described in the IFU document. *If the patient's dose is > 2 mL, a second injection will be required.*

Medication administration errors during training will be documented in the electronic Case Report Form (eCRF). If necessary, patients or their HCP may choose to continue administration of *emicizumab* ~~the study drug~~ within the clinic. Compliance in the home setting is to be monitored at each site by reviewing reported hemophilia medication use and recording collected used and unused vials.

If the patient forgets or cannot administer *emicizumab* ~~the study medication~~ on the scheduled dosing day, *emicizumab* ~~the study medication~~ should be administered *as soon as possible before the day of the next scheduled dose, and then the patient should resume the usual weekly dosing schedule. Do not double doses to make up for a missed dose. All four loading doses of 3 mg/kg should be taken, even if this is done over a period or more than four weeks.* ~~as soon as possible within a window of 3 days from the scheduled dosing date. If more than 3 days has passed, the missed dose should be skipped, and the patient should take their next dose at the next scheduled time. If this scenario occurs, study medication dosing should be resumed in accordance with the original dosing schedule.~~

Any overdose or incorrect administration of *emicizumab* ~~the study drug~~ should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of *emicizumab* ~~the study drug~~ should be recorded on the Adverse Event eCRF. Section 5.3.5.12 summarizes available safety data related to overdosing of emicizumab.

4.3.3 Investigational Medicinal Product Accountability

…

Used and unused ~~IMP~~ *emicizumab* vials will be returned by the patients to the study site and appropriately accounted for. Used *emicizumab* vials will then be disposed of at the study site according to institutional standard operating procedures.

4.3.4 Continued Access to Emicizumab

The Sponsor will offer continued access to ~~the IMP (~~emicizumab~~)~~ to study patients who have shown a demonstrable benefit from emicizumab treatment during this study (as measured by sustained clinical response and/or improvement in clinical symptoms).

Continued Access to *emicizumab* ~~the IMP~~ will be provided free of charge, through either an Open Label Extension trial, a Post-Trial Access Program, local Patient Support Programs, or other local access mechanisms according to each country regulation, as described per Global procedural document: Continued Access to Roche Investigational Medicinal Product

(SOP-0112895), in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, and the Declaration of Helsinki in its 2013 issue.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to initiation of *emicizumab* ~~study drug~~ to the Study Completion/Early Termination Visit *(or to the Safety Follow-up Visit, if applicable)*. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Any hemostatic medications (e.g. bypassing agents) and other medications used to treat or prevent bleeds in the 6-month period prior to starting emicizumab treatment will also be collected (see Section 4.5.5).

4.4.1 Permitted Therapy

Concomitant use of the following drugs and therapies will be permitted:

- *Drugs to treat existing conditions at time of study entry, as long as allowed based on eligibility criteria (Section 4.1.1 and Section 4.1.2).*
- *During the study, a*~~A~~ny medication to treat or prevent any medical condition as deemed necessary by the treating physician. *If prohibited treatment (see Section 4.4.2) is prescribed or considered medically necessary, the Medical Monitor should be consulted to discuss any changes in the benefit-risk profile and determine whether the patient should continue on the study.*
- Any over-the-counter medication used to treat the symptoms of hemophilia
- Supplementary vitamins and minerals.
- *Drugs and therapies to treat adverse events and the use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to enter the bloodstream and result in systemic exposure*

Concomitant use of the following hemostatic treatments will be permitted:

- *Drugs intended to control breakthrough bleeds (e.g. rFVII, FVIII, aPCC) or bleeds during surgeries should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase the patient's coagulation potential, the doses required to achieve hemostasis may be lower than doses used prior to starting emicizumab. At the start of the study, Investigators shall discuss with patients the recommended doses of any additional coagulation factors used, given the guidance below.*
- *The use of aPCC for breakthrough bleed treatment for patients on emicizumab should be avoided if possible, and rFVIIa should be the first option used to treat, starting with no more than 90 µg/kg as an initial dose. If aPCC needs to be used, no more than 50 IU/kg should be administered as an initial dose and doses of > 100 U/kg/24 hours or more should be avoided, as cases of TMA and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours aPCC was administered for 24 hours or more. Investigators should provide or remind patients of the exact dose and schedule of bypassing agents or FVIII required to treat any bleed.*

- ~~Drugs intended to control breakthrough bleeds (e.g. rFVIIa) should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase the patients' coagulation potential, the doses required to achieve hemostasis may be lower than the FVIII or bypassing agent doses used prior to starting the study:~~
  - ~~Caution should be used for patients who are taking rFVIIa (e.g., consideration should be given to using no more than 90 µg/kg rFVIIa as an initial dose)~~
  - *Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab*
- ~~aPCC should only be administered if it is the only available treatment for breakthrough bleeds. If used, the lowest dose expected to achieve hemostasis should be prescribed with no more than 50 units/kg of aPCC to be administered as an initial dose andthe recommended dose.~~
- **Other bypassing agents:** *other bypassing agents* (e.g., Byclot®) should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (e.g., no more than 60 mg/kg of Byclot®). For patients receiving Byclot® prior to study entry, a washout period of 72 hours prior to the first emicizumab dose is required
- The exact dose and schedule of FVIII or bypassing agents should be discussed with the patient at study entry and throughout the study. Repeated dosing of *FVIII,* rFVIIa, aPCC, or other bypassing agents should be performed only under medical supervision and consideration should be given to verifying the bleeds prior to repeated dosing. For rFVIIa, aPCC, and other bypassing agents, laboratory monitoring by additional local and central laboratory assessments should be performed as per the Schedule of Activities (see *Section 4.5.6.9*~~Appendix 1~~
  Schedule of Activities
-).
- ~~Drugs and therapies to treat adverse events and the use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to enter the bloodstream and result in systemic exposure~~
- ~~Drugs to treat an existing medical condition that is ongoing at study entry and do not violate the eligibility criteria (e.g., anti retroviral therapy for HIV infections).~~
- ~~Caution should be taken if anti fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab~~

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study:

…

- Use of aPCC for short-term prophylaxis
  - Use of aPCC for any reason should be avoided *if possible* during the study but use of aPCC to treat breakthrough bleeds is permitted (as described *in Section 4.4.1*~~above~~) if rFVIIa is not available or not an option for medical reasons (see Section 3.1).

- Use of *ITI therapy (*~~a concomitant~~ prophylactic regimen*s* with FVIII *and/*or bypassing agents*)*:
  - However, short-term prophylaxis around the time of surgery is permitted as deemed needed by the investigator *(see Section 4.4.1). FEIBA can not be used prophylactically.*
- *Use of anti-fibrinolytics in conjunction with aPCC or Byclot®*

4.5.1 Informed Consent Forms and Screening Log

…

The enrollment form will be completed after informed consent and/or assent is obtained. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes hemophilia-related history, clinically significant diseases, procedures *(including prior surgeries)*, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior ITI, anaphylaxis, or known thrombophilia. It should also include all medication taken in the 4 weeks prior to screening (including prescription drugs, over-the-counter drugs, and herbal/homeopathic remedies and therapies).

4.5.3 Physical Examinations

A complete physical examination be performed *during* ~~at~~ Screening and should include, but not necessarily be limited to, an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF. ~~Subsequently, a targeted (i.e., musculoskeletal, dermatological) examination should be conducted as noted in the schedule of activities (Appendix 1~~
Schedule of Activities

~~) or as clinically indicated.~~ *Targeted physical examinations (i.e., joints for bleeds and evidence of arthropathy; skin for bruises, hematomas and ISRs; other organ systems as clinically indicated) should be conducted at subsequent visits or as clinically indicated.* New or worsened clinically significant abnormalities from screening should be recorded as adverse events, if appropriate, on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurement of *body temperature (oral, rectal, axillary, or tympanic),* heart and respiratory rates, ~~temperature (oral, rectal, axillary, or tympanic), systolic and diastolic~~ blood pressure~~s, height,~~ and weight, and should be *measured* ~~recorded~~. *On treatment days, measurement should occur prior to emicizumab administration.* ~~before study drug administration.~~ *Height will be only measured at selected visits.* ~~Frequency of~~ *Additional* vital sign assessments ~~should follow the Schedule of Activities (Appendix 1~~
Schedule of Activities

~~) but~~ may also be taken anytime as unscheduled assessments as judged by the investigator. In addition, vital signs may be taken to help monitor for hypersensitivity reactions during or after injections at the investigator's discretion, although these data should not be entered into the eCRF.

4.5.5 Concomitant Medications

The definition of concomitant medications, as well as permitted and prohibited medications is described in Section 4.4. Concomitant medications used by a patient from 4 weeks prior to initiation of emicizumab to the Study Completion/Early Termination Visit (or the Safety Follow-up Visit, if applicable) should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Any hemostatic medications (e.g. bypassing agents) and other medications used to treat or prevent bleeds in the 6-month period prior to starting emicizumab treatment will also be collected. Treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), will be collected in the bleed records.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Central laboratory assessments will be performed as indicated *(see Table 9)* ~~in the Schedule of Activities (Appendix~~ 1
Schedule of Activities

~~)~~. *Unless otherwise specified,* additional analysis may be performed ~~as per the investigator's discretion~~ at a local laboratory*, as per the investigator's discretion. Any additional laboratory results which are required as part of the patient's safety assessment should be recorded in the unscheduled visit eCRFs. Central labs are part of the non-eCRF data which will be sent to the Sponsor directly by the central lab vendor.*

On treatment days, ~~the days of study drug administration,~~ blood collection should occur within 2 hours prior to emicizumab administration unless otherwise specified. ~~laboratory samples should be drawn before the administration of the study drug.~~

Table 9 Central vs Local Laboratory Assessments

Sample	*Laboratory*
Hematology and blood chemistry	*Central*

Sample	*Laboratory*
Pregnancy tests	*Local*
HIV and hepatitis serology	*Local*
Anti-FVIII antibodies	*Central*
Anti-emicizumab antibodies	*Central*
Pharmacokinetic samples	*Central*
Safety biomarkers	*Central*
Safety coagulation system biomarkers	*Central*
PD biomarkers	*Central*
Bone and joint biomarkers	*Central*
Extra testing with use of bypass agents	*Central*

4.5.6.1 *Hematology and Blood Chemistry*

Hematology and blood chemistry tests include: Samples for the following laboratory tests will be sent to the central laboratory for analysis:

…

- Serum chemistry (sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, *lactate dehydrogenase* (LDH), alkaline phosphatase, and creatine phosphokinase)

Laboratory assessments completed during Screening do not have to be repeated at Week 1, if the period between Screening and Week 1 is ≤ 5 days and there has been no change in the patient's health status as assessed by the investigator.
Samples will be sent to the central laboratory for analysis.

4.5.6.2 *Pregnancy Tests*

Female patients of childbearing potential (including those who have had a tubal ligation) will be required to have a negative serum pregnancy test result during Screening, and again within 7 days prior to the first dose of emicizumab. Urine pregnancy tests will be performed throughout the study treatment period. Pregnancy testing will be conducted at the local laboratory.

4.5.6.3 *HIV and Hepatitis Serology*

The specific tests utilized for hepatitis and HIV testing are per local standard of care. As this patient population is at high risk for HIV, hepatitis A, B and C, sites should consider testing for these. While the specific serological tests used is at the discretion of the Investigator, this is with the understanding that the status of that participants' hepatitis or HIV is confidently known at time at enrollment. HIV and hepatitis serology tests will be conducted at the local laboratory.

4.5.6.4 *Anti-FVIII Antibodies*

For the assessment of anti-FVIII antibodies (inhibitors), functional assays that utilize a clotting readout (classic Bethesda or Nijmegen assay) cannot be used for patients on emicizumab therapy as emicizumab drives clotting even in the presence of FVIII inhibitors, causing a false-negative test result (see Section 5.1.3). After the first dose, local measurement of FVIII inhibitors, if indicated, requires use of an ELISA-based test or a chromogenic Bethesda assay.

At the discretion of the local investigator, any additional urgent requests to assess FVIII inhibitors will need to be sent to the central laboratory (see Appendix 2
Schedule of Biomarker Samples

for additional information).

Plasma samples for anti-FVIII antibodies will be analysed at the central laboratory.

4.5.6.5 *Anti-emicizumab Antibodies*

Plasma samples are required for immunogenicity assessments to detect anti-emicizumab antibodies. Additional samples to detect anti-emicizumab antibodies may also be drawn at the time of hypersensitivity events or following suspected loss of efficacy. Samples will be analysed at the central laboratory.

4.5.6.6 *Pharmacokinetics*

Plasma samples are required for PK assessments. On days where PK samples are to be collected, the emicizumab injection will be performed in the clinical unit. One single pre-dose sample is required on the applicable visits. Samples will be analysed by the central laboratory.

4.5.6.7 *Biomarkers*

4.5.6.7.1 *Safety Biomarkers*

Plasma samples for safety biomarker assessment must be citrate plasma. Tests may include, but are not limited to, D-dimer. Samples will be analysed by the central laboratory. See Appendix 2.

4.5.6.7.2 *Safety Coagulation System Biomarkers*

Plasma samples for safety coagulation system biomarker assessment must be citrate plasma. Tests include FVIII:Ag, FIX:Ag and FX:Ag. Samples will be analysed by the central laboratory. See Appendix 2.

4.5.6.7.3 *PD Biomarkers*

Plasma samples for PD biomarker assessment must be citrate plasma. Tests will include, but are not limited to FVIII activity and modified aPTT (one stage). Additional plasma samples will be collected for future exploratory research, which may include tests such as CWA and others (see Appendix 2). Samples will be analysed by the central laboratory.

4.5.6.7.4 Bone and Joint Biomarkers

Serum and plasma ethylenediaminetetraacetic acid (EDTA) samples for bone and joint biomarkers must be collected after fasting (no food or drink other than water for at least 8 hours prior to the blood draw). Ideally these samples should be collected in the morning (before noon), in order to control for diurnal variation. Please consult the Central Laboratory Services Manual for details. The selection of exploratory bone and joint biomarkers to be tested will build on findings from biomarker analyses in other emicizumab trials and may include C-terminal telopeptide of collagen 1 (CTX-1), osteoprotegerin (OPG), procollagen type 1 amino-terminal propeptide (P1NP), and soluble receptor activator of nuclear factor kappa-B ligand (RANK-L) (see Appendix 2
Schedule of Biomarker Samples
). Samples will be analysed by the central laboratory.

~~The following additional study specific plasma samples will be collected and sent to a central laboratory for analysis:~~

- ~~Plasma samples for PK analysis~~
- ~~Plasma samples for immunogenicity assessments to detect anti emicizumab antibodies~~
- ~~Plasma samples for safety biomarker assessments (D-dimer)~~
- ~~Plasma samples for safety coagulation system biomarker assessments (FVIII:Ag, FIX:Ag, and FX:Ag)~~

The following biomarker samples will be collected and sent to a central laboratory for analysis (see Appendix 2
Schedule of Biomarker Samples
):

- ~~Plasma samples for PD biomarker assessments (aPTT and FVIII activity)~~
- ~~Plasma and serum samples for bone and joint biomarker assessments.~~

4.5.6.8 Extra Testing with Use of Bypass Agents

In the event of a breakthrough bleed that is treated with bypassing agents, it is recommended that the following laboratory tests will be performed within 24–48 hours of initial bypassing agent use (these tests will be conducted so that the investigator can monitor the patient for potential thromboembolic events and *microangiopathic hemolytic anemia or* TMA). *These tests include:* ~~These tests should ideally be conducted in the central laboratory:~~

…

- ~~Lactate dehydrogenase (~~LDH~~)~~

…

Ideally, samples for these tests should be analysed at the central laboratory. Exceptionally in urgent situations where results are required quickly, local laboratory testing can be used, with results recorded in the eCRF.

For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours until 24–48 hours after the last dose of bypassing agents is administered to treat a specific bleed. ~~If applicable,~~ *All* laboratory results *which are required as part of the patient's safety assessment* should be recorded in the unscheduled visit eCRFs.

4.5.6.9 Sampling Procedures and Sample Storage, Shipment and Destruction

For sampling procedures, storage conditions, and shipment instructions, see the *Central* Laboratory *Services* Manual.

~~HIV and hepatitis serology testing will be done in the local laboratory at screening. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening done in the local laboratory and again within 7 days prior to the first dose of emicizumab, if applicable. Urine pregnancy tests will be performed at every clinic visit at the local laboratory, except for Weeks 2 and 3.~~

…

- Plasma or serum samples, as applicable, collected for ~~anti-emicizumab antibody,~~ anti-FVIII antibody, PD biomarker, safety biomarker, safety coagulation system biomarker, ~~and~~ bone and joint biomarker assessments *and other future exploratory research* will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.5.7 Bleed Assessments

Patients will be trained on how to record their bleeds and hemophilia medication use using an ePRO device where possible. When bleeds occur, patients will need to record the site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. ~~Patients will need to record when they have bleeds or hemophilia medication use, including emicizumab, or at least every week.~~ *At least once a week, patients will need to record any hemophilia medication use (including emicizumab) and information regarding any bleeding events*. Investigator review of patient-reported bleed/medication records with the patient/caregiver will occur for completeness and accuracy throughout the study.

4.5.8 Surgical Events

Thorough documentation on surgical events will be requested, including type of surgery or procedures, treatments, outcomes, etc.

4.5.9 Patient-Reported Outcomes

…

The PRO questionnaire data will be collected to document the treatment benefit of emicizumab. The questionnaires, translated into the local language as required, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient/caregiver receives any information on disease status,

prior to the performance of non-PRO assessments, and prior to the administration of *emicizumab* ~~study treatment~~, unless otherwise specified.

4.5.9.1 HRQoL Assessments

The Haem-A-QoL *(version AU 3.0; UK English)* and the Hemophilia Quality of Life Short Form (Haemo-QoL-SF) *(version AU 2.0; UK English)* will be *completed electronically and* used to measure HRQoL in adults and adolescents, respectively ~~(see Appendix 33~~
EmiPref Patient Preference Questionnaire

~~and Appendix 44~~
Clinical Criteria for Diagnosing Anaphylaxis

~~)~~. *Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.*

4.5.9.2 Health Status Assessments (EQ-5D-5L)

The EQ-5D-5L *(version 2; UK English)* ~~(see Appendix 55 WHO~~ Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events

~~)~~ is a generic, self-report, preference-based health utility measure that consists of six questions *that are completed electronically* and is used to assess health status and inform pharmacoeconomic evaluations. *Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.* The EQ-5D-5L consists of two components. The first part, health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression (Herdman et al. 2011; Janssen et al. 2013). Published weights are available that permit the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The second part is a 0 to 100-point visual analog scale (VAS), which assesses current health status and higher scores are reflective of better health.

4.5.9.3 Treatment Preference Questionnaire

Patient preference will be assessed through *a paper version of* the EmiPref questionnaire (Appendix 3), which asks patients to specify the treatment they would prefer to continue to receive after receiving treatment with their previous episodic or prophylactic regimen and SC emicizumab. Patients who express a preference are then asked to identify the reasons which may have influenced their decision and indicate the top three reasons for their choice. Patients will complete this questionnaire after 3 months of treatment with emicizumab.

4.6 PATIENT, TREATMENT, STUDY AND SITE DISCONTINUATION

~~A Safety Follow-up Visit will be conducted 24 weeks after last dose of emicizumab in patients who discontinue emicizumab~~ Patients who discontinue emicizumab prior to the

completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first (see Appendix 1
Schedule of Activities
).

4.6.2 Study Treatment Discontinuation

Patients must discontinue *emicizumab* ~~study treatment~~ if they experience any of the following:

- Pregnancy
- *Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive emicizumab*
- *Investigator or Sponsor determines it is in the best interest of the patient*
- *Requirement of another medication not permitted per protocol*

The primary reason for *emicizumab* ~~study treatment~~ discontinuation should be documented on the appropriate eCRF. Patients who discontinue *emicizumab* ~~study treatment~~ prematurely will not be replaced. Patients who become pregnant should immediately discontinue treatment and be managed according to local guidelines.

5.1 SAFETY PLAN

Emicizumab is not approved *in all countries*, and clinical development is *still* ongoing. ~~Thus, the complete safety profile is not known at this time.~~ The safety plan for patients in this study is based on clinical experience with emicizumab in completed and ongoing studies. The anticipated important safety risks for emicizumab are outlined below. Please refer to the emicizumab Investigator's Brochure for a complete summary of safety information.

5.1.1.1 Injection-Site Reactions

In the completed and ongoing Japanese studies, ~~injection site reactions~~ *ISRs* have been observed in some patients with hemophilia A. These local ~~injection site reactions~~ *ISRs* included injection-site erythema, injection-site hematoma, injection-site rash, injection-site discomfort, injection-site pain, and injection-site pruritus. All local ~~injection site reactions~~ *ISRs* were of mild intensity. Further details on the observed ~~injection site reactions~~ *ISRs* are available in the Investigator's Brochure. To minimize the risk for ~~injection site reactions~~ *ISRs*, emicizumab should be injected subcutaneously using separate injection sites as described in Sections 3.3.1 and 4.3.2.1 and the IFU document.

5.1.1.2 Hypercoagulation and ~~Risk of Thrombosis~~*Thromboembolic Events*

As of *April 2017* ~~October 2016~~, there have been two *serious* thrombo*tic* ~~embolic~~ events reported in two patients ~~with hemophilia A with inhibitors~~ *who were treated with bypassing agents while receiving* ~~who received~~ emicizumab *prophylaxis* in Study BH29884.

- One patient self-administered greater than 200 units/kg/day of aPCC for two consecutive days and developed ~~a~~ cavernous sinus thrombosis. Treatment with emicizumab was interrupted*, no further aPCC was administered,* and the clot resolved without anticoagulation *in* ~~after~~ approximately 2.5 weeks. Emicizumab was restarted after approximately 10 days after the resolution of the serious adverse event *without recurrence*.
- The second patient developed severe skin necrosis (both legs) and *contemporaneous* superficial vein thrombosis in the right leg after self-administering two consecutive doses of 100 units/kg/day of aPCC. The patient ~~is recovering~~ *recovered* on supportive therapy (no anticoagulation). *For more details please refer to the emicizumab Investigator's Brochure.*

All thromboembolic events should be reported as adverse events of special interest (see Section 5.2.3), and also as serious adverse events if it meets criteria as described in Section 5.2.2. ~~should be reported as serious adverse events or adverse events of special interest as described in Sections 5.2.2 and 5.2.3, respectively.~~ HCPs should educate patients/caregivers ~~on how~~ to recognize signs and symptoms of potential thromboembolism or thrombosis (i.e., dyspnea, chest pain, leg pain or swelling; or if in the head, headache, numbness in the face, eye pain or swelling, or vision impairment; or if in the skin, blackening and associated pain~~, etc.~~) and ensure that they understand the importance of seeking appropriate medical attention. Patients and/or~~/~~ caregivers will also receive two alert cards to remind them of this information should thromboembolism be suspected.

5.1.1.3 Thrombotic Microangiopathy

TMA is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, central nervous system~~, etc~~. As of ~~October 2016~~ *April 2017*, *three* ~~two~~ cases of TMA were observed *in Study BH29884 involving patients with hemophilia A with inhibitors who were treated with bypassing agents while receiving emicizumab*~~in two patients with hemophilia A with inhibitors who received emicizumab in Study BH29884~~.

- The first patient self-administered two doses of *aPCC* 94 units/kg ~~aPCC~~ in 2 days to treat *his* left knee hemarthrosis. The ~~following~~ *next* day, ~~the patient~~ *he* started experiencing icterus and severe back pain and the patient self-administered two doses of *rFVIIa* 85 µg/kg ~~rFVIIa~~ and two doses of *aPCC* 94 units/kg ~~aPCC~~. The*n the* patient presented with thrombocytopenia, hyperbilirubinemia, and acute renal failure with schistocytes on peripheral blood smears. The patient was diagnosed with TMA and treated with plasmapheresis, hemodialysis, and supportive care and his condition improved and resolved after ~~15~~ *16* days. The patient discontinued treatment with emicizumab
- The second patient self-administered five doses of *aPCC* 74 units/kg ~~aPCC~~ over three consecutive days before the serious adverse event ~~occurred~~ *onset*. The patient had abdominal pain and emesis, acute renal failure, thrombocytopenia, elevated LDH, and a

low haptoglobin with schistocytes on peripheral blood smears. The patient was diagnosed with TMA and recovered without plasmapheresis or hemodialysis after ~~9~~ *18* days. The patient restarted treatment with emicizumab ~~approximately 10 days~~ after resolution of the serious adverse event *without recurrence of TMA*.

- *The third patient presented at the hospital complaining of rectal bleeding, postural dizziness, and exertional dyspnea. Of note,* [redacted]. *Multiple doses of rFVIIa were administered and various interventions (hemostatic powder application, absorbable hemostat packing, and embolization of rectal arteries) were used in an attempt to control bleeding. Despite these measures, the patient continued to have rectal hemorrhage. The patient's bypassing agent treatment was then changed to aPCC and temporary cessation of bleeding was achieved. Subsequently, the patient developed a serious adverse event of TMA following concomitant bypassing agent treatment. Emicizumab prophylaxis and aPCC were discontinued and therapeutic plasma exchange with albumin was provided. Three days later, investigators assessed the patient's TMA to be improving based on laboratory assessments (LDH and platelet count). However, the patient experienced recurrent rectal hemorrhage. Surgery and arterial embolization were no longer deemed to be feasible and the patient was placed on comfort care before passing away the same day. The investigator assessed the patient death as related to the serious adverse event of rectal hemorrhage and unrelated to emicizumab, and the TMA as related to emicizumab and aPCC. For more details please refer to the Emicizumab Investigator's Brochure.*

These events should be reported as adverse events of special interest (see Section 5.2.3), and also as serious adverse events if it meets criteria as described in Section 5.2.2. ~~TMA events should be reported as serious adverse events or adverse events of special interest as described in Sections 5.2.2 and 5.2.3, respectively.~~ HCPs should educate patients/caregivers to recognize signs and symptoms of potential TMA (i.e., confusion, weakness, swelling of arms and legs, yellowing of skin and eyes, vague abdominal or back pain, nausea, vomiting, or decreased urination, etc.) and ensure that they understand the importance of seeking appropriate medical attention. Patients and/or caregivers will also receive two alert cards to remind them of this information and these instructions should TMA be suspected.

5.1.1.4 Hypersensitivity

Since emicizumab is a biological product, acute systemic hypersensitivity reactions, including anaphylactic*/anaphylactoid* reactions, may occur. In Study ACE001JP, no severe hypersensitivity reactions or anaphylactic/anaphylactoid reactions have been observed. These events should be reported as serious adverse events or adverse events of special interest as described in Sections 5.2.2 and 5.2.3, respectively.

HCPs administering *emicizumab* ~~the study medication~~ in the clinic must be trained in the appropriate administration procedures; be able to recognize the signs and symptoms associated with potential hypersensitivity, anaphylactic, and anaphylactoid reactions; and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; see Appendix 4). HCPs should also instruct patients how to recognize the signs and symptoms of hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an

HCP or seek emergency care in case of any such occurrence. Patients/caregivers will also receive two alert cards to remind them of this information should any of these reactions occur.

5.1.2 Management of Patients Who Experience Specific Adverse Events

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
…	•
Hypercoagulation and risk of thrombosis	• Investigators should be vigilant for patients who exhibit signs/symptoms consistent with thrombotic disease and should immediately begin work up and treatment as per local guidelines. • If a patient has a thromboembolic event, further administration of *emicizumab* ~~study drug~~ should be interrupted. The investigator must contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk to determine if the patient should resume taking emicizumab and discuss the patient's continued study participation. • Please see Sections 4.4.1 and 4.5.6.9 for guidance on the management of breakthrough bleeds, including required laboratory monitoring.
TMA	• Investigators should be vigilant for patients who exhibit signs/symptoms consistent with TMA and immediately begin work-up and treatment, as per local guidelines. • If a patient has a TMA event, further administration of *emicizumab* ~~study drug~~ should be interrupted. The decision to resume taking emicizumab after a TMA event must be discussed with and approved by the Medical Monitor. • Please see Sections 4.4.1 and 4.5.6.9 for guidance on the management of breakthrough bleeds, including required laboratory monitoring.

ADA=anti-drug antibody; TMA=thrombotic microangiopathy

5.1.3 Interpretation of Coagulation Assays for Patients Receiving Emicizumab

Emicizumab interacts with standard laboratory assays used in the management of patients with hemophilia A *(see Table 11)*. In one-stage assays, emicizumab is associated with a supra-physiologically short time to clot formation and thus normalization of aPTT at sub-therapeutic levels ~~and an overestimation of true FVIII activity~~. Emicizumab is not recognized or neutralized by FVIII inhibitors, and therefore *FVIII inhibitors* cannot be detected *in the presence of emicizumab* by functional tests such as Bethesda or Nijmegen-Bethesda assays, which use a one-stage clotting-based readout. Emicizumab activity cannot be detected by chromogenic assays using purified bovine coagulation proteins, *thus chromogenic Bethesda assays using bovine proteins can be used to measure FVIII inhibitor titer in the*

presence of emicizumab. Emicizumab ~~and~~ *activity* can ~~only~~ be detected using ~~an~~ *chromogenic* assays composed of human proteins. See the Investigator's Brochure for additional details on which tests can be used and how the test results can be interpreted.

Table 11 *Coagulation Test Results Affected and Unaffected by Emicizumab*

Results Affected by Emicizumab	*Results Unaffected by Emicizumab*
aPTT *Bethesda assays (clotting-based) for FVIII inhibitor titers* *One-stage, aPTT-based, single-factor assays* *aPTT-based Activated Protein C Resistance* *Activated clotting time*	*Bethesda assays (bovine chromogenic) for FVIII inhibitor titers* *Thrombin time* *One-stage, prothrombin time-based, single-factor assays* *Chromogenic-based single-factor assays other than FVIII [a]* *Immuno-based assays (i.e., ELISA, turbidimetric methods)* *Genetic tests of coagulation factors (e.g., Factor V Leiden, Prothrombin 20210)*

ELISA = enzyme-linked immunosorbent assay

a. *For important considerations regarding FVIII chromogenic activity assays, see Drug Interactions listed in the US Package Insert*

5.3.5.1 Injection Reactions

An adverse event that occurs during or within 24 hours after *emicizumab* ~~study drug~~ administration and in the investigator's opinion is judged to be related to *emicizumab* ~~study drug~~ injection should be captured as an "injection-site reaction" on the Adverse Event eCRF. An injection-site reaction that is localized should be marked as a "local injection-site reaction." Associated signs and symptoms (e.g., injection-site erythema or injection-site rash) should be recorded on the dedicated Injection-Site Reaction eCRF. Systemic reactions should be recorded separately on the Adverse Event eCRF. The dedicated Injection-Site Reaction eCRF should only be used to capture the individual signs/symptoms for local injection-site reactions.

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship *to emicizumab* ~~to study drug~~, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of hemophilia A.

5.3.5.9 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present *during the study Screening Period* ~~at the screening visit for this study~~. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of *emicizumab* ~~study drug~~ should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to *emicizumab* ~~study drug~~:

5.4.1 Emergency Medical Contacts

~~**Medical Monitor Contact Information for all sites**~~

~~Medical Monitor:~~ ~~Dr~~ [redacted] ~~(Primary)~~
~~Telephone No.:~~ [redacted]
~~Mobile Telephone No.:~~ [redacted]
~~Medical Monitor:~~ ~~Dr~~ [redacted] ~~MD, MBA (Secondary)~~
~~Telephone No.:~~ [redacted]
~~Mobile Telephone No.:~~ [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible individual ~~(listed above and/or on the Roche Medical Emergency List)~~, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible individual contact information, will be distributed to all investigators.

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of *emicizumab* ~~study drug~~, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately

(i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of *emicizumab* ~~study drug~~, serious adverse events and adverse events of special interest will be reported until the last scheduled study visit (see Section 5.3.1). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of *emicizumab* ~~study drug~~. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue *emicizumab* ~~study drug~~ and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to *emicizumab* ~~study drug~~ should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis population is all patients who have received at least one dose of *emicizumab* ~~study medication~~ (safety population). The intent-to-treat (ITT) population includes all enrolled patients.

6.2 SUMMARIES OF CONDUCT OF STUDY

Flow of patients through the study will be displayed in a 'Consolidated Standards of Reporting Trials (CONSORT)' diagram. A clear account of all patients who enrolled in the study and who entered, discontinued, and completed the initial and maintenance phases of the study will be displayed. The reasons for premature discontinuation from study treatment and the reasons for study withdrawal will be described. In addition, the number of patients who received dose up-titration will also be described. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. ~~The type of~~ *Major* protocol ~~violations~~ *deviations* and the number of patients with at least one ~~violation~~ *major protocol deviation* will be summarized in terms of both the safety and ITT populations.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, and self-reported race and ethnicity) will be summarized using means, standard deviations, medians, and ranges for continuous variables and ~~proportions~~ *frequencies and percentages* for categorical variables, as appropriate. For each variable (continuous or categorical), the number of available observations will be reported. Medical history will be tabulated and previous concomitant medications will be summarized.

6.4 SAFETY ANALYSES

The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A who have *persistent* inhibitors against FVIII at enrollment. Of primary interest in this study are the incidence and severity of *all* adverse events, including thromboembolic *events*, *microangiopathic hemolytic anemia or* TMA, systemic hypersensitivity, anaphylaxis, and anaphylactoid events.

All adverse events will be assessed according to the WHO toxicity grading scale. The incidence, type, and grade of adverse events will be summarized according to the primary system-organ class (SOC) and, within each SOC, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. For each adverse event, data will be provided on the timing (start and stop date, time of onset in comparison with last dose of emicizumab received, and doses of emicizumab received), severity, relationship to *emicizumab* ~~study drug~~, outcome, and effect on therapy. The data may be presented together with two-sided 95% Clopper-Pearson CIs if appropriate.

In addition, as part of the safety evaluation, additional assessments will be summarized descriptively as follows:

…

- Laboratory parameters (hematology and chemistry):
  - These parameters will be presented in shift tables of WHO toxicity grade at baseline versus worst grade during the treatment period. Selected laboratory parameters will

be summarized in terms of mean, standard deviation, minimum, and maximum. Laboratory parameters will also be presented graphically over time*, if appropriate*.

All safety variables will be analyzed for the safety population. For each variable, the number of available observations will be reported. The safety population includes all patients who have received at least one dose of *emicizumab* ~~study medication~~.

…

The iDMC (see Section 9.4.1) will evaluate the study data, including the emerging safety results, at periodic reviews and recommend to the Sponsor whether *the protocol should be amended or* the study should be stopped early. All summaries and analyses will be prepared by the *Study Management Team (*SMT*)* statistician and presented for ~~review by the~~ iDMC review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

6.5 EFFICACY ANALYSES

…

The definition of a bleed is described in Section 4.5.7.1. ~~Patients will be asked to record when they have bleeds or hemophilia medication use, including emicizumab.~~ *Patients will be asked to record any hemophilia medication use (including emicizumab) and information regarding any bleeding events*. The patients should record this information at least every week even if they do not experience a bleed. The number of bleeds will be compared with patients' bleed rate prior to study entry and will be summarized descriptively.

…

As different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) will be used for adult and adolescent patients, all calculations and analyses will be conducted separately for each patient population. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively. The HRQoL scale scores for all patients will be evaluated after 6 months of treatment, a timepoint which is consistent with other recent registrational studies in hemophilia (Lentz et al. 2013; Mahlangu et al. 2014; Powell et al. 2013) and analyses of this type of data (Santagostino et al. 2014; Wyrwich et al. 2015). Paired t-tests will be used to compare the on-treatment scores with the baseline scale scores for each HRQoL measure. Within-patient changes from baseline for the different HRQoL scale scores will also be calculated for each of the on-treatment timepoints. The proportion of patients who report changes ~~in each group~~ that exceed clinically meaningful thresholds will be reported.

For each of the EQ-5D-5L assessments, the number and percentage of patients in each of the five categories for each question ~~for each group~~ will be evaluated. Changes in the EQ-5D-5L index utility score from baseline will also be *reported* ~~compared between groups~~. In addition, summary statistics including mean, standard deviation, median, minimum, and maximum will be calculated according to the patients' health state using the EuroQoL visual analogue scale (EQ-VAS) ~~both within and between groups~~. The proportion of patients who report changes ~~in each group~~ that exceed the clinically meaningful threshold on the EQ-5D-5L index and the EQ-VAS scores will be reported.

6.6 IMMUNOGENICITY ANALYSES

…

The immunogenicity analyses will include patients with at least one pre-dose and one post-dose anti-emicizumab antibody assessment. The numbers and proportions of antibody-positive patients and antibody-negative patients during the treatment period will be summarized. Patients are considered to be antibody-positive if they are negative at baseline but develop an anti-emicizumab antibody response following *emicizumab* ~~study drug~~ administration (treatment-induced antibody response), or if they are positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥ 0.60 titer units) than the titer of the baseline sample (treatment-enhanced antibody response). …

6.9.1 Planned Interim Analyses

The first *interim* analysis will be performed once *approximately* 100 patients have received treatment with emicizumab for at least 24 weeks. A second *interim* analysis will be performed when *approximately* 100 patients have received treatment with emicizumab for at least 52 weeks. The data from these analyses will subsequently be presented to the iDMC in order to enable them to effectively monitor the study (see Section 9.4.1).

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

PRO data will be collected electronically through the use of electronic devices provided by an ePRO vendor (HRQoL and EQ-5D-5L) or using a paper questionnaire (EmiPref). Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable. The electronic device is designed for entry of data in a manner that is attributable, secure, and accurate, in compliance with ~~U.S. FDA regulations for~~ electronic records: ~~(~~21 Code of Federal Regulations, Part 11~~)~~. The PRO data from the device will be transmitted electronically to the eCRF in real time. ~~to a centralized database at the ePRO vendor. The data from the ePRO devices will be available for viewing only through a secure access to a web portal provided by the ePRO vendor.~~ Only identified and trained users may view the data, and their actions (if any) will become part of the audit trail. The Sponsor will have view-only access to PRO data. ~~Regular data transfers will occur from the centralized database at the vendor to the database provided by the Sponsor.~~ The Sponsor will receive all data (including requested meta-data) entered by the patients on the ePRO devices and all relevant study documentation.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data ~~(if applicable)~~, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by

relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

9.4.1 Independent Data Monitoring Committee

An iDMC will be assembled to review the safety data collected during the study. The iDMC members will consist of, at minimum, independent hemostasis/thrombosis experts and a statistician, none of whom will be otherwise involved in the conduct of study. All analyses for review by the iDMC will be prepared by the SMT statistician. Monitoring and analysis of all significant safety events will be performed on a continuous basis. *A first interim a*~~A~~nalysis of the study data will be performed once *approximately* 100 patients have received treatment with emicizumab for at least 24 weeks (see Section 6.9.1)*, and a*~~.~~ ~~A~~ second *interim* analysis will be performed when *approximately* 100 patients have received treatment with emicizumab for at least 52 weeks. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor according to the emerging data.

The SMT statistician will perform analyses and provide tables and listings to support the study reviews by the iDMC. The safety data that will be provided will include demographic data, adverse events (the incidence and severity of *all* adverse events, including thromboembolic *events*, *microangiopathic hemolytic anemia or* TMA, systemic hypersensitivity, anaphylaxis, and anaphylactoid events), medication dose information, physical examination findings, vital sign data, and laboratory abnormalities (hematology and chemistry). If available, the efficacy data that will provided will include the number of bleeds over time, ABR data, the HRQoL of patients, the health status of patients according to EQ-5D-5L scores, and patient preference for the emicizumab regimen compared with the previous regimen used. Further information will be provided on request.

9.7 STUDY PARTICIPANT SURVEY

Consenting patients may be asked about their study experience via a short study-specific survey.

Survey questions will ask the patient to rate their study experience on a scale of 1-5 on topics that include the following: information provided prior to the study, the consent and enrolment process, study participation, study results and feeling appreciated as a study patient.

Patients will be asked to complete the survey at the end of the study. The goal of this survey is to identify areas where Roche is performing well and areas where improvement may be required.

Information will be provided to the Sponsor securely and on an anonymous basis and consent to the survey is totally voluntary and does not affect patient's enrolment to the study.

10. REFERENCES

…

~~Keizer RJ, Huitema ADR, Schellens JHM, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 2010;49:493–507.~~

…

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Appendix 1
Schedule of Activities

	Screening	Treatment												Early Termination / Study Completion	Safety Follow-up Visit [a]
Visits	**Wk -4 to Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**3 m**	**6 m**	**9 m**	**12 m**	**15 m [b]**	**18 m**	**21 m [b]**	**Unscheduled visit**	**2 years**	
Time Window, days			**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**	**± 14**	**± 30**	**± 30**		**± 30**	
Informed consent [c]	x														
Inclusion / exclusion criteria	x														
Medical history and demographics [d]	x														
Physical examination [e]	x	x	x	x	x	x	x	x	x		x		x	x	x
Vital signs [f]	x	x	x	x	x	x	x	x	x		x		x	x	x
Concomitant medications [g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
~~Safety laboratory assessments~~ Hematology and *blood* chemistry [h,r]	x	x	x	x	x	x	x	x	x		x		x	x	x
Pregnancy test [i,r]	x	x			x	x	x	x	x		x		x	x	
HIV and hepatitis serology [j]	x														
Anti-FVIII antibodies [k,r]	~~x~~	*x*			x	x	x		x		x			x	x

	Screening	Treatment												Early Termination / Study Completion	Safety Follow-up Visit [a]
Visits	**Wk -4 to Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**3 m**	**6 m**	**9 m**	**12 m**	**15 m [b]**	**18 m**	**21 m [b]**	**Unscheduled visit**	**2 years**	
Time Window, days			**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**	**± 14**	**± 30**	**± 30**		**± 30**	
Anti-emicizumab antibodies [l,r]		x			x	x	x		x		x			x	x
ePRO bleed / medication recording [m]	~~x~~	x	x	x	x	x	x	x	x	x	x	x	x	x	
Surgical events [n]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Adverse events [o]	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x
~~IMP~~ Management *of emicizumab* [p]		x	x	x	x	x	x	x	x	x	x	x	x	x	
HRQoL [q]		x				x	x		x		x			x	
Health status (EQ-5D-5L) [q]		x				x	x		x		x			x	
Treatment preference questionnaire (EmiPref) [r]						x									
PK assessment [s,t]		x	x	x	x	x	x		x		x			x	x
Safety biomarkers assessment [s,u]		x			x	x	x		x		x			x	x
Safety coagulation system biomarkers assessment [s,v]		x			x										

	Screening	Treatment												Early Termination / Study Completion	Safety Follow-up Visit [a]
Visits	**Wk -4 to Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**3 m**	**6 m**	**9 m**	**12 m**	**15 m [b]**	**18 m**	**21 m [b]**	**Unscheduled visit**	**2 years**	
Time Window, days			**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**	**± 14**	**± 30**	**± 30**		**± 30**	
PD biomarkers assessment [s,w]		x			x	x	x		x		x			x	~~x~~
Bone and joint biomarker assessment *(fasting)* [s,x]		x					x				x			x	~~x~~
Additional laboratory assessments [y]		*For breakthrough bleeds treated with bypassing agents*													
Emicizumab administration		Weekly subcutaneous injection													

d=day; eCRF=electronic Case Report Form; EQ-5D-5L=EuroQoL Five-Dimension-Five Levels Questionnaire; FVIII=Factor VIII; Haem-A-QoL=Hemophilia Adult Quality of Life Questionnaire; Haemo-QoL-SF=Hemophilia Quality of Life Short Form; HIV=human immunodeficiency virus; HRQoL=Health-Related Quality of Life; ~~IMP=investigational medicinal product;~~ m=months *(based on calendar months)*; PD=pharmacodynamic; PK=pharmacokinetic; Wk=week

Notes: the maximum allowable time between Screening and enrollment is 4 weeks; if the elapsed time between Screening and enrollment is more than 4 weeks, Screening must be repeated.

Except for the bleed/medication records, all other patient data will be collected during clinic visits.

~~On treatment days, pre-injection blood collection should be made 0–120 minutes before the injection.~~

~~The same assessments will also be completed at the Early Termination Visit (if required).~~

a. ~~A safety Follow-up Visit will occur 24 weeks after discontinuing emicizumab~~*Patients who discontinue emicizumab prior to the completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first.*

…

c. **Written informed consent ~~(or patient assent and parent written informed consent, if patient is an adolescent)~~** must be obtained before any study-specific screening ~~procedure~~ *tests or evaluations are* ~~is~~ performed. *For adolescents (i.e., patients who are 12–17 years of age), an Informed Assent Form will be*

completed instead. Parents or caregivers of adolescents will also complete an Informed Consent Form. The enrollment form will be completed after informed consent and/or assent is obtained. *All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.*

d. ***Medical history and demographics*** *d*~~D~~ata will be collected from patient medical records and documented in the eCRF. *Medical history includes hemophilia-related history, clinically significant diseases, procedures (including prior surgeries), use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior ITI, anaphylaxis, or known thrombophilia. It should also include all medication taken in the 4 weeks prior to screening (including prescription drugs, over-the-counter drugs, and herbal/homeopathic remedies and therapies). Any hemostatic medications (e.g. bypassing agents) and other medications used to treat or prevent bleeds in the 6-month period prior to starting emicizumab treatment will also be collected. Demographic data will include age, sex, and self-reported race and ethnicity.*

e. A complete **physical examination** will be performed ~~at~~ *during* Screening *and should include, but not necessarily be limited to, an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF.* ~~and targeted physical examinations will be performed at the visits indicated.~~ Targeted physical examinations *(i.e.,* ~~of~~ joints ~~(~~for bleeds, evidence of arthropathy; ~~) and~~ skin ~~(~~for bruises, hematomas~~,~~ and ~~injection site reactions~~*ISRs;* ~~), in addition to~~ other organ systems *as clinically indicated)*~~,~~ should be *conducted at subsequent visits or* ~~performed~~ as clinically indicated. *New or worsened clinically significant abnormalities from screening should be recorded as adverse events, if appropriate, on the Adverse Event eCRF.*

f. ***Vital signs*** *include measurement of* body temperature (oral, rectal, axillary, or tympanic), *heart and respiratory rates,* blood pressure~~,~~ ~~pulse, respiratory rate,~~ and weight ~~will be measured~~. *On treatment days, measurement should occur* ~~at each clinic visit~~ prior to ~~any~~ emicizumab *administration* ~~injection, if applicable~~. Height will be measured and recorded only *during* ~~at~~ Screening and 6 and 12 months after starting emicizumab. *Additional vital signs assessments may also be taken anytime as unscheduled assessments as judged by the investigator. In addition,* ~~At the investigator's discretion,~~ vital signs may be taken to help monitor for hypersensitivity reactions during or after injections *at the investigator's discretion,*~~,~~ *although these data* ~~but they~~ should not be entered into the eCRF.

g. ~~Patients will be asked about concomitant medications (e.g., extra pain medication following a bleed) at each clinic visit indicated, with the exception of treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), which will be collected in the bleed records. Any hemostatic medications used to treat or prevent bleeds in the week prior to starting emicizumab treatment will also be collected.~~ *The definition of* ***concomitant medications****, as well as permitted and prohibited medications is described in Section 4.4. Concomitant medications used by a patient from 4 weeks prior to initiation of emicizumab to the Study Completion/Early Termination Visit (or to the Safety Follow-up Visit, if applicable) should be reported to the investigator and recorded on the Concomitant Medications eCRF. Treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), will be collected in the bleed records.*

h. ***Hematology and blood chemistry*** ~~Laboratory~~ assessments will include a complete blood count with differential and serum chemistries *(see Section 4.5.6.1)*. ~~Safety~~ *L*~~l~~aboratory assessments completed ~~at~~ *during* Screening do not have to be repeated at Week 1, if the period between Screening and Week 1 is ≤ 5 days and there has been no change in the patient's health status as assessed by the investigator. ~~Laboratory assessments will be analysed at a central laboratory. Additional analysis will be performed at a local laboratory, as per the investigator's discretion.~~ *Samples will be sent to the central laboratory for analysis.*

i. ***Pregnancy tests:*** Female patients of childbearing potential (including those who have had a tubal ligation) will be required to have a negative serum pregnancy test result ~~at~~ *during* Screening ~~(~~and again within 7 days prior to the first dose of emicizumab~~)~~. ~~and~~ *U*~~u~~rine pregnancy tests *will be* performed *throughout the study treatment period.* ~~at every clinic visit, with the exception of Weeks 2 and 3.~~ Pregnancy testing will be *conducted*~~analysed~~ at the local laboratory.

j. ~~**HIV and hepatitis serology** will be conducted at Screening at the local laboratory.~~ *The specific tests utilized for **hepatitis and HIV serology** testing are per local standard of care. As this patient population is at high risk for HIV, hepatitis A, B and C, sites should consider testing for these. While the specific serological tests used is at the discretion of the Investigator, this is with the understanding that the status of that participants' hepatitis or HIV is confidently known at time at enrollment. HIV and hepatitis serology tests will be conducted at the local laboratory.*

k. *For the assessment of **anti-FVIII antibodies** (inhibitors), functional assays that utilize a clotting readout (classic Bethesda or Nijmegen assay) cannot be used for patients on emicizumab therapy as emicizumab drives clotting even in the presence of FVIII inhibitors, causing a false-negative test result (see Section 5.1.3). After the first dose, local measurement of FVIII inhibitors, if indicated, requires use of an ELISA-based test or a chromogenic Bethesda assay.* ~~anti-FVIII antibodies (FVIII inhibitor titer) will be analysed at Screening and at the visits indicated. Anti-FVIII antibody assessments will be conducted at a central laboratory. Additional analysis will be performed at a local laboratory, as per the investigator's discretion.~~ *At the discretion of the local investigator, any additional urgent request to assess FVIII inhibitors will need to be sent to the central laboratory (see Appendix 2 for additional information). Plasma samples for anti-FVIII antibodies will be analysed at the central laboratory*

l. *Plasma* samples *are required for immunogenicity assessments* to detect **anti-emicizumab antibodies** ~~will be~~. ~~collected at screening and prior to emicizumab administration at the visits indicated.~~ *Additional* samples to detect anti-emicizumab antibodies may also be drawn at the time of hypersensitivity events or following suspected loss of efficacy. ~~Anti-emicizumab antibody assessments will be conducted~~ *Samples will be analysed* at *the* ~~a~~ central laboratory. ~~Additional analysis will be performed at a local laboratory, as per the investigator's discretion.~~

m. ***ePRO bleed / medication recording:*** At the Week 1 visit, patients will be trained on how to record their bleeds and hemophilia medication use *on the ePRO device where possible*. Data that need to be recorded will include the site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. *At least once a week, patients will need to record any hemophilia medication use (including emicizumab) and information regarding any bleeding events.*~~Patients will record when they have bleeds or hemophilia medication use, including emicizumab, or at least every week.~~ Investigator review of patient-reported bleed/medication records with the patient/caregiver will occur for completeness and accuracy at all of the visits during the treatment period, at study completion, at any unscheduled visits (if required), and at the Early Termination Visit (if required).

*n. Thorough documentation on **surgical events** will be requested, including type of surgery or procedures, treatments, outcomes, etc.*

o. ***Adverse events:*** *After informed consent has been obtained but prior to initiation of emicizumab, only serious adverse events caused by a protocol-mandated intervention should be reported.* Injection-site reaction adverse events will be collected on ~~a~~ *the injection site reaction form.* ~~separate form from the adverse event form.~~

p. ***Management of emicizumab:*** Drug dispensation will not occur at the Study Completion Visit or the Early Termination Visit (if required). Patients will only receive *emicizumab* ~~IMP~~ during an unscheduled visit if drug dispensation is required at this time.

q. ***HRQoL and EQ-5D-5L:*** ~~Prior to the first emicizumab administration; at the 3, 6, 12, and 18 month assessments; and at study completion (2 years),~~ *P*~~p~~atients will be ~~prompted~~ *requested* to complete Haem-A-QoL (adults age: ≥ 18 years) or the Haemo-QoL-SF (adolescents ages: 12−17 years) questionnaire and the EQ-5D-5L questionnaire. *Questionnaires will be self-administered electronically before the patient/caregiver receives any information on disease status, prior to the performance of non-PRO assessments, and prior to emicizumab administration (if on a treatment day). Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.*

r. ***EmiPref:*** At the 3-month assessment, patients will be prompted to complete *a paper version of* the EmiPref questionnaire *(Appendix 3). The questionnaire will be self-administered before the patient/caregiver receives any information on disease status, prior to the performance of non-PRO assessments, and prior to emicizumab administration (if on a treatment day*).

s. *On treatment days, blood collection should occur within 2 hours prior to emicizumab administration unless otherwise specified.* ~~Samples for this assessment should be taken prior to emicizumab injection.~~ *Unless otherwise specified,* ~~On days where samples are to be collected, emicizumab injection will be performed in the clinical unit.~~*additional analysis will be performed at a local laboratory, as per the investigator's discretion. Any additional laboratory results which are required as part of the patient's safety assessment should be recorded in the unscheduled visit eCRFs. Central labs are part of the non-eCRF data which will be sent to the Sponsor directly by the central lab vendor.*

t. *Plasma samples are required for* ***PK assessments.*** *On days where samples are to be collected, the emicizumab injection will be performed in the clinical unit. One single pre-dose sample is required on the applicable visits.* ~~All biomarker assessments will be conducted at a~~*Samples will be analysed by the* central laboratory.~~. Additional analysis will be performed at a local laboratory, as per the investigator's discretion.~~

u. *Plasma samples for* ***safety biomarkers*** *must be citrate plasma. Tests may include, but are not limited to, D-dimer. Samples will be analysed by the central laboratory. See Appendix 2.* ~~Plasma samples for D-dimer testing will be taken at the visits indicated.~~

v. Plasma samples for **safety coagulation system biomarker** assessments *must be citrate plasma. Tests include* ~~(~~FVIII:Ag, FIX:Ag and FX:Ag.~~) will be taken at the visits indicated.~~ *Samples will be analysed by the central laboratory. See Appendix 2.*

w. *Plasma samples for* ***PD biomarker assessments*** *must be citrate plasma. Tests will include, but are not limited to,* FVIII activity and modified aPTT (one stage). ~~will be~~*Time windows for sample collection are specified in Appendix 2*
Schedule of Biomarker Samples

x. . ~~assessed at Week 1 (Day 1, Cycle 1); Week 5 (± 2 days); 3 and 6 months (± 7 days); 12 months (± 14 days); and 18 months and study completion (± 30 days). All samples must be citrate plasma.~~ Additional plasma samples will be collected for future exploratory research, which may include tests such as clot waveform analysis (CWA) and others (see Appendix 2
Schedule of Biomarker Samples

y.). *Samples will be analysed by the central laboratory.*

z. ~~Bone and joint biomarkers will be assessed at Week 1 (Day 1, Cycle 1); 6 months (± 7 days); and 18 months and study completion (± 30 days).~~ Serum and plasma EDTA samples *for* ***bone and joint biomarkers*** must be collected after fasting (no food or drink other than water for at least 8 hours prior to the blood draw). Ideally these samples should be collected in the morning (before noon), in order to control for diurnal variation. Please consult the Central Laboratory Services Manual for details. The selection of exploratory bone and joint biomarkers to be tested will build on findings from biomarker analyses in other emicizumab trials and may include CTX-1, OPG, P1NP, and soluble RANK-L (see Appendix 2
Schedule of Biomarker Samples

aa.). *Samples will be analysed by the central laboratory.*

bb. ***Additional laboratory assessments****: In the event of a breakthrough bleed that is treated with bypassing agents, it is recommended that the following laboratory tests will be performed within 24–48 hours of initial bypassing agent use (these tests will be conducted so that the investigator can monitor the patient for potential thromboembolic events and microangiopathic hemolytic anemia or TMA). These tests include platelet count, serum creatinine, LDH and schistocytes. A plasma sample should also be provided for central laboratory monitoring of prothrombin fragment F1+2, fibrinogen and D-dimer.* Samples for these tests should ideally be analysed at the central laboratory. *Exceptionally in urgent situations where results are required quickly, local laboratory testing can be used, with results recorded in the eCRF. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours until 24–48 hours after the last dose of bypassing agents is administered to treat a specific bleed. If applicable, laboratory results should be recorded in the unscheduled visit eCRFs.*

Appendix 2
Schedule of Biomarker Samples

Sample	Visit [a]	*Time window*	Biomarker assays [b,~~c~~]
Safety biomarkers [c]	*Week 1*	*Day 1*	*May include, but are not limited to, D-dimer*
	Week 5	*± 2 days*	
	3 months	*± 7 days*	
	6 months	*± 7 days*	
	12 months	*± 14 days*	
	18 months	*± 30 days*	
	Study completion	*± 30 days*	
	Safety Follow-up Visit (if applicable)		
Safety coagulation system biomarkers [c]	*Week 1*	*Day 1*	*FVIII:Ag, FIX:Ag and FX:Ag*
	Week 5	*± 2 days*	
PD *biomarkers* [c~~d,e~~]	Week 1	*Day 1*	*Will include, but are not limited to:* *FVIII inhibitor titer,* Modified aPTT (one-stage), FVIII activity
	Week 5	*± 2 days*	
	3 months	*± 7 days*	
	6 months	*± 7 days*	
	12 months	*± 14 days*	
	18 months	*± 30 days*	
	Study completion	*± 30 days*	
Bone and joint *biomarkers (fasting)* [*d*~~f,g~~]	Week 1	*Day 1*	Exploratory biomarkers of bone turnover and joint health *[e]*
	6 months	*± 7 days*	
	18 months	*± 30 days*	
	Study completion	*± 30 days*	

aPTT=activated partial thromboplastin time; CTX-1=C-terminal telopeptide of collagen 1; CWA=clot waveform analysis; EDTA=ethylenediaminetetraacetic acid; OPG=osteoprotegerin; P1NP=procollagen type 1 amino-terminal propeptide; PD=pharmacodynamic; RANK-L=receptor activator of nuclear factor kappa-B ligand

~~Except for Day 1 of Cycle 1, all other study visits and assessments should be conducted within the following timeframes Week 5, ± 2 days; 3 and 6 months, ± 7 days; 12 months, ± 14 days; 18 months and study completion, ± 30 days.~~

a. All samples are to be collected *within 2 hours* prior to emicizumab injection (if applicable) *unless otherwise specified.*

b. Assays that will be tested are listed. Blood volumes and processing procedures will be specified in the *Central* Laboratory *Services* Manual. *Biomarker assessments will be conducted at the central laboratory. Additional analysis will be performed at a local laboratory, as per the investigator's discretion.*

~~c.~~ *S*~~Biomarker assessments will be conducted at a central laboratory. Additional analysis will be performed at a local laboratory, as per the investigator's discretion.~~

d. ~~All s~~amples are required to be citrate plasma. Additional plasma will be collected for future exploratory research, which may include tests such as CWA and others.

~~Appendix 3~~
~~Haem-A-QoL (United States/English)~~

Questionnaire deleted

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)

~~Appendix 3~~
~~Haem-A-QoL (United States/English) (cont.)~~

Trial ID:	Page 2/7
VISIT X	
Subject No.:	☐☐☐☐☐☐

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

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

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

In the past month...	never	rarely	sometimes	often	all the time
1. ... my hemophilia was a burden for me	☐	☐	☐	☐	☐
2. ... my hemophilia made me angry	☐	☐	☐	☐	☐
3. ... I was worried because of my hemophilia	☐	☐	☐	☐	☐
4. ... I felt excluded	☐	☐	☐	☐	☐

HAEM-A-QOL - USA/English - Final version - 29 Jun 07 -

~~Appendix 3~~
~~Haem-A-QoL (United States/English) (cont.)~~

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

3. How does hemophilia affect your VIEW OF YOURSELF?

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

4. These questions are about SPORTS AND LEISURE

In the past month...	never	rarely	some-times	often	all the time	not applicable
1. ... I had to avoid sports that I like because of my hemophilia	☐	☐	☐	☐	☐	☐
2. ... I had to avoid sports like football	☐	☐	☐	☐	☐	☐
3. ... I played sports just as much as others	☐	☐	☐	☐	☐	☐
4. ... I didn't have the freedom to travel where I wanted	☐	☐	☐	☐	☐	☐
5. ... it was necessary for me to plan everything in advance	☐	☐	☐	☐	☐	☐

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VISIT X

Subject No.: ☐☐☐☐☐☐

5. These questions are about WORK AND SCHOOL

In the past month...	never	rarely	some-times	often	all the time	not applicable
1. ... I was able to go to work/school regularly in spite of my hemophilia	☐	☐	☐	☐	☐	☐
2. ... I was able to work/study like healthy colleagues	☐	☐	☐	☐	☐	☐
3. ... my everyday work/school activities were jeopardized by my hemophilia	☐	☐	☐	☐	☐	☐
4. ... I found it difficult to pay attention at work/school because I was in pain	☐	☐	☐	☐	☐	☐

6. The next questions are about DEALING WITH HEMOPHILIA

In the past month...	never	rarely	sometimes	often	all the time
1. ... I tried to recognize early on when a bleed developed	☐	☐	☐	☐	☐
2. ... I was able to tell whether or not I was bleeding	☐	☐	☐	☐	☐
3. ... I was able to control my bleeds	☐	☐	☐	☐	☐

HAEM-A-QOL - USA/English - Final version - 29 Jun 07 -

Trial ID: Page 5/7

VISIT X

Subject No.: |_|_|_|_|_|_|

7. and what about your TREATMENT?

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

HAEM-A-QOL - USA/English - Final version - 29 Jun 07 -

Trial ID:	Page 6/7
VISIT X	
Subject No.:	

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	☐	☐	☐	☐	☐
2. ... I have been expecting that things will get better in the future	☐	☐	☐	☐	☐
3. ... I have been worrying that my condition is worsening	☐	☐	☐	☐	☐
4. ... my life plans have been influenced by my hemophilia	☐	☐	☐	☐	☐
5. ... I have been afraid that I will need a wheelchair	☐	☐	☐	☐	☐

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

Recently...	never	rarely	some-times	often	all of the time	not applicable
1. ... I have had difficulties having children	☐	☐	☐	☐	☐	☐
2. ... I have been afraid that I cannot have children	☐	☐	☐	☐	☐	☐
3. ... I have been afraid that I will not be able to take care of my children	☐	☐	☐	☐	☐	☐
4. ... I have been worrying about not being able to raise a family	☐	☐	☐	☐	☐	☐

HAEM-A-QOL - USA/English - Final version - 29 Jun 07 -

~~Appendix 3~~
~~Haem-A-QoL (United States/English) (cont.)~~

Trial ID:	Page 7/7
VISIT X	
Subject No.:	

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	☐	☐	☐	☐	☐
2 ... I have been insecure in my relationships with women because of my hemophilia	☐	☐	☐	☐	☐
3. ... I haven't been able to have a normal relationship because of my hemophilia	☐	☐	☐	☐	☐

THANK YOU FOR YOUR ASSISTANCE!

HAEM-A-QOL - USA/English - Final version - 29 Jun 07 -

~~*Appendix 4*~~
~~*Haemo-QoL-SF (United States/English)*~~

Questionnaire deleted

~~Appendix 4~~
~~Haemo-QoL-SF (United States/English) (cont.)~~

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

Questionnaire deleted

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 ❑

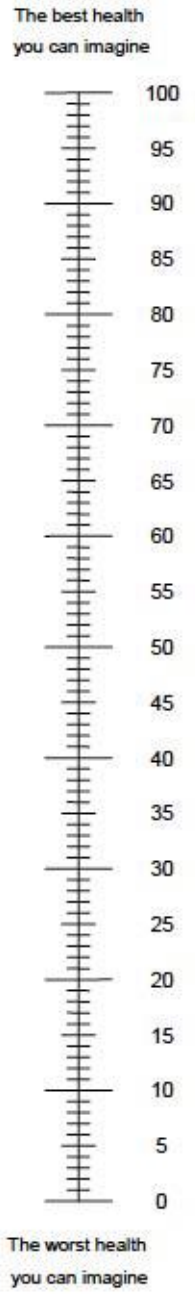
ANXIETY / DEPRESSION

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 ❑

~~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 = ☐



Appendix *3*~~6~~
EmiPref Patient Preference Questionnaire
~~(United Kingdom/English)~~

(Paper Version, United Kingdom / English)

...

SAMPLE INFORMED CONSENT FORMS

The sample Informed Consent Form and Assent Form have been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A SINGLE-ARM, MULTICENTER PHASE IIIB CLINICAL TRIAL TO EVALUATE THE SAFETY AND TOLERABILITY OF PROPHYLACTIC EMICIZUMAB IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	MO39129
VERSION NUMBER:	3
EUDRACT NUMBER:	2016-004366-25
TEST PRODUCT:	Emicizumab (RO5534262)
MEDICAL MONITOR:	Dr. [redacted] MD, MBA
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A SINGLE-ARM, MULTICENTER PHASE IIIB CLINICAL TRIAL TO EVALUATE THE SAFETY AND TOLERABILITY OF PROPHYLACTIC EMICIZUMAB IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	MO39129
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2016-004366-25
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	IIIb
INDICATION:	Hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety and tolerability of emicizumab in patients with *congenital* hemophilia A who have *persistent* inhibitors against Factor VIII (FVIII) at enrolment. Specific objectives and corresponding endpoints for the study are outlined below (Table 1).

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Objective:	
• To evaluate the overall safety and tolerability of prophylactic administration of emicizumab	• Incidence and severity of *all* adverse events, including thromboembolic *events*, *microangiopathic hemolytic anemia or* thrombotic microangiopathy (TMA) *(e.g. hemolytic uremic syndrome)*, systemic hypersensitivity, anaphylaxis, and anaphylactoid events • Changes in physical examination findings, vital signs, and laboratory parameters
Secondary Objective:	
• To evaluate the efficacy of prophylactic administration of emicizumab	• To evaluate the efficacy of prophylactic administration of emicizumab on the basis of the number of bleeds over time • To evaluate the HRQoL of patients according to Haem-A-QoL (≥ 18 y) or Haemo-QoL-SF (ages 12−17) scores over time • To evaluate the health status of patients according to EQ-5D-5L scores over time • To assess patient preference for the emicizumab regimen compared with the previous regimen used
Immunogenicity Objective:	
• To evaluate the immuno-genicity of emicizumab	• To assess the incidence and clinical significance of anti-emicizumab antibodies

Objectives	Corresponding Endpoints
PK Objective:	
• To obtain emicizumab PK data	• To obtain PK data for emicizumab at defined timepoints

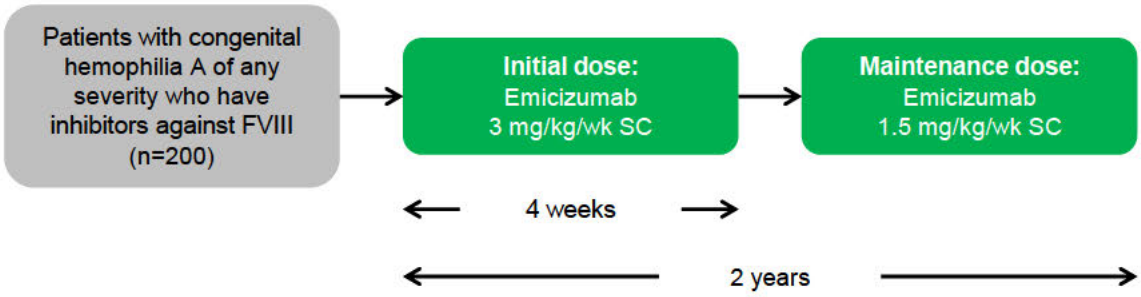
EQ-5D-5L=EuroQoL Five-Dimension-Five Levels Questionnaire; Haem-A-QoL=Hemophilia Adult Quality of Life Questionnaire; Haemo-QoL-SF=Hemophilia Quality of Life Short Form; HRQoL=Health-Related Quality of Life; PK=pharmacokinetic; TMA=thrombotic microangiopathy

Study Design

Description of Study

This single-arm, multicenter, open label, Phase IIIb clinical study will enroll patients aged 12 years or older with *congenital* hemophilia A who have persistent inhibitors against FVIII at enrollment. Approximately 200 patients with inhibitors will be enrolled globally. Patients will receive prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period (Figure 1).

Figure 1 Study Design



FVIII=Factor VIII; SC=subcutaneous

The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A who have persistent inhibitors against FVIII at enrollment. In order to achieve this objective, all adverse events, including adverse events of special interest, will be captured on an ongoing basis, as they occur during the study. Physical examinations, vital signs, and laboratory values will be assessed as per the Schedule of Activities (Appendix 1
Schedule of Activities
).

The secondary objective of this study is to evaluate the efficacy of prophylactic administration of emicizumab. As part of this objective, the number of bleeds over time will be recorded for all of the enrolled patients.

The final analysis will be conducted when all patients have completed 2 years of treatment or have withdrawn, whichever occurs sooner. Patients, or their legally authorized representative, will be asked to report bleed information *on an electronic patient-reported outcome (ePRO) device where possible*, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. Health-Related Quality of Life (HRQoL) will be assessed and the EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) will be completed prior to the first emicizumab administration *(Week 1)*, at the *Month* 3, 6, 12, and 18 assessments, and at study completion as outlined in the Schedule of Activities (Appendix 1
Schedule of Activities
). Additional secondary endpoints include assessing patient preference for the emicizumab regimen compared with the previous regimen using a questionnaire (EmiPref).

Immunogenicity will be monitored by incidence and clinical significance of antibodies to emicizumab. In addition, pharmacokinetic (PK) data for emicizumab will be obtained at defined timepoints as per

the Schedule of Activities (Appendix 1
Schedule of Activities
).

Drugs intended to control breakthrough bleeds (e.g. rFVII, FVIII, activated prothrombin complex concentrate [aPCC]) or bleeds during surgeries should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase the patient's coagulation potential, the doses required to achieve hemostasis may be lower than doses used prior to starting emicizumab. Investigators shall discuss at the start of the study with patients recommended doses of any additional coagulation factors used, following the guidance below.

The use of aPCC for breakthrough bleed treatment for patients on emicizumab should be avoided if possible, and recombinant activated human Factor VII (rFVIIa) should be the first option used to treat, starting with no more than 90 µg/kg as an initial dose. If aPCC needs to be used, no more than 50 IU/kg should be administered as an initial dose and doses of > 100 U/kg/24 hours or more should be avoided, as cases of TMA and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours aPCC was administered for 24 hours or more. Investigators should provide or remind patients of the exact dose and schedule of bypassing agents or FVIII required to treat any bleed.

When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information *on an ePRO device where possible*, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed (e.g., other than emicizumab in case of breakthrough bleeds). The reason for the use of rFVIIa will be documented (e.g., bleeding, preventative dose before activity). Thorough documentation of the treatments for bleeds *and/or surgeries* will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. Local and central laboratory assessments are required to monitor the risk for thromboembolic events or *microangiopathic hemolytic anemia or* TMA, as per the Schedule of Activities (Appendix 1
Schedule of Activities
), if bypassing agents are used to treat a breakthrough bleed.

Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of emicizumab in order to discuss a potential increase in emicizumab dose to 3 mg/kg/week and additional laboratory evaluations (e.g., coagulation tests), as well as to re-evaluate the patient's individual benefit-risk for continuing treatment.

An independent Data Monitoring Committee (iDMC) will be responsible for monitoring safety throughout the duration of the study.

Number of Patients

This global study will enroll approximately 200 patients with congenital hemophilia A *who have persistent* inhibitors against FVIII at enrollment. The patients are expected to be enrolled at approximately 85 sites globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. *As per the investigator's judgement, a w*illingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the patient-reported outcome (PRO) questionnaires and bleed diaries through the use of an electronic device *or paper*
3. Aged 12 years or older at the time of informed consent
4. Diagnosis of congenital hemophilia A with persistent inhibitors against FVIII
5. Documented treatment with bypassing agents or FVIII concentrates in the last 6 months (on-demand or prophylaxis). Prophylaxis needs to be discontinued the latest by a day before starting emicizumab

6. Adequate hematologic function, defined as platelet count ≥ 100,000/μL and hemoglobin ≥ 8 g/dL (≥ 4.97 mmol/L) at the time of screening
7. Adequate hepatic function, defined as total bilirubin ≤ 1.5 × the upper limit of normal (ULN) (excluding Gilbert's syndrome) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 ×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
8. Adequate renal function, defined as serum creatinine ≤ 2.5 × ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min
9. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method with a failure rate of < 1% per year during the treatment period and for at least five elimination half-lives (24 weeks) after the last dose of emicizumab:
    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
    - Examples of highly effective contraceptive methods with a failure rate of < 1% per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

<u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

1. Inherited or acquired bleeding disorder other than hemophilia A
2. Ongoing (or plan to receive during the study) immune tolerance induction (ITI) therapy (prophylaxis regimens with FVIII and/or bypassing agents must be discontinued prior to enrollment). Patients receiving ITI therapy will be eligible following the completion of a 72-hour washout period prior to the first emicizumab administration
3. History of illicit drug or alcohol abuse within 12 months prior to screening, as per the investigator's judgment
4. High risk for TMA (e.g., have a previous medical or family history of TMA), as per the investigator's judgment
5. Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or current signs of thromboembolic disease
6. Other conditions (e.g., certain autoimmune diseases) that may increase the risk of bleeding or thrombosis
7. History of a clinically significant hypersensitivity reaction associated with monoclonal antibody therapies or components of the emicizumab injection
8. Known human immunodeficiency virus (HIV) infection with CD4 count < 200 cells/μL within 6 months prior to screening
9. Use of systemic immunomodulators (e.g., interferon or rituximab) at enrollment or planned use during the study, with the exception of antiretroviral therapy

10. Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
11. Receipt of:
    - Emicizumab in a prior investigational study
    - An investigational drug to treat or reduce the risk of hemophilic bleeds within five half-lives of last drug administration
    - A non-hemophilia-related investigational drug within last 30 days or five half-lives, whichever is shorter
    - Any concurrent investigational drug.
12. Pregnancy or lactation, or intent to become pregnant during the study
13. Positive serum pregnancy test result within 7 days prior to initiation of *emicizumab* (females only)

End of Study and Length of Study

The approximate length of the entire study from the first patient enrolled to the last patient, last visit (LPLV; see below) is approximately 3 years. For each individual patient, the study is expected to last approximately 2 years (patients will receive 3 mg/kg/week emicizumab for the first 4 weeks followed by 1.5 mg/kg/week emicizumab for the remainder of the 2-year treatment period). *Patients who discontinue emicizumab prior to the completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first.*

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., LPLV). The study will end when all patients have been treated with emicizumab for 2 years, or earlier, if one of the following is documented:

Withdrawal of consent

OR

Completed the Safety Follow-up Visit 24 weeks after discontinuing emicizumab

OR

Lost to follow-up

OR

Death.

Investigational Medicinal Products

Test Product (Investigational Drug)

Emicizumab will be administered at a dose of 3 mg/kg/week subcutaneously for 4 weeks when initiating treatment, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period. There will be an option to increase the dose to 3 mg/kg/week in cases of insufficient control of bleeds on the 1.5 mg/kg/week emicizumab dose. If the investigator believes that a specific patient warrants dose up-titration following the occurrence of, for example, at least two spontaneous bleeds, significant bleeds, or a traumatic bleed out of proportion to the degree of injury, they must discuss the case with the Medical Monitor for consideration and potential approval.

To support home administration of the drug, patients/caregivers will be required to complete in-person, instructional training on how to administer emicizumab as a subcutaneous (SC) injection. Patients/caregivers will be taught to perform the injections utilizing the Instructions for Use document. *In addition, the healthcare provider (HCP) is to inform the patient/caregiver of the volumetric dose to be administered and the dosing frequency. The patients/caregivers* will observe at least one SC injection performed by a HCP and will need to successfully administer at least one SC injection under an HCP's supervision prior to starting home administration. *The patient/caregiver will also have the opportunity to ask any questions to the HCP before starting home administration.* The first three weekly treatments will be administered in a monitored setting, such as an infusion center, clinic, or hospital, in conjunction with emicizumab PK and pharmacodynamic (PD) assessments. Patients will be observed

for a minimum of 60 minutes after the first three doses. Patients/caregivers will be instructed on how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. Each site will have the discretion to provide additional training or include additional observation (e.g., after the third or fifth doses), if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject emicizumab, a trained and proficient caregiver or HCP should be identified to administer the SC injections. Patients/caregivers will be provided with contact information for the clinic in case they have questions related to self-administration between visits.

Compliance in the home setting is to be monitored at each site by reviewing reported hemophilia medication use and recording collected used and unused vials.

Statistical Methods

Primary Safety Analyses

The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A who have *persistent* inhibitors against FVIII at enrollment. Of primary interest in this study are the incidence and severity of *all* adverse events, including thromboembolic *events*, *microangiopathic hemolytic anemia or* TMA, systemic hypersensitivity, anaphylaxis, and anaphylactoid events.

All adverse events will be assessed according to the World Health Organization (WHO) toxicity grading scale. The incidence, type, and grade of adverse events will be summarized according to the primary system-organ class (SOC) and, within each SOC, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. For each adverse event, data will be provided on the timing (start and stop date, time of onset in comparison with last dose of emicizumab received, and doses of emicizumab received), severity, relationship to *emicizumab*, outcome, and effect on therapy. The data may be presented together with two-sided 95% Clopper-Pearson confidence intervals (CIs) if appropriate.

In addition, as part of the safety evaluation, additional assessments will be summarized descriptively as follows:

1. Cumulative *emicizumab* doses, dose modifications (delays and interruptions), and duration of exposure
2. Compliance with respect to emicizumab intake (planned vs. received)
3. Changes from baseline in physical examination findings
4. Vital signs over time:
    - Vital signs will be analyzed using descriptive statistics for continuous variables and presented graphically over time with associated 95% CIs.
5. Laboratory parameters (hematology and chemistry):
    - These parameters will be presented in shift tables of WHO toxicity grade at baseline versus worst grade during the treatment period. Selected laboratory parameters will be summarized in terms of mean, standard deviation, minimum, and maximum. Laboratory parameters will also be presented graphically over time.

All safety variables will be analyzed for the safety population. For each variable, the number of available observations will be reported. The safety population includes all patients who have received at least one dose of *emicizumab*.

The primary safety analysis will occur at the end of the study.

The iDMC will evaluate the study data, including the emerging safety results, at periodic reviews and recommend to the Sponsor whether the protocol should be amended or the study should be stopped early. All summaries and analyses will be prepared by the Study Management Team (SMT) statistician and presented for iDMC review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

A detailed description of the statistical methods that will be used for the primary and secondary analyses will be provided in the Statistical Analysis Plan (SAP).

Determination of Sample Size

A sample size of approximately 200 patients is planned for this study.

For the purpose of the sample size calculation, the incidence of adverse events was chosen as the safety endpoint of primary interest.

If the observed incidence of adverse events is between 2.5% and 15%, the precision for the estimated incidence rate is presented below according to the 95% Clopper-Pearson CIs (Table 2).

Table 2 Clopper-Pearson 95% CIs for the Incidence of AEs (Based on N=200)

Number of AE Events (Observed AE Incidence)	95% Clopper-Pearson CIs
5 (2.5%)	0.8%–5.7%
10 (5.0%)	2.4%–9.0%
20 (10.0%)	6.2%–15.0%
30 (15.0%)	10.4%–20.7%

AE=adverse event, CI=confidence interval

Interim Analyses

The first *interim* analysis will be performed once *approximately* 100 patients have received treatment with emicizumab for at least 24 weeks. A second *interim* analysis will be performed when *approximately* 100 patients have received treatment with emicizumab for at least 52 weeks. The data from these analyses will subsequently be presented to an iDMC in order to enable them to effectively monitor the study.

Details regarding the planned interim analyses will be provided in the SAP and iDMC charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	annualized bleeding rate
ADA	anti-drug antibody
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{τ}	area under the curve during the dosage interval
BU	Bethesda unit
BUN	blood urea nitrogen
CI	confidence interval
C_{max}	maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CRO	contract research organization
C_{trough}	concentration at the end of the dosage interval
CTX	*C-terminal telopeptide of collagen 1*
CVAD	central venous access device
CWA	clot waveform analysis
cyFcγR	cynomolgus monkey Fcγ receptor
EC	Ethics Committee
ECG	electrocardiogram
ECL	*electrochemiluminescence*
eCRF	electronic Case Report Form
EDC	electronic data capture
EDTA	*ethylenediaminetetraacetic acid*
ELISA	enzyme linked immunosorbent assay
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL Five-Dimension-Five Levels Questionnaire
EQ-VAS	EuroQoL visual analogue scale
E.U.	European Union
FDA	Food and Drug Administration
FEIBA	Factor eight inhibitor bypassing activity
FIX	Factor IX
FIXa	activated Factor IX
FIX:Ag	Factor IX antigen
FVIIa	activated Factor VII

Abbreviation	Definition
FVIII	Factor VIII
FVIII:Ag	Factor VIII antigen
FX	Factor X
FX:Ag	Factor X antigen
Haem-A-QoL	Hemophilia Adult Quality of Life Questionnaire
Haemo-QoL	Hemophilia Quality of Life
Haemo-QoL-SF	Hemophilia Quality of Life Short Form
HCP	healthcare provider
hFcγR	human Fcγ receptor
HIV	human immunodeficiency virus
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IFU	Instructions for Use
IgE	immunoglobulin E
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITI	immune tolerance induction
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice or web-based response system
LDH	lactate dehydrogenase
LPLV	last patient, last visit
MABEL	minimal anticipated biological effect level
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NIS	*non-interventional study*
NOAEL	no observed adverse effect level
OPG	*osteoprotegerin*
P1NP	*procollagen type 1 amino-terminal propeptide*
PD	pharmacodynamic(s)
pdFVIII	plasma-derived Factor VIII
PK	pharmacokinetic(s)
PRO	patient-reported outcome

Abbreviation	Definition
PT	prothrombin time
RANK-L	*receptor activator of nuclear factor kappa-B ligand*
RBC	red blood cell
rFVIIa	recombinant activated human Factor VII
rFVIII	recombinant Factor VIII
SAD	single ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
SMT	*Study Management Team*
SOC	system-organ class
SSC	Scientific and Standardization Committee
$t_{1/2}$	terminal plasma half-life
TMA	thrombotic microangiopathy
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
U.S.	United States
VAS	visual analog scale
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON HEMOPHILIA A WITH INHIBITORS

Hemophilia A is a rare bleeding disorder that is attributable to a congenital absence or hypofunctioning of Factor VIII (FVIII) (Acharya 2013; Witmer and Young 2013). The gene that encodes FVIII is located on the X chromosome. Genetic defects are expressed through X-linked recessive inheritance or *de novo* FVIII mutations, and more than 99% of hemophilia patients are males. The prevalence of hemophilia A is approximately 1 in 5,000 live-born males or 1 out of every 10,000 live births (CDC 2016; Franchini and Mannucci 2013; NIH 2013). No racial differences have been reported, and the numbers of patients registered in 2014 in various regions included 4,870 in Japan, 21,052 in North America, and 11,029 in just two European nations (United Kingdom and France) (World Federation of Hemophilia 2014).

Hemophilia A is most commonly caused by an inherited FVIII gene mutation within the Xq28 region of the X chromosome. It occurs almost exclusively in males who have one defective copy of the relevant gene on their X chromosome. As an affected male will transmit a normal Y chromosome to all his sons and an abnormal X chromosome to all his daughters, his sons will not be affected and all of his daughters will be carriers. For female carriers, with each birth there is a 50% chance to transmit the disorder to male infants and a 50% chance for female infants to be a carrier. Females who are carriers of hemophilia A may experience bleeding symptoms similar to those seen in men with mild hemophilia A, as approximately 10% of carriers have a FVIII activity that is less than 35% (Plug et al. 2006). Rarely, women have more severe bleeding symptoms requiring treatment and may develop FVIII inhibitors. Approximately 30% of patients with hemophilia A do not have a family history of the disorder; these cases arise from spontaneous FVIII gene mutations.

The main bleeding sites are intra-articular, intramuscular, subcutaneous (SC), intraoral, intracranial, gastrointestinal, and intranasal (Karaman et al. 2015; Srivastava et al. 2013). Repeated intra-articular bleeding is a major factor that decreases health-related quality of life (HRQoL) in patients with hemophilia A, because it may progress to hemophilic arthropathy with walking difficulties, and joint replacement surgery may eventually be necessary.

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of hemophilia A is classified in accordance with endogenous FVIII activity in the blood. Patients with FVIII activity of less than 1% have severe disease, those with activity between 1% and 5% have moderate disease, and those with activity greater than 5% and less than 40% have mild disease. Patients who have severe hemophilia who do not initiate and/or comply with rigorous FVIII prophylaxis regimens, or do not have access to FVIII products, experience bleeding episodes several times a month, which is much more frequent than in patients with moderate or mild disease. In addition, patients with severe hemophilia have a high frequency of spontaneous bleeding. Hence, the maintenance of plasma FVIII activity at 1% or higher is important to prevent the onset of recurrent bleeding episodes, reduce comorbidities such as arthropathy, and improve HRQoL in patients with severe hemophilia A (Srivastava et al. 2013).

The standard therapy for patients with hemophilia A is intravenous (IV) FVIII replacement therapy with recombinant Factor VIII (rFVIII) products or plasma-derived Factor VIII (pdFVIII) concentrates. FVIII replacement treatment regimens can be broadly categorized into two types: episodic or on-demand therapy (in which FVIII concentrates are administered in response to the occurrence of bleeding symptoms) and prophylactic (in which they are administered on a scheduled basis to prevent the onset of bleeding symptoms). Prophylaxis has been shown to markedly reduce the bleed rate in adult patients with severe hemophilia A (Manco-Johnson et al. 2013; Valentino et al. 2012). Prophylactic therapy aims to maintain FVIII activity levels above 1% or higher and effectively prevents the onset or progression of hemophilic arthropathy by providing a minimum concentration of FVIII to avert spontaneous bleeding, particularly in the case of repeated bleeding into joints. The treatment regimens used to achieve optimal prevention of bleeding events vary on an individual basis; some patients will need trough FVIII levels of 1%, whereas others require higher trough FVIII levels to achieve the desired therapeutic outcome (Ahnström et al. 2004; Collins et al. 2010). Current standard prophylactic regimens commonly use infusion therapy administered three times weekly; other regimens require every other day administration, depending on the patient's needs (Shapiro 2013). In developed countries, the availability and overall utilization of FVIII prophylaxis has increased in recent years due to the therapeutic advantages conferred by this type of therapy and expansion of the rFVIII concentrate supply (Geraghty et al. 2006). In such countries, the current standard of care for children with severe hemophilia A is primary prophylaxis, which involves regular FVIII infusions that are started following their first bleed, or by 2 years of age, with the aim of avoiding the development of any joint abnormality in the future (Astermark 2003; Manco-Johnson et al. 2007).

The required adherence to demanding therapeutic regimens, that involve frequent morning infusions to achieve adequate hemostatic coverage during periods of highest activity, reduces patient compliance thereby making these regimens less effective and compromising their cost-benefit ratio (Thornburg 2010). Major issues with current regimens are the need for adequate venous access and patient/family compliance with regular prophylaxis, especially in the very young pediatric population. In this population, central venous access devices (CVADs) have been used to overcome technical difficulties. Although CVADs make prophylaxis feasible in young children, they are associated with complications, including mechanical failure, dehiscence of the skin over the reservoir, infection, and thrombosis (Ewenstein et al. 2004). In addition, significant healthcare provider (HCP) efforts are required to manage optimal treatment solutions and to overcome identified issues (Schrijvers et al. 2013). Thus, both the disease and potential therapeutic options have the potential to affect HRQoL, the latter through limitations on daily activities.

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%−30% of patients with severe hemophilia A and in 3%−13% of those with moderate or mild disease (Franchini and Mannucci 2013). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with a history of a high-titer inhibitor (≥ 5 Bethesda units [BU]/mL) following a re-challenge with FVIII administration (high-responding inhibitor), the only hemostatic options currently available are pro-thrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., "bypassing agents"). Bypassing products include Factor eight inhibitor bypassing activity (FEIBA), an activated prothrombin complex concentrate (aPCC; FEIBA will be referred to as

aPCC throughout this document), and NovoSeven® (recombinant activated human Factor VII [rFVIIa]; NovoSeven® will be referred to as rFVIIa throughout this document) (Srivastava et al. 2013). Both of these products have been used as prophylactic therapies to prevent bleeding in patients with inhibitors against FVIII. However, in most countries, the only available product for this indication is the aPCC FEIBA.

aPCCs may be associated with side effects, such as thromboembolic events, hypersensitivity reactions, myocardial infarction, and disseminated intravascular coagulation (Bui et al. 2002; Dentali et al. 2011; Tjønnfjord 2004; Wójcik et al. 2009). Both aPCC and rFVIIa are administered intravenously, with aPCC prophylaxis requiring every other day dosing and rFVIIa requiring daily (or more frequent) dosing.

The development of effective prophylactic treatment options with less frequent dosing requirements is a high, unmet medical need in the population of patients with hemophilia A with FVIII inhibitors. Reducing the time and burden associated with frequent IV dosing and the impact of the disease on aspects of physical health and other areas of functioning and well-being, while promoting increased efficacy, may further improve HRQoL. This hypothesis is supported by a study in which patients receiving a prophylactic treatment with FEIBA had improved HRQoL than those who received episodic therapy (i.e., administered following bleeds) with FEIBA (Gringeri et al. 2013). Therefore, despite major therapeutic advances in the treatment of hemophilia A, opportunities still remain to optimize and transform therapy, in particular for patients with inhibitors.

1.2 BACKGROUND ON EMICIZUMAB

Emicizumab (also known as ACE910, CH5534262, and RO5534262) is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated Factor IX (FIXa) and Factor X (FX), thereby mimicking the co-factor function of FVIII. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. Emicizumab therefore has no potential to induce or enhance the development of direct inhibitors to FVIII or other coagulation factors. In addition, emicizumab offers the possibility of SC administration, removing the need for venous access. Finally, because of the expected pharmacokinetic (PK) properties of this antibody, markedly extending the dosing interval to once weekly or even more, this compound has the potential to improve the treatment of patients with hemophilia A with and without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

1.2.1 Preclinical Experience

As mentioned above, emicizumab binds with moderate affinity in the low µM range to FIXa and FX and mimics the co-factor activity of FVIII. Preclinical studies have shown that mimicking FVIII activity promotes the activation of FX by FIXa and subsequent activation of downstream coagulation factors, considerable increases in thrombin generation, and the achievement of hemostasis at the site of bleeding in patients with hemophilia A who have hypofunctional levels of, or entirely lack, FVIII, irrespective of the presence of FVIII inhibitors (Sampei et al. 2013). Preclinical studies investigating emicizumab binding to cynomolgus monkey Factor IX (FIX) and FX found that similar affinities were observed in both humans and monkeys. Mechanistic *in vitro* studies were conducted in human and cynomolgus FVIII-

neutralized plasma and in various coagulation factor-specific assay testing systems. These studies revealed that emicizumab shortened activated partial thromboplastin time (aPTT) and promoted thrombin generation.

Binding experiments of emicizumab to a panel of human Fcγ receptors (hFcγRs) and cynomolgus monkey Fcγ receptors (cyFcγRs) showed that comparable binding to hFcγR and to cyFcγR was observed with emicizumab and two commercial therapeutic antibodies, namely rituximab and natalizumab. Likewise, binding of emicizumab to the human and cynomolgus monkey neonatal Fc receptor was comparable to that of natalizumab.

In vivo pharmacology experiments were conducted using a hemophilia A cynomolgus monkey model where endogenous FVIII levels were neutralized by a FVIII specific monoclonal antibody. This model mimics the essential characteristics of patients with hemophilia A and was used to test *in vivo* pharmacodynamics (PD) and efficacy of emicizumab. In a needle−induced trauma investigation, the SC and IV administration of emicizumab inhibited the decrease in hemoglobin level compared with the control group and also significantly reduced the area of bruising on the skin surface. SC administration of high dose (200 mg/kg) emicizumab demonstrated pro-coagulant activity, with a significant reduction in bleeding tendency. In addition, increased levels of aPTT (due to FVIII neutralization) were completely normalized by 200 mg/kg emicizumab compared to untreated controls. In a cynomolgus monkey FVIII−neutralized hemophilia A spontaneous−bleeding investigation, emicizumab prevented intra-articular bleeding and other bleeding symptoms characteristic of hemophilia A following repeated weekly SC doses of 1 mg/kg/week subsequent to a single SC starting dose of 3.97 mg/kg. Overall, no increased bleeding tendency has been observed in any of the cynomolgus monkey studies.

Potential prothrombotic risks associated with emicizumab-induced FVIII mimetic activity were further explored in an *in vivo* cynomolgus monkey venous stasis model. In this model, thrombus formation was evaluated in the presence of emicizumab, FVIII, or bypass agents activated Factor VII (FVIIa). Emicizumab did not induce more thrombus formation than that seen with FVIIa and FVIII.

Overall, the preclinical pharmacology program is considered to have fully characterized the preclinical profile of emicizumab. The conducted *in vitro* and *in vivo* studies demonstrated the mode of action of emicizumab and provided supportive data on efficacious dose levels, through the use of a relevant hemophilia A disease model, which were subsequently used for dose extrapolation to humans.

The PK/toxicokinetics of emicizumab were assessed in cynomolgus monkeys after single and multiple doses were administered IV and through the intended clinical SC route. After a single IV dose of 6 mg/kg emicizumab to male cynomolgus monkeys, the plasma clearance was 3.69 mL/day/kg and the terminal plasma half-life ($t_{1/2}$) of emicizumab was 19.4 days. The volume of distribution at steady state (V_{ss}) was 98.1 mL/kg, which is approximately twice the plasma volume in monkeys, suggesting that emicizumab has low tissue penetration. A single SC administration study (dose levels: 0.06, 0.6, and 6 mg/kg) indicated that emicizumab exhibited slow (time to maximum plasma concentration [t_{max}]: 3.0−5.3 days) and complete absorption (bioavailability [BA]: 102% at 6 mg/kg). IV and SC multiple dosing studies (toxicokinetic monitoring) revealed a $t_{1/2}$ in the range of 14.9−30.8 days. Overall, exposures, in terms of maximum plasma concentration (C_{max}) and area under the curve

(AUC), increased in an approximately dose proportional manner. No differences in PK parameters were observed between sexes.

The formation of anti-emicizumab antibodies (which is expected with humanized monoclonal antibodies) was observed in a subset of the cynomolgus monkeys treated with repeated doses of emicizumab. In addition, a few animals also developed neutralizing antibodies. The formation of anti-emicizumab antibodies and neutralizing antibodies in cynomolgus monkeys is not thought to be predictive of the response observed in humans.

Acute and repeat-dose toxicity, including local tolerance assessments, were evaluated in cynomolgus monkeys in 4-, 13-, and 26-week SC dose toxicity studies (doses up to 30 mg/kg weekly) and a 4-week IV dose toxicity study (doses up to 100 mg/kg weekly). No toxicologically relevant changes attributable to the SC or IV administration of emicizumab were observed; the no observed adverse effect level (NOAEL) was the highest tested dose in each toxicity study.

Refer to the emicizumab Investigator's Brochure for additional details on the preclinical studies with emicizumab.

1.2.2 Clinical Experience

Currently available experience with emicizumab in humans includes data from two completed Phase I studies (ACE001JP and JP29574), one ongoing Phase I/II study (ACE002JP) extension in hemophilia A patients, and two ongoing Phase III studies in hemophilia A patients with inhibitors (adult patients - BH29884; pediatric patients – BH29992).

The clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) is ongoing for emicizumab. Refer to the emicizumab Investigator's Brochure for details on the preclinical and clinical studies.

1.2.2.1 *Studies ACE001JP and ACE002JP*

ACE001JP was a single study conducted in three parts, which included both healthy subjects (Part A and Part B) and patients with hemophilia A (Part C). The objective of Parts A and B in healthy subjects was to investigate the tolerability, safety, PK, and PD response of SC-administered emicizumab in adult Japanese and Caucasian men and to evaluate for racial differences, if any, in their PK and PD response. A total of 64 healthy *male* volunteers were enrolled in Parts A and B. In Part C, the objective was to investigate the tolerability, safety, PK, and PD response of SC-administered emicizumab in patients *12–59 years of age* with *congenital* hemophilia A *who* had previous documentation of bleeds and/or coagulation factor treatment in the last 6 months. A total of 18 patients were enrolled *in Part C*.

Patients who participated in Part C of Study ACE001JP were offered the opportunity to continue in the extension study (ACE002JP). In order to be eligible for the extension study, patients must have completed 12 weeks of assigned treatment in Study ACE001JP and had bleeds prior to study entry.

After administration of emicizumab to patients with hemophilia A, annualized bleeding rates (ABRs) decreased in all patients in Studies ACE001JP and ACE002JP compared with the pre-treatment period, regardless of whether or not they had FVIII inhibitors, with the exception of one patient in the

3 mg/kg/week group who was previously treated with FVIII prophylaxis and had a baseline ABR of 0 (in this patient, the ABR was maintained at 0 while receiving emicizumab). Among all patients, percentage reduction in ABR ranged from 22.8% to 100% in the 0.3 mg/kg/week group, from 57.5% to 100% in the 1 mg/kg/week group, and from 90.1% to 100% in the 3 mg/kg/week group.

The safety data from completed studies of healthy male volunteers (Japanese and Caucasian) in ACE001JP Parts A and B (n=48) showed that emicizumab was well tolerated and the incidence of adverse events was similar in the emicizumab dosing groups and the placebo group. Moreover, no racial differences or dose-dependent increases in the incidence of adverse events were observed. There were no serious adverse events, adverse events leading to discontinuation, or deaths in either study. From ACE001JP Part C and its ongoing extension ACE002JP (as of the cut-off date 15 February 2016), most adverse events were of mild or moderate intensity, except for 2 severe adverse events (appendicitis and mesenteric hematoma). The majority of the adverse events were not considered related to emicizumab (see the Emicizumab Investigator's Brochure).

1.2.2.2 *JP29574*

Completed Study JP29574 included 5 groups of 12 healthy Japanese volunteers. This study investigated the relative bioavailability between Phase I/II 80 mg/mL formulation and Phase III 150 mg/mL formulation materials and among three different sites of injection, as well as the absolute bioavailability. Results showed no significant difference in the incidence of adverse events observed by formulation, injection site, or administration route.

1.2.2.3 *Studies BH29884 and BH29992*

The HAVEN 1 study (BH29884; NCT02622321) was a randomized, multicenter, open-label, clinical trial in 109 adult and adolescent males (aged 12 to 75 years and > 40 kg) with hemophilia A with FVIII inhibitors who previously received either episodic (on-demand) or prophylactic treatment with bypassing agents. Patients received weekly emicizumab prophylaxis (Arms A, C, and D), 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter, or no prophylaxis (Arm B). Dose up-titration to 3 mg/kg once weekly was allowed after 24 weeks on emicizumab prophylaxis in case of suboptimal efficacy (i.e., ≥ 2 spontaneous and clinically significant bleeds). During the study, two patients underwent up-titration of their maintenance dose to 3 mg/kg once weekly.

Fifty-three patients previously treated with episodic (on-demand) bypassing agents were randomized in a 2:1 ratio to receive emicizumab prophylaxis (Arm A) or no prophylaxis (Arm B), with stratification by prior 24-week bleed rate (< 9 or ≥ 9). Patients randomized to Arm B could switch to emicizumab prophylaxis after completing at least 24 weeks without prophylaxis.

Forty-nine patients previously treated with prophylactic bypassing agents were enrolled into Arm C to receive emicizumab prophylaxis. Seven patients previously treated with episodic (on-demand) bypassing agents who had participated in a non-interventional study (NIS) prior to enrollment, but were unable to enroll into HAVEN 1 prior to the closure of Arms A and B, were enrolled into Arm D to receive emicizumab prophylaxis.

Efficacy was evaluated based on the ABR requiring treatment with coagulation factors (minimum of 24 weeks or date of discontinuation) among patients previously treated with episodic bypassing

agents who were randomized to emicizumab prophylaxis (Arm A) compared with those receiving no prophylaxis (Arm B). The trial also evaluated the randomized comparison of Arms A and B for the efficacy of weekly emicizumab prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds, as well as patient-reported symptoms and physical functioning.

The study also evaluated the efficacy of weekly emicizumab prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agents in patients who had participated in the NIS prior to enrollment (Arms A and C, respectively). Only patients from the NIS were included in this comparison, because bleed and treatment data were collected with the same level of granularity in both periods.

The efficacy results of emicizumab prophylaxis compared with no prophylaxis in bleed rate for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds are shown in Table 1.

Table 2 Annualized Bleed Rate with Emicizumab Prophylaxis Arm versus No Prophylaxis Arm in Patients ≥ 12 Years of Age

Endpoint	*Emicizumab Prophylaxis (N = 35)*	*No Prophylaxis (N = 18)*
Treated Bleeds		
ABR (95% CI) [a]	*2.9 (1.7, 5.0)*	*23.3 (12.3, 43.9)*
% reduction (95% CI) *p-value*	*87% (72.3%, 94.3%)* *< 0.0001*	
% patients with 0 bleeds (95% CI)	*62.9 (44.9, 78.5)*	*5.6 (0.1, 27.3)*
Median ABR (IQR)	*0 (0, 3.7)*	*18.8 (13.0, 35.1)*
All Bleeds		
ABR (95% CI) [a]	*5.5 (3.6, 8.6)*	*28.3 (16.8, 47.8)*
% reduction (95% CI) *p-value*	*80% (62.5%, 89.8%)* *< 0.0001*	
% patients with 0 bleeds (95% CI)	*37.1 (21.5, 55.1)*	*5.6 (0.1, 27.3)*
Treated Spontaneous Bleeds		
ABR (95% CI) [a]	*1.3 (0.7, 2.2)*	*16.8 (9.9, 28.3)*
% reduction (95% CI) *p-value*	*92% (84.6%, 96.3%)* *< 0.0001*	
% patients with 0 bleeds (95% CI)	*68.6 (50.7, 83.1)*	*11.1 (1.4, 34.7)*
Treated Joint Bleeds		
ABR (95% CI) [a]	*0.8 (0.3, 2.2)*	*6.7 (2.0, 22.4)*
% reduction (95% CI) *p-value*	*89% (48%, 97.5%)* *0.0050*	
% patients with 0 bleeds (95% CI)	*85.7 (69.7, 95.2)*	*50.0 (26.0, 74.0)*
Treated Target Joint Bleeds		
ABR (95% CI) [a]	*0.1 (0.03, 0.6)*	*3.0 (1.0, 9.1)*

Endpoint	Emicizumab Prophylaxis (N = 35)	No Prophylaxis (N = 18)
% reduction (95% CI) p-value	95% (77.3%, 99.1%) 0.0002	
% patients with 0 bleeds (95% CI)	94.3 (80.8, 99.3)	50.0 (26.0, 74.0)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

a. Based on negative binomial regression.

In the intra-patient analysis, emicizumab prophylaxis resulted in a statistically significant (p = 0.0003) reduction (79%) in bleed rate for treated bleeds compared with previous bypassing agent prophylaxis collected in the NIS prior to enrollment (Table 2).

Table 3 **Intra-Patient Comparison of Annualized Bleed Rate with Emicizumab Prophylaxis versus Previous Bypassing Agent Prophylaxis**

Endpoint	Emicizumab Prophylaxis (N = 24)	Previous Bypassing Agent Prophylaxis (N = 24)
Treated Bleeds		
ABR (95% CI) [a]	3.3 (1.3, 8.1)	15.7 (11.1, 22.3)
% reduction (95% CI) p-value	79% (51.4%, 91.1%) 0.0003	
% patients with 0 bleeds (95% CI)	70.8 (48.9, 87.4)	12.5 (2.7, 32.4)
Median ABR (IQR)	0 (0, 2.2)	12 (5.7, 24.2)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

a. Based on negative binomial regression.

The study evaluated patient-reported hemophilia-related symptoms (painful swellings and presence of joint pain) and physical functioning (pain with movement and difficulty walking far) using the Physical Health Score of the Haemophilia Adult Quality of Life Questionnaire (Haem-A-QoL) for patients aged ≥ 18 years. The weekly emicizumab prophylaxis arm (Arm A) showed an improvement compared with the no prophylaxis arm (Arm B) in the Haem-A-QoL Physical Health Subscale score at the Week 25 assessment (Table 3). The improvement in the Physical Health Score was further supported by the Total Score as measured by the Haem-A-QoL at Week 25.

Table 4 *Change in Haem-A-QoL Physical Health Score in Patients (≥ 18 Years of Age) with No Prophylaxis versus Emicizumab Prophylaxis at Week 25*

Haem-A-QoL Scores at week 25	*Emicizumab Prophylaxis (N = 25 [a])*	*No Prophylaxis (N = 14 [a])*
Physical Health Score (Score range 0 to 100) [b]		
Adjusted mean [c]	*32.6*	*54.2*
Difference in adjusted means (95% CI)	*21.6 (7.9, 35.2)*	
p-value	*0.0029*	

a. *Number of patients ≥ 18 years who completed the Haem-A-QoL questionnaire.*
b. *Lower scores are reflective of better functioning.*
c. *Adjusted for baseline, and baseline by treatment group interaction.*

The HAVEN 2 study (BH29992; NCT02795767) was a single-arm, multicenter, open-label, clinical study in pediatric males (age < 12 years, or 12–17 years who weigh < 40 kg) with hemophilia A with FVIII inhibitors. Patients received emicizumab prophylaxis at 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter.

The study evaluated the efficacy of weekly emicizumab prophylaxis, including the efficacy of weekly emicizumab prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agent treatment in patients who had participated in a NIS prior to enrollment (intra-patient analysis).

At the time of the interim analysis, efficacy was evaluated in 23 pediatric patients who were < 12 years old and had been receiving weekly emicizumab prophylaxis for at least 12 weeks, including 19 patients age 6 to < 12 years and 4 patients age 2 to < 6 years.

ABR and percent of patients with zero bleeds were calculated for 23 patients (Table 4). The median observation time for these patients was 38.1 weeks (12.7–41.6 weeks).

Table 5 *Annualized Bleed Rate with Emicizumab Prophylaxis in Pediatric Patients < 12 Years of Age (Interim Analysis)*

Endpoint	*ABR [a] (95% CI) N = 23*	*Median ABR (IQR) N = 23*	*% Zero Bleeds (95% CI) N = 23*
Treated Bleeds	*0.2 (0.1, 0.6)*	*0 (0, 0)*	*87 (66.4, 97.2)*
All Bleeds	*2.9 (1.8, 4.9)*	*1.5 (0, 4.5)*	*34.8 (16.4, 57.3)*
Treated Spontaneous Bleeds	*0.1 (0, 0.5)*	*0 (0, 0)*	*95.7 (78.1, 99.9)*
Treated Joint Bleeds	*0.1 (0, 0.5)*	*0 (0, 0)*	*95.7 (78.1, 99.9)*
Treated Target Joint Bleeds	*Not Estimable [b]*	*0 (0, 0)*	*100 (85.2, 100)*

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

a. *Based on negative binomial regression*
b. *No treated target joint bleeds reported*

In the intra-patient analysis, 13 pediatric patients who had participated in the NIS had an ABR of 17.2 (95% CI [12.4, 23.8]) on previous bypassing agent treatment (prophylactic treatment in 12

patients and on-demand treatment for one patient). Weekly emicizumab prophylaxis resulted in an ABR for treated bleeds of 0.2 (95% CI [0.1, 0.8]) based on negative binomial regression, corresponding to a 99% reduction in bleed rate. On emicizumab prophylaxis, 11 patients (84.6%) had zero treated bleeds.

Safety

The following adverse reactions are based on pooled data from a randomized trial (HAVEN 1), single-arm trial (HAVEN 2), and a dose-finding trial, in which a total of 189 male patients with hemophilia A received at least one dose of emicizumab as routine prophylaxis. Ninety-four patients (50%) were adults (18 years and older), 38 (20%) were adolescents (12 years up to less than 18 years), 55 (29%) were children (2 years up to less than 12 years), and two (1%) were infants (1 month up to less than 2 years). Seven of the 189 patients (4%) included in the safety population were patients without FVIII inhibitors from the dose-finding trial. The median duration of exposure across the studies was 38 weeks (0.8 to 177.2 weeks).

The most frequently reported adverse reactions observed in ≥ 10% of patients treated with at least one dose of emicizumab were injection-site reactions (ISRs), headache, and arthralgia.

Four patients (2.1%) in the clinical trials receiving emicizumab prophylaxis withdrew from treatment due to adverse reactions, which were thrombotic microangiopathy (TMA), skin necrosis and superficial thrombophlebitis, and ISR.

Adverse reactions observed in patients who received emicizumab are shown in Table 5.

Table 6 Adverse Reactions Reported in ≥ 5% of Patients from Pooled Clinical Trials with Emicizumab

Body System	*Adverse Reaction*	*Number of Patients n (%) (N = 189)*
General Disorders and Administration Site Conditions	*Injection site reaction [a]*	*35 (19%)*
	Pyrexia	*13 (7%)*
Nervous System Disorders	*Headache*	*28 (15%)*
Gastrointestinal Disorders	*Diarrhea*	*12 (6%)*
Musculoskeletal and Connective Tissue Disorders	*Arthralgia*	*18 (10%)*
	Myalgia	*9 (5%)*

a. *Includes injection site bruising, injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticarial, and injection site warmth.*

Characterization of aPCC Treatment in Pooled Clinical Trials

There were 125 instances of aPCC treatment in 36 patients, of which 13 instances (10.4%) consisted of on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more; two of the 13 were associated with thrombotic events and three of the 13 were associated with TMA (Table 6). No TMA or thrombotic events were associated with the remaining instances of aPCC treatment.

Table 7 Characterization of aPCC Treatment in Pooled Clinical Trials

Duration of aPCC treatment	Average cumulative amount of aPCC over 24 hours (U/kg/24 hours)		
	< 50	50 – 100	> 100
< 24 hours	7	76	18
24 – 48 hours	0	6	3 [b]
> 48 hours	1	4	10 [a,a,a,b]

* *An instance of aPCC treatment is defined as all doses of aPCC received by a patient, for any reason, until there was a 36-hour treatment-free break.*

a. *Thrombotic microangiopathy*

b. *Thrombotic event*

Injection Site Reactions

In total, 35 patients (19%) reported ISRs. All ISRs observed in emicizumab clinical trials were reported as mild to moderate intensity and 88% resolved without treatment. The commonly reported ISR symptoms were injection site erythema (7.4%), injection site pruritus (5.3%), and injection site pain (5.3%).

1.2.2.4 *Pharmacokinetics*

Emicizumab exhibited linear PK in healthy adult male volunteers in Study ACE001JP. Following a single SC injection, the elimination $t_{1/2}$ (4–5 weeks) of emicizumab was similar to that of other human IgG antibodies.

Following repeated SC administration to patients with hemophilia A in Study ACE001JP/ACE002JP (cut-off date 15[h] February 2016), emicizumab trough plasma concentrations have increased in a dose-proportional manner with weekly injections across the dosing groups (0.3, 1, and 3 mg/kg/week). Furthermore, a plateau (steady state) has been achieved after approximately 12 weeks in the first two dose groups (in which a loading dose was administered) and after approximately 24 weeks in the highest dose group, in which no loading dose was administered.

Based on data from Study JP29574 in healthy Japanese subjects, comparison of PK profiles between Japanese and Caucasian healthy volunteers did not reveal racial differences. *Also, similar PK profiles were observed following SC injections in abdomen, upper arm, and thigh, which suggests that emicizumab can be interchangeably injected in these three locations.*

1.2.2.5 *Anti-drug Antibodies*

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to emicizumab-kxwh in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of emicizumab was evaluated using an enzyme-linked immunosorbent assay (ELISA) or an electrochemiluminescence (ECL) assay. No patients tested positive for anti-emicizumab antibodies in HAVEN 1 and HAVEN 2 (n = 171). Four patients tested positive for anti-emicizumab antibodies in the dose-finding trial (n = 18). The anti-emicizumab antibody positive rate may be under-reported due to the limitation of the assay (US Prescribing Information).

1.2.2.6 *Peri-Operative Management of Patients on Emicizumab*

The safety and efficacy of emicizumab has not been specifically tested in patients undergoing procedures or surgeries. Limited data are available from pivotal clinical trials, where hemophilia A patients with inhibitors receiving emicizumab prophylaxis underwent procedures and surgeries, either with or without the additional use of bypassing agents. The use of bypassing agents was at the investigator's discretion.

Procedures/surgeries that were performed without peri-operative bypassing agent use and did not result in a bleed included skin biopsy, tooth extraction or restoration, esophagogastroduodenoscopy with biopsy, ultrasound fluid aspiration, and port or central line removal. Other procedures/surgeries which were performed with peri-operative bypassing agent use (preventive and/or treatment for bleeds) included central line catheter placement, tooth extractions and appendectomy. One hip replacement was performed with peri-operative bypassing agent (rFVIIa) and FVIII use (preventive and treatment for bleed) as well as tranexamic acid.

No emicizumab dose adjustments are recommended for patients undergoing procedures or surgeries. Thorough documentation of surgeries will be requested.

The available data are insufficient to provide specific dosing guidance for the use of bypassing agents or FVIII in peri-operative settings. If bypassing agents or FVIII are required in the peri-operative period, please refer to the dosing guidance for those concomitant medications in Section 4.4 and in the emicizumab Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

For patients with hemophilia A who are diagnosed with inhibitors, permanent eradication of these inhibitors is currently the ultimate aim of therapy. This can be achieved by means of intensive FVIII administration over many months with immune tolerance induction (ITI), which is successful in approximately 60%−80% of treated patients with inhibitors (Hay and DiMichele 2012; Santagostino et al. 2009). However, effective hemostatic management may be challenging during the time interval required to achieve ITI success. Furthermore, ITI is not viewed as a viable option for patients with inhibitors in many countries, owing to its high cost, the scarce local supply of FVIII concentrates, practical issues and potential complications associated with CVADs, and the psychological stress on patients and their families of this highly demanding therapeutic endeavor. Finally, even with successful implementation, ITI will fail to eradicate inhibitors in a sizeable proportion (21%−47%) of treated patients (Mariani et al. 2003).

For those patients with inhibitors who are unable to eradicate their inhibitors or are not candidates for ITI, bypassing agents are required to treat or prevent bleeds. Unfortunately, the hemostatic effect of bypassing agents is unstable in comparison with that of FVIII concentrates. In addition, as opposed to the 8−12-hour $t_{1/2}$ and 15−20-minute infusion time

of FVIII, rFVIIa has a short $t_{1/2}$ of only 2−3 hours and aPCC requires a 25−50-minute infusion (with a $t_{1/2}$ of 4−7 hours). rFVIIa therefore requires frequent and aPCC requires extended IV infusions. In practice, some patients with inhibitors will have bleeds that respond better to rFVIIa while other patients will respond better to aPCC. Several publications evaluating the efficacy of prophylactic therapy in adults and children with the bypassing agents rFVIIa (Konkle et al. 2007) and aPCC (Antunes et al. 2014; Ettingshausen and Kreuz 2010; Leissinger et al. 2011, 2007) indicated that these treatments decreased bleeding rates compared with episodic treatment. Following the clinical results obtained, aPCC was approved by the Food and Drug Administration (FDA) as a prophylactic treatment in inhibitor patients in December 2013. Despite this, the use of prophylactic bypassing agents has yet to be established as the standard of care.

Given the hemostatic management challenges in adults and children with inhibitors, there is a clinical need for therapeutics that have a lower treatment burden, more reliable efficacy, and an extended $t_{1/2}$ that can be used for preventing bleeding in patients with hemophilia A.

In the Phase I/II study (ACE001JP) 18 Japanese patients with hemophilia A, either with or without inhibitors, were treated with emicizumab at three different dosing regimens (0.3 mg/kg/week, 1 mg/kg/week, or 3 mg/kg/week). During the course of emicizumab administration, the ABR significantly decreased in all patients compared with the ABR prior to study enrollment, regardless of whether or not the patient had inhibitors, with the exception of one patient without inhibitors in the 3 mg/kg/week group (see Section 1.2.2).

Emicizumab has been well tolerated in patients in the Phase I/II studies (cut-off date 15th February 2016). The majority of adverse events have been mild in intensity, with the most common being *ISRs*. The majority of the adverse events have not been considered to be related to emicizumab. In these studies, no thromboembolic or systemic hypersensitivity adverse events have been observed. However, as of *April 2017*, *three* cases of TMA, and *three* thromboembolic events *in two patients,* have been observed in the ongoing Phase III Study BH29884 in patients who received emicizumab as well as bypassing agents for the treatment of breakthrough bleeds. *Four* of these patients have fully recovered and the *fifth patient died (death due to serious adverse event of rectal haemorrhage unrelated to emicizumab, with the TMA related to emicizumab and aPCC)* (see Sections 0 and 0).

Given the unmet need to develop novel therapeutics for use in hemophilia A patients with inhibitors and the positive risk-benefit assessment observed, a Phase IIIb safety study with emicizumab is warranted in this patient population.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety and tolerability of emicizumab in patients with *congenital* hemophilia A who have *persistent* inhibitors against FVIII at enrollment. Specific objectives and corresponding endpoints for the study are outlined below (Table).

Table 8 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Objective:	
• To evaluate the overall safety and tolerability of prophylactic administration of emicizumab	• Incidence and severity of *all* adverse events, including thromboembolic *events, microangiopathic hemolytic anemia or* TMA *(e.g. hemolytic uremic syndrome),* systemic hypersensitivity, anaphylaxis, and anaphylactoid events • Changes in physical examination findings, vital signs, and laboratory parameters
Secondary Objective:	
• To evaluate the efficacy of prophylactic administration of emicizumab	• To evaluate the efficacy of prophylactic administration of emicizumab on the basis of the number of bleeds over time • To evaluate the HRQoL of patients according to Haem-A-QoL (≥ 18 y) or Haemo-QoL-SF (ages 12−17) scores over time • To evaluate the health status of patients according to EQ-5D-5L scores over time • To assess patient preference for the emicizumab regimen compared with the previous regimen used
Immunogenicity Objective:	
• To evaluate the immunogenicity of emicizumab	• To assess the incidence and clinical significance of anti-emicizumab antibodies
PK Objective:	
• To obtain emicizumab PK data	• To obtain PK data for emicizumab at defined timepoints

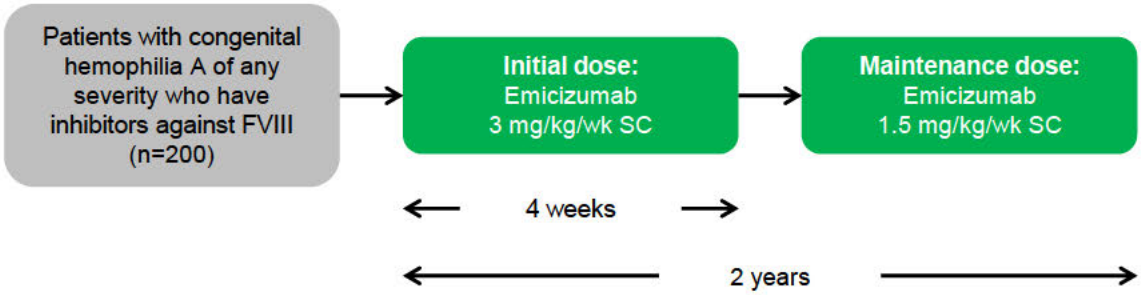
EQ-5D-5L=EuroQoL Five-Dimension-Five Levels Questionnaire; Haem-A-QoL=Hemophilia Adult Quality of Life Questionnaire; Haemo-QoL-SF=Hemophilia Quality of Life Short Form; HRQoL=Health-Related Quality of Life; PK=pharmacokinetic; TMA=thrombotic microangiopathy

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This single-arm, multicenter, open label Phase IIIb clinical study will enroll patients aged 12 years or older with *congenital* hemophilia A who have persistent inhibitors against FVIII at enrollment. Approximately 200 patients with inhibitors will be enrolled globally. Patients will receive prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period (Figure 1).

Figure 1 Study Design



FVIII=Factor VIII; SC=subcutaneous

The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A who have persistent inhibitors against FVIII at enrollment. In order to achieve this objective, all adverse events, including adverse events of special interest, will be captured on an ongoing basis, as they occur during the study. Physical examinations, vital signs, and laboratory values will be assessed as per the Schedule of Activities (Appendix 1
Schedule of Activities
).

The secondary objective of this study is to evaluate the efficacy of prophylactic administration of emicizumab. As part of this objective, the number of bleeds over time will be recorded for all of the enrolled patients.

The final analysis will be conducted when all patients have completed 2 years of treatment or have withdrawn, whichever occurs sooner. Patients, or their legally authorized representative, will be asked to report bleed information *on an electronic patient-reported outcome (ePRO) device where possible*, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. HRQoL will be assessed and the EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) will be completed prior to the first emicizumab administration *(Week 1)*, at the *Month* 3, 6, 12, and 18 assessments, and at study completion as outlined in the Schedule of Activities (Appendix 1
Schedule of Activities
). Additional secondary endpoints include assessing patient preference for the emicizumab regimen compared with the previous regimen using a questionnaire (EmiPref).

Immunogenicity will be monitored by incidence and clinical significance of antibodies to emicizumab. In addition, PK data for emicizumab will be obtained at defined timepoints as per the Schedule of Activities (Appendix 1
Schedule of Activities
).

Drugs intended to control breakthrough bleeds (e.g. rFVII, FVIII, aPCC) or bleeds during surgeries should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase the patient's coagulation potential, the doses required to achieve hemostasis may be lower than doses used prior to starting emicizumab. Investigators shall discuss at the start of the

study with patients recommended doses of any additional coagulation factors used, following the guidance below.

The use of aPCC for breakthrough bleed treatment for patients on emicizumab should be avoided if possible, and rFVIIa should be the first option used to treat, starting with no more than 90 µg/kg as an initial dose. If aPCC needs to be used, no more than 50 IU/kg should be administered as an initial dose and doses of > 100 U/kg/24 hours or more should be avoided, as cases of TMA and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours aPCC was administered for 24 hours or more. Investigators should provide or remind patients of the exact dose and schedule of bypassing agents or FVIII required to treat any bleed.

When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information *on an ePRO device where possible*, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed (e.g., other than emicizumab in case of breakthrough bleeds). The reason for the use of rFVIIa will be documented (e.g., bleeding, preventative dose before activity). Thorough documentation of the treatments for bleeds *and/or surgeries* will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. Local and central laboratory assessments are required to monitor the risk for thromboembolic events or *microangiopathic hemolytic anemia or* TMA, as per the Schedule of Activities (Appendix 1
Schedule of Activities

), if bypassing agents are used to treat a breakthrough bleed.

Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of emicizumab in order to discuss a potential increase in emicizumab dose to 3 mg/kg/week and additional laboratory evaluations (e.g., coagulation tests), as well as to re-evaluate the patient's individual benefit-risk for continuing treatment.

An independent Data Monitoring Committee (iDMC) will be responsible for monitoring safety the duration of the study.

3.2 END OF STUDY AND LENGTH OF STUDY

The approximate length of the entire study from the first patient enrolled to the last patient, last visit (LPLV; see below) is approximately 3 years. For each individual patient, the study is expected to last approximately 2 years (patients will receive 3 mg/kg/week emicizumab for the first 4 weeks followed by 1.5 mg/kg/week emicizumab for the remainder of the 2-year treatment period). *Patients who discontinue emicizumab prior to the completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first.*

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., LPLV). The study will end when all patients have been treated with emicizumab for 2 years, or earlier, if one of the following is documented:

Withdrawal of consent

OR

Completed the Safety Follow-up Visit 24 weeks after discontinuing emicizumab

OR

Lost to follow-up

OR

Death.

3.3 RATIONALE FOR STUDY DESIGN

The primary *objective* of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A *who have persistent inhibitors against FVIII*. This study is being conducted to build on the safety data that have been obtained as part of the clinical program. The results from this study will be used to substantiate the safety database and provide long-term additional data in patients with hemophilia A who have inhibitors against FVIII. The specific focus will be to characterize any thromboembolic events, *microangiopathic hemolytic anemia or* TMA, *systemic* hypersensitivity reactions*, anaphylaxis and anaphylactoid events* that may occur in patients with hemophilia A treated with emicizumab.

The study will enroll approximately 200 patients who will receive emicizumab over a 2-year treatment period. This study design has been proposed to permit the long-term evaluation of the safety and tolerability of emicizumab in a large population of patients with hemophilia A.

3.3.1 Rationale for Emicizumab Dose and Schedule

In this study, patients will initially receive prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period.

The safety results from studies ACE001JP/ACE002JP and BH29884 have *shown* that emicizumab has been well tolerated in patients with hemophilia A. The maximum clinical dose of 3 mg/kg weekly is associated with a 10.3-fold and 11.2-fold safety margin based on C_{max} and area under the curve during the dosage interval (AUC_T) results, respectively. No clear differences in the plasma concentrations of emicizumab have been observed between adolescent and adult patients.

A substantial reduction in bleeding events has been observed following prophylactic emicizumab treatment, especially at doses ≥ 1 mg/kg weekly (Table 9). ABR decreased in all patients, regardless of age or the presence of FVIII inhibitors.

Table 9 Mean Change (%) in Annualized Bleeding Rates in Patients Enrolled in ACE001JP/ACE002JP

Emicizumab dose	0.3 mg/kg weekly	1 mg/kg weekly	3 mg/kg weekly
ABR reduction	-74.5	-86.2	-96.5

ABR=annualized bleeding rate

Median ABRs of 1 and 0 were achieved with weekly maintenance doses of 1 and 3 mg/kg emicizumab.

In study BH29884, the ABR was 2.9 events (95% CI, 1.7 to 5.0) among participants who were randomly assigned to emicizumab prophylaxis (Group A, 35 participants) versus 23.3 events (95% CI, 12.3 to 43.9) among those assigned to no prophylaxis (Group B, 18 participants), representing a significant difference of 87% in favor of emicizumab prophylaxis (p<0.001). A total of 22 participants in Group A (63%) had zero bleeding events, as compared with 1 participant (6%) in Group B. Among 24 participants in Group C who had participated in a NIS, emicizumab prophylaxis resulted in a bleeding rate that was significantly lower by 79% than the rate with previous bypassing-agent prophylaxis (p<0.001) (Oldenburg et al. 2017).

The exposure-response relationship for emicizumab was quantitatively characterized and simulations suggested that the trough concentration of emicizumab needed for almost complete inhibition of bleeding onset is ≥ 45 µg/mL. On the basis of population PK modeling, a median trough plasma concentration of 45 µg/mL is predicted to be achieved after treatment with 4 weekly doses of 3 mg/kg and maintained, thereafter, with weekly doses of 1.5 mg/kg. In light of this finding, the loading dose of 3 mg/kg emicizumab per week for 4 weeks was chosen in order to rapidly achieve the effective trough concentration of 45 µg/mL without exceeding the maximum dose of 3 mg/kg weekly investigated in the Phase I/II studies. Thereafter, a dose and schedule of 1.5 mg/kg weekly was chosen in order to reduce the peak-trough fluctuations and to maintain emicizumab plasma concentrations above 45 µg/mL over the entire dosing interval. This dosing regimen (i.e., 3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly) will, therefore, be investigated in this study.

A study duration of approximately 2 years for each individual patient has been chosen in order to thoroughly assess the long-term safety of prophylactic use of emicizumab.

3.3.2 Rationale for Patient Population

Patients with congenital hemophilia A *who have persistent* inhibitors against FVIII at enrollment will comprise the primary population for this Phase IIIb study investigating the safety, *tolerability,* efficacy, immunogenicity, and PK of prophylactic administration of emicizumab.

Patients may have received episodic or prophylactic treatment before enrollment; at least one documented treatment with bypassing agents or FVIII concentrates is required within the last 6 months to indicate the need for prophylactic emicizumab treatment.

Based on current treatment algorithms for patients with hemophilia A with inhibitors (Kempton and White II 2009; Srivastava et al. 2013), it is anticipated that the majority of adults and adolescents treated with emicizumab will have previously undergone ITI without success or are not candidates for ITI. As clinical safety data relating to the concomitant use of prophylactic emicizumab during ITI are not available at this time, patients currently receiving ITI will not be eligible for this study. *Patients receiving ITI therapy will be eligible following the completion of a 72-hour washout period prior to the first emicizumab administration.* Owing to the fact that the presence or amount of FVIII inhibitors in their plasma does not impact the efficacy of emicizumab, patients' inhibitor titers at the time of study entry will not influence their study eligibility.

3.3.3 Rationale for Control Group

This study involves the use of a single-arm study design and therefore a control group will not be used. The primary endpoint of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A *who have persistent inhibitors against FVIII*. As hemophilia A is a rare disease (Acharya 2013) and the study is designed to investigate the broad safety profile of emicizumab, approximately 200 patients will be enrolled. Given the size of the patient population, a single-arm study design without a control group is considered an appropriate method to capture the safety data that will be observed following the use of emicizumab. This type of study design has been used extensively in previous clinical studies involving patients with rare diseases (Bell and Tudur Smith 2014).

3.3.4 Rationale for Biomarker Assessments

The identity of effective PD, safety, and bone and joint biomarkers has not been fully elucidated and further testing is required to determine which assays and technical conditions are most suitable for use with emicizumab treatment. Plasma and serum samples will be collected for PD, safety, and bone and joint biomarker assessments at specific clinic visits in order to obtain evidence of the biologic activity of emicizumab in patients (see Appendix 2

Schedule of Biomarker Samples

).

The PD biomarkers include, but are not limited to, coagulation assays such as aPTT and FVIII activity assays. The results of the Phase I/II study have *shown* that a dose-response relationship was apparent between aPTT and emicizumab concentration (for more information, see the Investigator's Brochure). The aPTT assay will be run in a modified form to ensure that the assay range covers all levels of emicizumab exposure. In addition, clot waveform analysis (CWA) may be run as an exploratory PD coagulation assay.

The safety biomarkers will be used to monitor patient safety throughout the study and may include, but are not limited to, D-dimer.

Exploratory safety coagulation system biomarkers will include Factor VIII antigen (FVIII:Ag), Factor IX antigen (FIX:Ag), and Factor X antigen (FX:Ag) to assess whether drug treatment causes alterations in the circulating levels of the coagulation factors that are the binding targets for emicizumab. Measurement of other coagulation or hemophilia-related factors may also be conducted.

The bone and joint biomarkers will include exploratory biomarkers of bone turnover and joint health. The selection of bone and joint biomarkers that will be tested will be based on findings from biomarker analyses in other emicizumab trials (see Appendix 2
Schedule of Biomarker Samples

).

Residual blood and/or, plasma, and serum from collected *biomarker* samples may be stored for *up to* 5 years after the *final Clinical Study Report has been completed* and may be used for additional exploratory emicizumab-related research, to guide development of potential *in*

vitro diagnostic assay(s) related to emicizumab plasma concentration, FVIII inhibitor titre and/or coagulation activity.

3.3.5 Rationale for Pharmacokinetic Sample Collection Schedule

PK samples will be collected throughout the *2-year* study *period* in order to further investigate the PK of emicizumab (see the Schedule of Activities; Appendix 1
Schedule of Activities

).

3.3.6 Rationale for Immunogenicity Sample Collection

Immunogenicity will be monitored by investigating the incidence and clinical significance of antibodies to emicizumab at specified time points (see the Schedule of Activities; Appendix 1

Schedule of Activities

). The emergence of *anti-drug antibodies (*ADAs*)* has been previously observed in clinical studies involving monoclonal antibodies of the IgG4 class (Lundkvist et al. 2012; Vennegoor et al. 2013).

3.3.7 Rationale for Disease Response–based Endpoints

The secondary objective of this study is to evaluate the efficacy of prophylactic administration of emicizumab. This objective will be achieved by investigating the number of bleeds over time under emicizumab treatment, *assessing* HRQoL, *and evaluating health status according to EQ-5D-5L and patient preference for the emicizumab regimen compared with the previous regimen*. As mentioned in Section 0, this analysis will occur when all patients have completed 2 years of treatment or have withdrawn, whichever occurs sooner. In order to obtain comprehensive data on each bleed, patients will be asked to report bleed information *on an ePRO device where possible*, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed.

Conducting the efficacy analysis after 2 years of therapy is supported by the results of previous clinical studies that have demonstrated the benefits of long-term prophylactic therapy in patients with hemophilia (Gringeri et al. 2011; Khawaji et al. 2012; Manco-Johnson et al. 2007). The results of these studies showed that prophylactic treatment could effectively prevent joint damage, decrease the frequency of joint and other hemorrhages, and lead to improvements in the patients' HRQoL.

3.3.8 Rationale for Primary Endpoint Selection

As stated in Section 0, the primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab. In order to achieve this objective, *the incidence and severity of* all adverse events, including adverse events of special interest, will be captured on an ongoing basis, as they occur during the study. Physical examinations, vital signs, and laboratory values will be assessed as per the Schedule of Activities (Appendix 1
Schedule of Activities

).

The bypassing agents that are currently used for treating patients with hemophilia A are associated with specific side effects, such as thromboembolic events, hypersensitivity reactions, myocardial infarction, and disseminated intravascular coagulation (Bui et al. 2002; Dentali et al. 2011; Tjønnfjord 2004; Wójcik et al. 2009). In addition, these agents are administered according to a frequent dosing schedule, which may reduce patient compliance thereby making these regimens less effective and compromising their cost-benefit ratio (Thornburg 2010). Therefore, there currently exists an unmet need to develop novel therapeutics for use in hemophilia A patients with inhibitors. This study will provide long-term safety data on the prophylactic use of emicizumab.

3.3.9 Rationale for Interim Analyses

Owing to the long-term nature of this study, interim analyses will be conducted in order to obtain accurate information on the safety, efficacy, immunogenicity, and PK of prophylactic emicizumab at specific points throughout the study. The first interim analysis will be performed once *approximately* 100 patients have received treatment with emicizumab for at least 24 weeks. A second *interim* analysis will be performed when *approximately* 100 patients have received treatment with emicizumab for at least 52 weeks. The data from these analyses will subsequently be presented to the iDMC in order to enable them to effectively monitor the study.

3.3.10 Rationale for Patient-reported Outcome (PRO) Assessments

During the study, electronic capture of HRQoL, health status (EQ-5D-5L) will be obtained using an ePRO device. *Patient preference data (EmiPref) will be collected on paper forms.*

HRQoL is an important outcome in the care of patients with hemophilia (Brown et al. 2009). HRQoL in hemophilic patients is multifaceted and is affected by disease symptoms (e.g., pain, bleeding), treatment (prophylactic, on demand, side effects), limitations on daily functioning, anxiety / depression, and time spent in hospital.

The goal of measuring HRQoL is to quantify any treatment benefits from the patient perspective. Previous studies that have used the *Hemophilia Quality of Life questionnaire (*Haemo-QoL), a measure of HRQoL parameters affected by hemophilia in children and adolescents, have reported improvements in physical health, feelings, view of self, family relations, friend relations, perceived support, relation with others, participation in sports, dealing with hemophilia, views of treatment, views of the future, and relationships (Santagostino et al. 2014). Improvements in physical health, feelings, view of self, and participation in work have also been observed on the adult version of the measure, the Haem-A-QoL (Stasyshyn et al. 2014).

The HRQoL measures employed in the current study will be used to investigate the impact of prophylactic administration of emicizumab in adolescents and adults with hemophilia A. In addition, the measures will be used to evaluate the longitudinal changes in HRQoL with emicizumab compared with the previous treatment regimen that the patients received.

The EQ-5D-5L is a standardized, preference-based measure of generic health status that is applicable to a wide range of health conditions and treatments. It measures five dimensions

of health: mobility, ability to self-care, ability to undertake usual activities, pain / discomfort, and anxiety / depression. The EQ-5D-5L also assesses current overall health. The goal of measuring EQ-5D-5L is to assess the impact of treatment with emicizumab over time on overall health and the different health dimensions. Data from the EQ-5D-5L can also be used to inform pharmacoeconomic evaluations.

The study will also evaluate patient preference for treatment (EmiPref). Previous studies have noted that patients express preference for treatments that do not have negative effects (e.g., pain that results from infusions), are not time-consuming, are not associated with high treatment burden, and have a goal of achieving a "normal life" (Cimino et al. 2014). The inclusion of a fit-for-purpose preference survey after the completion of 3 months of emicizumab treatment will provide information on whether SC emicizumab is preferred to the previous treatment and explore the potential underlying reasons for any findings. This assessment will be performed after 3 months as the patients will have gained sufficient experience with emicizumab and SC injection, while still being reliably able to recall their experience with their prior therapy.

4. MATERIALS AND METHODS

4.1 PATIENTS

This global study will enroll approximately 200 patients with congenital hemophilia A *who have persistent* inhibitors against FVIII at enrollment. The patients are expected to be enrolled at approximately 85 sites globally.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. *As per the investigator's judgement, a w*illingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the PRO questionnaires and bleed diaries through the use of an electronic device *or paper*
3. Aged 12 years or older at the time of informed consent
4. Diagnosis of congenital hemophilia A with persistent inhibitors against FVIII
5. Documented treatment with bypassing agents or FVIII concentrates in the last 6 months (on-demand or prophylaxis). Prophylaxis needs to be discontinued the latest by a day before starting emicizumab.
6. Adequate hematologic function, defined as platelet count ≥ 100,000/μL and hemoglobin ≥ 8 g/dL (≥ 4.97 mmol/L) at the time of screening
7. Adequate hepatic function, defined as total bilirubin ≤ 1.5 × the upper limit of normal (ULN) (excluding Gilbert's syndrome) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 ×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
8. Adequate renal function, defined as serum creatinine ≤ 2.5 × ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min

9. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method with a failure rate of < 1% per year during the treatment period and for at least five elimination half-lives (24 weeks) after the last dose of emicizumab:

    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
    - Examples of highly effective contraceptive methods with a failure rate of < 1% per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Inherited or acquired bleeding disorder other than hemophilia A
2. Ongoing (or plan to receive during the study) ITI therapy (prophylaxis regimens with FVIII and/or bypassing agents must be discontinued prior to enrollment). Patients receiving ITI therapy will be eligible following the completion of a 72-hour washout period prior to the first emicizumab administration
3. History of illicit drug or alcohol abuse within 12 months prior to screening, as per the investigator's judgment
4. High risk for TMA (e.g., have a previous medical or family history of TMA), as per the investigator's judgment
5. Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or current signs of thromboembolic disease
6. Other conditions (e.g., certain autoimmune diseases) that may increase the risk of bleeding or thrombosis
7. History of clinically significant hypersensitivity reaction associated with monoclonal antibody therapies or components of the emicizumab injection
8. Known human immunodeficiency virus (HIV) infection with CD4 count < 200 cells/μL within 6 months prior to screening
9. Use of systemic immunomodulators (e.g., interferon or rituximab) at enrollment or planned use during the study, with the exception of antiretroviral therapy

10. Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
11. Receipt of:
    - Emicizumab in a prior investigational study
    - An investigational drug to treat or reduce the risk of hemophilic bleeds within five half-lives of last drug administration
    - A non-hemophilia-related investigational drug within last 30 days or five half-lives, whichever is shorter
    - Any concurrent investigational drug.
12. Pregnancy or lactation, or intent to become pregnant during the study
13. Positive serum pregnancy test result within 7 days prior to initiation of *emicizumab* (females only)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Study MO39129 is a single-arm, open-label study and therefore no treatment blinding will occur during this study.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is emicizumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Emicizumab

Emicizumab drug product will be supplied by the Sponsor as a sterile colourless to pale yellow liquid for SC injection in *a* single-dose 3-mL glass vial *containing 1 mL of emicizumab*. The recommended storage condition for emicizumab drug product is between 2°C and 8°C (36°F to 46°F), and protected from light. Vials should not be frozen or shaken.

Each single-use vial contains 150 mg/mL emicizumab in a histidine-aspartic acid buffered solution (approximately pH 6.0), which contains arginine and Poloxamer 188. For information on the formulation and handling of emicizumab, see the Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Emicizumab

*E*micizumab will be administered at a dose of 3 mg/kg/week subcutaneously for 4 weeks when initiating treatment, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period. There will be an option to increase the dose to 3 mg/kg/week in cases of insufficient control of bleeds on the 1.5 mg/kg/week emicizumab dose. If the investigator believes that a specific patient warrants dose up-titration following the occurrence of, for example, at least two spontaneous bleeds, significant bleeds, or a

traumatic bleed out of proportion to the degree of injury, they must discuss the case with the Medical Monitor for consideration and potential approval.

Recommended injection sites include the front of middle of the patient's thighs, or the lower part of the patient's abdomen below the navel. Avoid injecting within a 2″ radius around the navel. If a caregiver is giving the injection, the outer area of the upper arms may also be used. For additional information re the administration of emicizumab, refer to the Instructions for Use (IFU) document.

If a patient has a systemic hypersensitivity reaction or a severe adverse reaction that may be attributable to emicizumab, subsequent doses should be withheld until the situation is discussed with the Medical Monitor and approval to resume dosing is provided. Should certain, unanticipated events occur during the study that require treatment with multiple daily administrations of bypassing agents or FVIII concentrates for multiple days (e.g., non-elective surgery or severe/life-threatening bleeds), the investigator should contact the Medical Monitor immediately to discuss such cases and the management of future emicizumab doses. In order to be eligible for inclusion in the study, prophylaxis regimens with FVIII and/or bypassing agents must be discontinued prior to enrollment. Any other emicizumab dose adjustment request will require discussion of the clinical case with, and approval from, the Medical Monitor.

Study site HCPs will be initially trained on how to properly prepare *emicizumab* and administer the correct calculated dose subcutaneously as described in the IFU document.

To support home administration of the drug, patients/caregivers will be required to complete in-person, instructional training on how to administer emicizumab as a SC injection. Patients/caregivers will also be taught how to perform the injections through the use of the IFU document. In addition, the HCP is to inform the patient/caregiver of the volumetric dose to be administered and the dosing frequency. The patients/caregivers will observe at least one SC injection performed by a HCP and will need to successfully administer at least one SC injection under an HCP's supervision prior to starting home administration. The patient/caregiver will also have the opportunity to ask any questions to the HCP before starting home administration. The first three weekly treatments will be administered in a monitored setting, such as an infusion center, clinic, or hospital, in conjunction with emicizumab PK and PD assessments. Patients will be observed for a minimum of 60 minutes after the first three doses. Patients/caregivers will be instructed on how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. Each site will have the discretion to provide additional training or include additional observation (e.g., after the third or fifth doses), if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject emicizumab, a trained and proficient caregiver or HCP should be identified to administer the SC injections. Patients/caregivers will be provided with contact information for the clinic in case they have questions related to self-administration between visits.

In order to minimize the number of injections for patients in certain weight categories, the administration of a single injection of up to 2 mL drug product solution may be permitted. This administration will require the combination of emicizumab drug product solution from *up to two 1-mL vials* (i.e., vial pooling) *aseptically* into a single syringe, using a new transfer

needle for each vial. *T*he detailed procedure for vial pooling will be described in the IFU document. *If the patient's dose is* > *2 mL, a second injection will be required.*

Medication administration errors during training will be documented in the electronic Case Report Form (eCRF). If necessary, patients or their HCP may choose to continue administration of *emicizumab* within the clinic. Compliance in the home setting is to be monitored at each site by reviewing reported hemophilia medication use and recording collected used and unused vials.

If the patient forgets or cannot administer *emicizumab* on the scheduled dosing day, *emicizumab* should be administered *as soon as possible before the day of the next scheduled dose, and then the patient should resume the usual weekly dosing schedule. Do not double doses to make up for a missed dose. All four loading doses of 3 mg/kg should be taken, even if this is done over a period or more than four weeks.*

Any overdose or incorrect administration of *emicizumab* should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of *emicizumab* should be recorded on the Adverse Event eCRF. Section 0 summarizes available safety data related to overdosing of emicizumab.

Patients and/or caregivers will be provided with alert cards, which they will be requested to carry at all times. These will include guidance on recognizing the signs/symptoms of thromboembolic events or allergic/anaphylactic/anaphylactoid reactions and how to obtain emergency care. In addition, alert cards are designed to notify non-study HCPs that emicizumab will interfere with certain coagulation laboratory tests (see the Investigator's Brochure for more information) and that the investigator should be contacted for assistance in interpreting the test results.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.1.

4.3.3 Investigational Medicinal Product Accountability

Emicizumab, the only IMP in the study, will be provided by the Sponsor. Accountability for each vial is required and the study site will acknowledge the receipt of IMP using the interactive voice or web-based response system (IxRS) to confirm shipment condition and content. Any damaged shipments will be replaced.

Used and unused *emicizumab* vials will be returned by the patients to the study site and appropriately accounted for. Used *emicizumab* vials will then be disposed of at the study site according to institutional standard operating procedures.

Instructions regarding how to handle unused vials should be obtained from the Sponsor. If the investigator prefers to destroy the IMP at his or her site, the site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Emicizumab

The Sponsor will offer continued access to emicizumab to study patients who have shown a demonstrable benefit from emicizumab treatment during this study (as measured by sustained clinical response and/or improvement in clinical symptoms).

Continued Access to *emicizumab* will be provided free of charge, through either an Open Label Extension trial, a Post-Trial Access Program, local Patient Support Programs, or other local access mechanisms according to each country regulation, as described per Global procedural document: Continued Access to Roche Investigational Medicinal Product (SOP-0112895), in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, and the Declaration of Helsinki in its 2013 issue.

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for hemophilia A
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for hemophilia A
- Provision of study drug is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to initiation of *emicizumab* to the Study Completion/Early Termination Visit *(or to the Safety Follow-up Visit, if applicable)*. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Any hemostatic medications (e.g. bypassing agents) and other medications used to treat or prevent bleeds in the 6-month period prior to starting emicizumab treatment will also be collected (see Section 4.5.5).

4.4.1 Permitted Therapy

Concomitant use of the following drugs and therapies will be permitted:

- *Drugs to treat existing conditions at time of study entry, as long as allowed based on eligibility criteria (Section 4.1.1 and Section 4.1.2).*
- *During the study, a*ny medication to treat or prevent any medical condition as deemed necessary by the treating physician. *If prohibited treatment (see Section 4.4.2) is prescribed or*

considered medically necessary, the Medical Monitor should be consulted to discuss any changes in the benefit-risk profile and determine whether the patient should continue on the study.

- Any over-the-counter medication used to treat the symptoms of hemophilia
- Supplementary vitamins and minerals.
- *Drugs and therapies to treat adverse events and the use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to enter the bloodstream and result in systemic exposure*

Concomitant use of the following hemostatic treatments will be permitted:

- *Drugs intended to control breakthrough bleeds (e.g. rFVII, FVIII, aPCC) or bleeds during surgeries should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase the patient's coagulation potential, the doses required to achieve hemostasis may be lower than doses used prior to starting emicizumab. At the start of the study, Investigators shall discuss with patients the recommended doses of any additional coagulation factors used, given the guidance below.*
- *The use of aPCC for breakthrough bleed treatment for patients on emicizumab should be avoided if possible, and rFVIIa should be the first option used to treat, starting with no more than 90 µg/kg as an initial dose. If aPCC needs to be used, no more than 50 IU/kg should be administered as an initial dose and doses of > 100 U/kg/24 hours or more should be avoided, as cases of TMA and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours aPCC was administered for 24 hours or more. Investigators should provide or remind patients of the exact dose and schedule of bypassing agents or FVIII required to treat any bleed.*
    - *Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab*
- **Other bypassing agents:** *other bypassing agents* (e.g., Byclot®) should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (e.g., no more than 60 mg/kg of Byclot®). For patients receiving Byclot® prior to study entry, a washout period of 72 hours prior to the first emicizumab dose is required

The exact dose and schedule of FVIII or bypassing agents should be discussed with the patient at study entry and throughout the study. Repeated dosing of *FVIII,* rFVIIa, aPCC, or other bypassing agents should be performed only under medical supervision and consideration should be given to verifying the bleeds prior to repeated dosing. For rFVIIa, aPCC, and other bypassing agents, laboratory monitoring by additional local and central laboratory assessments should be performed as per the Schedule of Activities (see *Section 4.5.6.9*Appendix 1 Schedule of Activities

-).

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Use of systemic immunomodulators (e.g., rituximab, interferon) other than antiretroviral therapy
- Use of other investigational drugs
- Use of aPCC for short-term prophylaxis
  - Use of aPCC for any reason should be avoided *if possible* during the study but use of aPCC to treat breakthrough bleeds is permitted (as described *in Section 4.4.1*) if rFVIIa is not available or not an option for medical reasons (see Section 0).
- Use of *ITI therapy (*prophylactic regimens with FVIII *and/*or bypassing agents*)*:
  - However, short-term prophylaxis around the time of surgery is permitted as deemed needed by the investigator *(see Section 4.4.1). FEIBA can not be used prophylactically.*
- *Use of anti-fibrinolytics in conjunction with aPCC or Byclot®*

If prohibited therapy is administered for any reason, it should be recorded on the eCRF. If prohibited treatment is prescribed or considered medically necessary, the Medical Monitor should be consulted to discuss any changes in the benefit-risk profile and determine whether the patient should continue on the study.

4.5 STUDY ASSESSMENTS

Please see Appendix 1
Schedule of Activities

for the Schedule of Activities to be performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. For adolescents (i.e., patients who are 12−17 years of age), an Informed Assent Form will be completed instead. Parents or caregivers of adolescents will also complete an Informed Consent Form.

The enrollment form will be completed after informed consent and/or assent is obtained. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes hemophilia-related history, clinically significant diseases, procedures *(including prior surgeries)*, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior ITI, anaphylaxis, or known thrombophilia. It should also include all medication taken in the 4 weeks prior to screening (including prescription drugs, over-the-counter drugs, and herbal/homeopathic remedies and therapies).

Demographic data will include age, sex, and self-reported race and ethnicity.

4.5.3 Physical Examinations

A complete physical examination be performed *during* Screening and should include, but not necessarily be limited to, an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF. *Targeted physical examinations (i.e., joints for bleeds and evidence of arthropathy; skin for bruises, hematomas and ISRs; other organ systems as clinically indicated) should be conducted at subsequent visits or as clinically indicated.* New or worsened clinically significant abnormalities from screening should be recorded as adverse events, if appropriate, on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurement of *body temperature (oral, rectal, axillary, or tympanic),* heart and respiratory rates, blood pressure and weight, and should be *measured. On treatment days, measurement should occur prior to emicizumab administration. Height will be only measured at selected visits. Additional* vital sign assessments may also be taken anytime as unscheduled assessments as judged by the investigator. In addition, vital signs may be taken to help monitor for hypersensitivity reactions during or after injections at the investigator's discretion, although these data should not be entered into the eCRF.

4.5.5 *Concomitant Medications*

The definition of concomitant medications, as well as permitted and prohibited medications is described in Section 4.4. Concomitant medications used by a patient from 4 weeks prior to initiation of emicizumab to the Study Completion/Early Termination Visit (or the Safety Follow-up Visit, if applicable) should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Any hemostatic medications (e.g. bypassing agents) and other medications used to treat or prevent bleeds in the 6-month period prior to starting emicizumab treatment will also be collected. Treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), will be collected in the bleed records.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Central laboratory assessments will be performed as indicated *(see Table 9). Unless otherwise specified,* additional analysis may be performed at a local laboratory*, as per the investigator's discretion. Any additional laboratory results which are required as part of the patient's safety assessment should be recorded in the unscheduled visit eCRFs. Central labs are part of the non-eCRF data which will be sent to the Sponsor directly by the central lab vendor.*

On *treatment days, blood collection should occur within 2 hours prior to emicizumab administration unless otherwise specified.*

Table 10 ***Central vs Local Laboratory Assessments***

Sample	*Laboratory*

Sample	*Laboratory*
Hematology and blood chemistry	*Central*
Pregnancy tests	*Local*
HIV and hepatitis serology	*Local*
Anti-FVIII antibodies	*Central*
Anti-emicizumab antibodies	*Central*
Pharmacokinetic samples	*Central*
Safety biomarkers	*Central*
Safety coagulation system biomarkers	*Central*
PD biomarkers	*Central*
Bone and joint biomarkers	*Central*
Extra testing with use of bypass agents	*Central*

4.5.6.1 *Hematology and Blood Chemistry*

Hematology and blood chemistry tests include:

- Hematology (hemoglobin, hematocrit, platelet count, red blood cell [RBC] count, white blood cell [WBC] count, absolute or non-absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC distribution width, prothrombin time [PT] in seconds, and international normalized ratio [INR; the PT/INR ratio will be calculated])
- Serum chemistry (sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, *lactate dehydrogenase (*LDH), alkaline phosphatase, and creatine phosphokinase)

Laboratory assessments completed during Screening do not have to be repeated at Week 1, if the period between Screening and Week 1 is ≤ 5 days and there has been no change in the patient's health status as assessed by the investigator.

Samples will be sent to the central laboratory for analysis.

4.5.6.2 *Pregnancy Tests*

Female patients of childbearing potential (including those who have had a tubal ligation) will be required to have a negative serum pregnancy test result during Screening, and again within 7 days prior to the first dose of emicizumab. Urine pregnancy tests will be performed throughout the study treatment period. Pregnancy testing will be conducted at the local laboratory.

4.5.6.3 *HIV and Hepatitis Serology*

The specific tests utilized for hepatitis and HIV testing are per local standard of care. As this patient population is at high risk for HIV, hepatitis A, B and C, sites should consider testing for these. While the specific serological tests used is at the discretion of the Investigator, this is with the understanding that the status of that participants' hepatitis or HIV is confidently known at time at enrollment. HIV and hepatitis serology tests will be conducted at the local laboratory.

4.5.6.4 *Anti-FVIII Antibodies*

For the assessment of anti-FVIII antibodies (inhibitors), functional assays that utilize a clotting readout (classic Bethesda or Nijmegen assay) cannot be used for patients on emicizumab therapy as emicizumab drives clotting even in the presence of FVIII inhibitors, causing a false-negative test result (see Section 5.1.3). After the first dose, local measurement of FVIII inhibitors, if indicated, requires use of an ELISA-based test or a chromogenic Bethesda assay.

At the discretion of the local investigator, any additional urgent requests to assess FVIII inhibitors will need to be sent to the central laboratory (see Appendix 2
Schedule of Biomarker Samples
for additional information).

Plasma samples for anti-FVIII antibodies will be analysed at the central laboratory.

4.5.6.5 *Anti-emicizumab Antibodies*

Plasma samples are required for immunogenicity assessments to detect anti-emicizumab antibodies. Additional samples to detect anti-emicizumab antibodies may also be drawn at the time of hypersensitivity events or following suspected loss of efficacy. Samples will be analysed at the central laboratory.

4.5.6.6 *Pharmacokinetics*

Plasma samples are required for PK assessments. On days where PK samples are to be collected, the emicizumab injection will be performed in the clinical unit. One single pre-dose sample is required on the applicable visits. Samples will be analysed by the central laboratory.

4.5.6.7 *Biomarkers*

4.5.6.7.1 *Safety Biomarkers*

Plasma samples for safety biomarker assessment must be citrate plasma. Tests may include, but are not limited to, D-dimer. Samples will be analysed by the central laboratory. See Appendix 2.

4.5.6.7.2 *Safety Coagulation System Biomarkers*

Plasma samples for safety coagulation system biomarker assessment must be citrate plasma. Tests include FVIII:Ag, FIX:Ag and FX:Ag. Samples will be analysed by the central laboratory. See Appendix 2.

4.5.6.7.3 *PD Biomarkers*

Plasma samples for PD biomarker assessment must be citrate plasma. Tests will include, but are not limited to FVIII activity and modified aPTT (one stage). Additional plasma samples will be collected for future exploratory research, which may include tests such as CWA and others (see Appendix 2). Samples will be analysed by the central laboratory.

4.5.6.7.4 *Bone and Joint Biomarkers*

Serum and plasma ethylenediaminetetraacetic acid (EDTA) samples for bone and joint biomarkers must be collected after fasting (no food or drink other than water for at least 8 hours prior to the blood draw). Ideally these samples should be collected in the morning (before noon), in order to control for diurnal variation. Please consult the Central Laboratory Services Manual for details. The selection of exploratory bone and joint biomarkers to be tested will build on findings from biomarker analyses in other emicizumab trials and may include C-terminal telopeptide of collagen 1 (CTX-1), osteoprotegerin (OPG), procollagen type 1 amino-terminal propeptide (P1NP), and soluble receptor activator of nuclear factor kappa-B ligand (RANK-L) (see Appendix 2

Schedule of Biomarker Samples

). Samples will be analysed by the central laboratory.

4.5.6.8 *Extra Testing with Use of Bypass Agents*

In the event of a breakthrough bleed that is treated with bypassing agents, it is recommended that the following laboratory tests will be performed within 24–48 hours of initial bypassing agent use (these tests will be conducted so that the investigator can monitor the patient for potential thromboembolic events and *microangiopathic hemolytic anemia or* TMA). *These tests include:*

- Platelet count
- Serum creatinine
- LDH
- Schistocytes
- A plasma sample should also be provided for central laboratory monitoring of prothrombin fragment F1+2, fibrinogen and D-dimer.

Ideally, samples for these tests should be analysed at the central laboratory. Exceptionally in urgent situations where results are required quickly, local laboratory testing can be used, with results recorded in the eCRF.

For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours until 24–48 hours after the last dose of bypassing agents is administered to treat a specific bleed. *All* laboratory results *which are required as part of the patient's safety assessment* should be recorded in the unscheduled visit eCRFs.

4.5.6.9 *Sampling Procedures and Sample Storage, Shipment and Destruction*

For sampling procedures, storage conditions, and shipment instructions, see the *Central* Laboratory *Services* Manual.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma or serum samples, as applicable, collected for anti-FVIII antibody, PD biomarker, safety biomarker, safety coagulation system biomarker, bone and joint biomarker assessments *and other future exploratory research* will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.7 Bleed Assessments

Patients will be trained on how to record their bleeds and hemophilia medication use using an ePRO device where possible. When bleeds occur, patients will need to record the site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. *At least once a week, patients will need to record any hemophilia medication use (including emicizumab) and information regarding any bleeding events*. Investigator review of patient-reported bleed/medication records with the patient/caregiver will occur for completeness and accuracy throughout the study.

4.5.7.1 Definition of a Bleed

For the purposes of the efficacy analyses, a standardized definition of bleed, adapted from the standard criteria defined by the FVIII and FIX Subcommittee of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), that is similar to the definition used in a recent clinical investigation, will be utilized in this study (Blanchette et al. 2014; Mahlangu et al. 2014):

- An event is considered a bleed if coagulation factors are administered to treat signs or symptoms of bleeding (pain, swelling, etc.). An additional definition of all reported bleeds (irrespective of treatment with coagulation factors) will be applied for a separate analysis.
- Bleeds starting from the first sign of a bleed and ending 72 hours after the last treatment for the bleed, which have any symptoms of bleeding at the same location or injections are ≤ 72 hours apart, are considered the same bleed.
- Any injection to treat the bleed, taken > 72 hours after the preceding injection, is considered the first injection to treat a new bleed at the same location.
- In case of trauma with multiple different locations of bleed, this will be considered as one bleed for the analyses. However, all data will be collected, including the various locations of the different bleeds.
- Any bleed with a different etiology is considered a separate bleed regardless of time from last injection.

4.5.7.2 Definition of a Target Joint

A target joint is defined as:

- A major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of at least three bleeds into the same joint over the last 24 weeks prior to study entry).

4.5.7.3 Bleed Sites

The bleed sites are defined as follows:

- Joint bleeds, which are defined as having an unusual sensation ("aura") in the joint in combination with any of the following:
  - Increasing swelling or warmth of the skin over the joint
  - Increasing pain
  - Progressive loss of range of motion or difficulty in using the limb as compared with baseline.
- Muscle bleeds
- Other bleeds.

4.5.7.4 Definitions of Bleed Types

Bleed assessments will be separated into spontaneous bleeds, traumatic bleeds, and bleeds related to procedures. Both spontaneous bleeds (i.e., the occurrence of hemorrhage where neither the patient nor a caregiver can identify a reason) and traumatic bleeds (i.e., hemorrhage occurring secondary to an event such as trauma, "strenuous" activity, or "overuse") will be collected. The definitions for the different type of bleeds are as follows:

- **Spontaneous bleeds**. Bleeds will be classified as spontaneous if a patient records a bleed when there is no known contributing factor such as definite trauma, antecedent "strenuous" activity, "overuse", or procedure/surgery. The determination of what constitutes "strenuous" or "overuse" will be at the discretion of the patient. For example, light jogging may be considered "non-strenuous" while sprinting may be considered "strenuous"; lifting of weights for a short period of time may be considered "moderate use" while repetitive weightlifting may be considered "overuse"
- **Traumatic bleeds**. Bleeds should be classified as traumatic if a patient records a bleed when there is a known or believed reason for the bleed. For example, if a patient were to exercise "strenuously" and then have a bleed in the absence of any obvious injury, the bleed would be recorded as a traumatic bleed because, although no injury occurred, there was antecedent "strenuous" activity. Bleeds with preceding injuries would certainly be classified as traumatic. In addition, bleeds related to surgery, such as hematomas resulting from any surgeries, will also be classified as traumatic bleeds. Bleeds related to surgeries will not be associated with any trauma except surgery-induced trauma
- **Bleeds related to procedures**. This category would include hematomas resulting from any invasive procedure (e.g., tooth extractions, venepuncture, or SC drug administrations) or invasive diagnostic procedures (e.g., lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy, etc.) or surgeries. Any instances of these bleeds would not be counted as bleeds in the context of the study, but the relevant

data will be collected. Bleeds related to procedures will not be associated with any trauma except procedure-induced trauma.

4.5.8 *Surgical Events*

Thorough documentation on surgical events will be requested, including type of surgery or procedures, treatments, outcomes, etc.

4.5.9 Patient-Reported Outcomes

The PRO data that will be collected during this study include bleed/medication assessments (see Section 4.5.7) and HRQoL, health status (EQ-5D-5L), and treatment preference (EmiPref) questionnaires.

The PRO questionnaire data will be collected to document the treatment benefit of emicizumab. The questionnaires, translated into the local language as required, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient/caregiver receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of *emicizumab*, unless otherwise specified.

4.5.9.1 HRQoL Assessments

The Haem-A-QoL *(version AU 3.0; UK English)* and the Hemophilia Quality of Life Short Form (Haemo-QoL-SF) *(version AU 2.0; UK English)* will be *completed electronically and* used to measure HRQoL in adults and adolescents, respectively. *Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.*

The Haem-A-QoL was designed for adult patients with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, feelings, view of yourself, sports and leisure, work and school, dealing with hemophilia, treatment, future, family planning, and partnerships and sexuality) and a scale representing total score. Items are rated according to five response options, although for some items there is also a 'not applicable' option (Mackensen and Gringeri 2010; Wyrwich et al. 2015).

The Haemo-QoL has been developed as a series of age-related questionnaires to measure HRQoL in children and adolescents with hemophilia (Bullinger et al. 2002; Pollak et al. 2006; Von Mackensen and Bullinger 2004). These questionnaires include a 77-item long form, a 35-item short form, and an 8-item index form. Long versions for three different age groups contain 21−77 items and cover 8−12 dimensions of HRQoL. Furthermore, two age-specific short form measures containing 16 and 35 items have been developed. The short version for older children (8−16 years) containing 35 items was selected for this study. This version covers nine dimensions considered relevant for the children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports, dealing with hemophilia, and treatment). Items are rated with respect to five response options: never, rarely, sometimes, often, and all the time.

4.5.9.2 Health Status Assessments (EQ-5D-5L)

The EQ-5D-5L *(version 2; UK English)* is a generic, self-report, preference-based health utility measure that consists of six questions *that are completed electronically* and is used to assess health status and inform pharmacoeconomic evaluations. *Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.* The EQ-5D-5L consists of two components. The first part, health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression (Herdman et al. 2011; Janssen et al. 2013). Published weights are available that permit the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The second part is a 0 to 100-point visual analog scale (VAS), which assesses current health status and higher scores are reflective of better health.

4.5.9.3 Treatment Preference Questionnaire

Patient preference will be assessed through *a paper version of* the EmiPref questionnaire (Appendix 3), which asks patients to specify the treatment they would prefer to continue to receive after receiving treatment with their previous episodic or prophylactic regimen and SC emicizumab. Patients who express a preference are then asked to identify the reasons which may have influenced their decision and indicate the top three reasons for their choice. Patients will complete this questionnaire after 3 months of treatment with emicizumab.

4.6 PATIENT, TREATMENT, STUDY AND SITE DISCONTINUATION

Patients who discontinue emicizumab prior to the completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first (see Appendix 1
Schedule of Activities

).

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient's inability or unwillingness to comply with protocol requirements
- Non-compliance despite appropriate education measures taken by the clinical site.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue *emicizumab* if they experience any of the following:

- Pregnancy
- *Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive emicizumab*
- *Investigator or Sponsor determines it is in the best interest of the patient*
- *Requirement of another medication not permitted per protocol*

The primary reason for *emicizumab* discontinuation should be documented on the appropriate eCRF. Patients who discontinue *emicizumab* prematurely will not be replaced. Patients who become pregnant should immediately discontinue treatment and be managed according to local guidelines.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence (e.g., bleed/medication data not checked by investigator/co-investigator for > 8 weeks)
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled).

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Emicizumab is not approved *in all countries*, and clinical development is *still* ongoing. The safety plan for patients in this study is based on clinical experience with emicizumab in completed and ongoing studies. The anticipated important safety risks for emicizumab are outlined below. Please refer to the emicizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at high risk for toxicities. Patients

will undergo safety monitoring during the study, including assessment of the nature, frequency, and grade of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Emicizumab

5.1.1.1 Injection-Site Reactions

In the completed and ongoing Japanese studies, *ISRs* have been observed in some patients with hemophilia A. These local *ISRs* included injection-site erythema, injection-site hematoma, injection-site rash, injection-site discomfort, injection-site pain, and injection-site pruritus. All local *ISRs* were of mild intensity. Further details on the observed *ISRs* are available in the Investigator's Brochure. To minimize the risk for *ISRs*, emicizumab should be injected subcutaneously using separate injection sites as described in Sections 0 and 0 and the IFU document.

5.1.1.2 Hypercoagulation and *Thromboembolic Events*

As of *April 2017*, there have been two *serious* thrombo*tic* events reported in two patients *who were treated with bypassing agents while receiving* emicizumab *prophylaxis* in Study BH29884.

- One patient self-administered greater than 200 units/kg/day of aPCC for two consecutive days and developed cavernous sinus thrombosis. Treatment with emicizumab was interrupted*, no further aPCC was administered,* and the clot resolved without anticoagulation *in* approximately 2.5 weeks. Emicizumab was restarted after approximately 10 days after the resolution of the serious adverse event *without recurrence*.
- The second patient developed severe skin necrosis (both legs) and *contemporaneous* superficial vein thrombosis in the right leg after self-administering two consecutive doses of 100 units/kg/day of aPCC. The patient *recovered* on supportive therapy (no anticoagulation). *For more details please refer to the emicizumab Investigator's Brochure.*

All thromboembolic events *should be reported as adverse events of special interest (see Section 5.2.3), and also as serious adverse events if it meets criteria as described in Section 5.2.2.* HCPs should educate patients/caregivers to recognize signs and symptoms of potential thromboembolism *or thrombosis* (i.e., dyspnea, chest pain, leg pain or swelling*; or if in the head, headache, numbness in the face, eye pain or swelling, or vision impairment; or if in the skin, blackening and associated pain*) and ensure that they understand the importance of seeking appropriate medical attention. Patients *and/or* caregivers will also receive two alert cards to remind them of this information should thromboembolism be suspected.

5.1.1.3 Thrombotic Microangiopathy

TMA is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, central nervous system. As of *April 2017*, *three* cases of TMA were observed *in Study BH29884 involving patients with hemophilia A with inhibitors who were treated with bypassing agents while receiving emicizumab*.

- The first patient self-administered two doses of *aPCC* 94 units/kg in 2 days to treat *his* left knee hemarthrosis. The *next* day, *he* started experiencing icterus and severe back pain and the patient self-administered two doses of *rFVIIa* 85 µg/kg and two doses of *aPCC* 94 units/kg. The*n the* patient presented with thrombocytopenia, hyperbilirubinemia, and acute renal failure with schistocytes on peripheral blood smears. The patient was diagnosed with TMA and treated with plasmapheresis, hemodialysis, and supportive care and his condition improved and resolved after *16* days. The patient discontinued treatment with emicizumab
- The second patient self-administered five doses of *aPCC* 74 units/kg over three consecutive days before the serious adverse event *onset*. The patient had abdominal pain and emesis, acute renal failure, thrombocytopenia, elevated LDH, and a low haptoglobin with schistocytes on peripheral blood smears. The patient was diagnosed with TMA and recovered without plasmapheresis or hemodialysis after *18* days. The patient restarted treatment with emicizumab after resolution of the serious adverse event *without recurrence of TMA*.
- *The third patient presented at the hospital complaining of rectal bleeding, postural dizziness, and exertional dyspnea. Of note,* [redacted]. *Multiple doses of rFVIIa were administered and various interventions (hemostatic powder application, absorbable hemostat packing, and embolization of rectal arteries) were used in an attempt to control bleeding. Despite these measures, the patient continued to have rectal hemorrhage. The patient's bypassing agent treatment was then changed to aPCC and temporary cessation of bleeding was achieved. Subsequently, the patient developed a serious adverse event of TMA following concomitant bypassing agent treatment. Emicizumab prophylaxis and aPCC were discontinued and therapeutic plasma exchange with albumin was provided. Three days later, investigators assessed the patient's TMA to be improving based on laboratory assessments (LDH and platelet count). However, the patient experienced recurrent rectal hemorrhage. Surgery and arterial embolization were no longer deemed to be feasible and the patient was placed on comfort care before passing away the same day. The investigator assessed the patient death as related to the serious adverse event of rectal hemorrhage and unrelated to emicizumab, and the TMA as related to emicizumab and aPCC. For more details please refer to the Emicizumab Investigator's Brochure.*

These events should be reported as adverse events of special interest (see Section 5.2.3), and also as serious adverse events if it meets criteria as described in Section 5.2.2. HCPs should educate patients/caregivers to recognize signs and symptoms of potential TMA (i.e., confusion, weakness, swelling of arms and legs, yellowing of skin and eyes, vague abdominal or back pain, nausea, vomiting, or decreased urination, etc.) and ensure that they understand the importance of seeking appropriate medical attention. Patients and/or caregivers will also receive two alert cards to remind them of this information and these instructions should TMA be suspected.

5.1.1.4 Hypersensitivity

Since emicizumab is a biological product, acute systemic hypersensitivity reactions, including anaphylactic*/anaphylactoid* reactions, may occur. In Study ACE001JP, no severe hypersensitivity reactions or anaphylactic/anaphylactoid reactions have been observed.

These events should be reported as serious adverse events or adverse events of special interest as described in Sections 5.2.2 and 5.2.3, respectively.

HCPs administering *emicizumab* in the clinic must be trained in the appropriate administration procedures; be able to recognize the signs and symptoms associated with potential hypersensitivity, anaphylactic, and anaphylactoid reactions; and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; see Appendix 4). HCPs should also instruct patients how to recognize the signs and symptoms of hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an HCP or seek emergency care in case of any such occurrence. Patients/caregivers will also receive two alert cards to remind them of this information should any of these reactions occur.

Patients with a history of clinically significant hypersensitivity reaction associated with monoclonal antibody therapies or to the components of the emicizumab injection will be excluded from study participation.

5.1.2 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 1.

Table 11 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Injection-site reactions	• Injection-site reactions should be treated as clinically indicated. • Emicizumab should not be injected into areas where the skin is red, bruised, tender, or hard or into areas where there are moles or scars. • In the clinic setting, patients will be monitored for signs of injection-site reactions in the period immediately following injections. Patients will be given guidance on how to report injection-site reactions when administering drug at home or after they leave the clinic.

Event	Action to Be Taken
Hypersensitivity	• Suspected cases should be fully evaluated and treated as clinically indicated. • Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) and resuscitation equipment must be available for immediate use during the initial administrations of emicizumab in the infusion center, clinic, or hospital. • If a patient has symptoms of anaphylaxis or severe hypersensitivity, administration of emicizumab must be immediately stopped and treatment of the reaction must be initiated. • The investigator should contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk, to determine if and when the patient should resume taking emicizumab, and discuss the patient's continued study participation. If patient continues in the study, the next two scheduled doses must be in a monitored setting with at least a 60-minute observation period and resuscitation treatment immediately available. After each of these two doses in the clinic, the site will call the patient 24 hours after each dose to assess the status of the patient. • Investigators may order any pertinent laboratory tests, including an unscheduled ADA evaluation, in the event that any of these reactions occur.
Hypercoagulation and risk of thrombosis	• Investigators should be vigilant for patients who exhibit signs/symptoms consistent with thrombotic disease and should immediately begin work up and treatment as per local guidelines. • If a patient has a thromboembolic event, further administration of *emicizumab* should be interrupted. The investigator must contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk to determine if the patient should resume taking emicizumab and discuss the patient's continued study participation. • Please see Sections 0 and 0.9 for guidance on the management of breakthrough bleeds, including required laboratory monitoring.
TMA	• Investigators should be vigilant for patients who exhibit signs/symptoms consistent with TMA and immediately begin work-up and treatment, as per local guidelines. • If a patient has a TMA event, further administration of *emicizumab* should be interrupted. The decision to resume taking emicizumab after a TMA event must be discussed with and approved by the Medical Monitor. • Please see Sections 0 and 0.9 for guidance on the management of breakthrough bleeds, including required laboratory monitoring.

ADA=anti-drug antibody; TMA=thrombotic microangiopathy

5.1.3 Interpretation of Coagulation Assays for Patients Receiving Emicizumab

Emicizumab interacts with standard laboratory assays used in the management of patients with hemophilia A *(see Table 11)*. In one-stage assays, emicizumab is associated with a supra-physiologically short time to clot formation and thus normalization of aPTT at sub-therapeutic levels. Emicizumab is not recognized or neutralized by FVIII inhibitors, and therefore *FVIII inhibitors* cannot be detected *in the presence of emicizumab* by functional tests such as Bethesda or Nijmegen-Bethesda assays, which use a one-stage clotting-based readout. Emicizumab activity cannot be detected by chromogenic assays using purified bovine coagulation proteins*, thus chromogenic Bethesda assays using bovine proteins can be used to measure FVIII inhibitor titer in the presence of emicizumab. Emicizumab activity* can be detected using *chromogenic* assays composed of human proteins. See the Investigator's Brochure for additional details on which tests can be used and how the test results can be interpreted.

Table 12 *Coagulation Test Results Affected and Unaffected by Emicizumab*

Results Affected by Emicizumab	*Results Unaffected by Emicizumab*
aPTT *Bethesda assays (clotting-based) for FVIII inhibitor titers* *One-stage, aPTT-based, single-factor assays* *aPTT-based Activated Protein C Resistance* *Activated clotting time*	*Bethesda assays (bovine chromogenic) for FVIII inhibitor titers* *Thrombin time* *One-stage, prothrombin time-based, single-factor assays* *Chromogenic-based single-factor assays other than FVIII [a]* *Immuno-based assays (i.e., ELISA, turbidimetric methods)* *Genetic tests of coagulation factors (e.g., Factor V Leiden, Prothrombin 20210)*

ELISA = enzyme-linked immunosorbent assay

a. *For important considerations regarding FVIII chromogenic activity assays, see Drug Interactions listed in the US Package Insert*

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 0.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

Bleeds considered as serious adverse events should be reported on the appropriate adverse event eCRF page, regardless of whether the bleeds are consistent with the patient's pre-study disease state (the bleed will also be recorded in the patient's bleed/medication records). New, non-serious bleeds consistent with patients' pre-study disease state will not be considered adverse events and will not be recorded on the eCRF but will be captured in the patient's bleed/medication records.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as Grade 1–4, according to the World Health Organization [WHO] toxicity grading scale for determining the severity of adverse events; see Section 5.3.3); the

event itself may be of relatively minor medical significance (such as Grade 3 headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions (see Sampson's Criteria in Appendix 4)
- Thromboembolic events
- Microangiopathic hemolytic anemia or TMA (e.g. hemolytic uremic syndrome).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 0–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 0).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until the patient completes his or her last study visit.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The WHO toxicity grading scale (see Appendix 5) will be used for assessing adverse event severity. Table 13 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 13 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

WHO=World Health Organization

Note: developed by the Division of Microbiology and Infectious Diseases.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug

- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

An adverse event that occurs during or within 24 hours after *emicizumab* administration and in the investigator's opinion is judged to be related to *emicizumab* injection should be captured as an "injection-site reaction" on the Adverse Event eCRF. An injection-site reaction that is localized should be marked as a "local injection-site reaction." Associated signs and symptoms (e.g., injection-site erythema or injection-site rash) should be recorded on the dedicated Injection-Site Reaction eCRF. Systemic reactions should be recorded separately on the Adverse Event eCRF. The dedicated Injection-Site Reaction eCRF should only be used to capture the individual signs/symptoms for local injection-site reactions.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 0), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF, if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy

- Is clinically significant in the investigator's judgment.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment.

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × baseline value) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as

defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship *to emicizumab*, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of hemophilia A.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of hemophilia A, "hemophilia A progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present *during the study Screening Period*. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Hemophilia A

Medical occurrences or symptoms of deterioration that are anticipated as part of hemophilia A should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When

recording an unanticipated worsening of hemophilia A on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated hemophilia A").

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event.

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of *emicizumab* should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No information about overdose is currently available. Accidental overdose may result in enhanced procoagulant effects of emicizumab. As with any medication overdose, patients may be more susceptible to both known and unknown risks and should be closely monitored as appropriate by the investigator.

5.3.5.13 Patient-Reported Outcome Data

The PRO measurements are described in Section 4.5.8. The methods for collecting and analyzing PRO data are different from those used for observed or volunteered adverse events. Owing to these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events. All adverse events will be reported by the

investigator on the Adverse Event eCRF. The PRO data will be presented in separate tables, figures, and data listings from the adverse event data, and will be included in the appropriate section of the final study report.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to *emicizumab*:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details).

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board/Ethics Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible individual, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible individual contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of *emicizumab*, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately

(i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of *emicizumab*, serious adverse events and adverse events of special interest will be reported until the last scheduled study visit (see Section 5.3.1). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the patient has completed the 2-year treatment period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of *emicizumab*. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue *emicizumab* and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Although embryo-fetal development studies are not available, condom use will not be required in male patients enrolled in the study, as the margin between the minimal anticipated biological effect level (MABEL) plasma concentration (7 ng/mL) and the estimated maternal C_{max} (for both the 1.5 and 3.0 mg/kg per week dosing regimens) is greater than 10-fold (Banholzer et al. 2012). At this time, very little emicizumab is thought to transfer into semen, and there are no known reproductive risks to female partners of male patients treated with emicizumab. Therefore, contraception use by male patients is not

required for participation in the study, and to be consistent with this, no proactive collection of pregnancy information for female partners of male patients treated with emicizumab will be required.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to *emicizumab* should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. At the time of pregnancy outcome, reporting instructions provided in Section 0 should be followed.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as the end of the 2-year treatment period), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events

directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Emicizumab Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis population is all patients who have received at least one dose of *emicizumab* (safety population). The intent-to-treat (ITT) population includes all enrolled patients.

No formal statistical hypothesis tests will be performed and all analyses are considered descriptive.

6.1 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 200 patients is planned for this study.

For the purpose of the sample size calculation, the incidence of adverse events was chosen as the safety endpoint of primary interest.

If the observed incidence of adverse events is between 2.5% and 15%, the precision for the estimated incidence rate is presented below according to the 95% Clopper-Pearson confidence intervals (CIs) (Table 14).

Table 14 Clopper-Pearson 95% CIs for the Incidence of AEs (Based on N=200)

Number of AE Events (Observed AE Incidence)	95% Clopper-Pearson CIs
5 (2.5%)	0.8%–5.7%
10 (5.0%)	2.4%–9.0%
20 (10.0%)	6.2%–15.0%
30 (15.0%)	10.4%–20.7%

AE=adverse event, CI=confidence interval

6.2 SUMMARIES OF CONDUCT OF STUDY

Flow of patients through the study will be displayed in a 'Consolidated Standards of Reporting Trials (CONSORT)' diagram. A clear account of all patients who enrolled in the study and who entered, discontinued, and completed the initial and maintenance phases of the study will be displayed. The reasons for premature discontinuation from study treatment and the reasons for study withdrawal will be described. In addition, the number of patients who received dose up-titration will also be described. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. *Major* protocol *deviations* and the number of patients with at least one *major protocol deviation* will be summarized in terms of both the safety and ITT populations.

Observation time and duration of follow-up will be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, and self-reported race and ethnicity) will be summarized using means, standard deviations, medians, and ranges for continuous variables and *frequencies and percentages* for categorical variables, as appropriate. For each variable (continuous or categorical), the number of available observations will be reported. Medical history will be tabulated and previous concomitant medications will be summarized.

6.4 SAFETY ANALYSES

The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with *congenital* hemophilia A who have *persistent* inhibitors against FVIII at enrollment. Of primary interest in this study are the incidence and severity of *all* adverse events, including thromboembolic *events*, *microangiopathic hemolytic anemia or* TMA, systemic hypersensitivity, anaphylaxis, and anaphylactoid events.

All adverse events will be assessed according to the WHO toxicity grading scale. The incidence, type, and grade of adverse events will be summarized according to the primary system-organ class (SOC) and, within each SOC, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. For each adverse event, data will be provided on the timing (start and stop date, time of onset in comparison with last dose of emicizumab received, and doses of emicizumab received), severity, relationship to *emicizumab*, outcome,

and effect on therapy. The data may be presented together with two-sided 95% Clopper-Pearson CIs if appropriate.

In addition, as part of the safety evaluation, additional assessments will be summarized descriptively as follows:

- Cumulative study medication doses, dose modifications (delays and interruptions), and duration of exposure
- Compliance with respect to emicizumab intake (planned vs. received)
- Changes from baseline in physical examination findings
- Vital signs over time:
  - Vital signs will be analyzed using descriptive statistics for continuous variables and presented graphically over time with associated 95% CIs.
- Laboratory parameters (hematology and chemistry):
  - These parameters will be presented in shift tables of WHO toxicity grade at baseline versus worst grade during the treatment period. Selected laboratory parameters will be summarized in terms of mean, standard deviation, minimum, and maximum. Laboratory parameters will also be presented graphically over time*, if appropriate*.

All safety variables will be analyzed for the safety population. For each variable, the number of available observations will be reported. The safety population includes all patients who have received at least one dose of *emicizumab*.

The primary safety analysis will occur at the end of the study.

The iDMC (see Section 0) will evaluate the study data, including the emerging safety results, at periodic reviews and recommend to the Sponsor whether *the protocol should be amended or* the study should be stopped early. All summaries and analyses will be prepared by the *Study Management Team (*SMT*)* statistician and presented for iDMC review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

A detailed description of the statistical methods that will be used for the primary analyses will be provided in the Statistical Analysis Plan (SAP).

6.5 EFFICACY ANALYSES

The efficacy analyses will involve evaluating the number of bleeds over time, the HRQoL of patients, the health status of patients according to EQ-5D-5L scores, and assessing patient preference for the emicizumab regimen compared with the previous regimen used.

The definition of a bleed is described in Section 4.5.7.1. *Patients will be asked to record any hemophilia medication use (including emicizumab) and information regarding any bleeding events*. The patients should record this information at least every week even if they do not experience a bleed. The number of bleeds will be compared with patients' bleed rate prior to study entry and will be summarized descriptively.

HRQoL (using the Haem-A-QoL or the Haemo-QoL-SF), health status (using the EQ-5D-5L), and patient treatment preference will be assessed as per the Schedule of Activities (Appendix 1
Schedule of Activities

).

Adherence with the HRQoL, health status, and patient treatment preference measures will be summarized.

As different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) will be used for adult and adolescent patients, all calculations and analyses will be conducted separately for each patient population. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively. The HRQoL scale scores for all patients will be evaluated after 6 months of treatment, a timepoint which is consistent with other recent registrational studies in hemophilia (Lentz et al. 2013; Mahlangu et al. 2014; Powell et al. 2013) and analyses of this type of data (Santagostino et al. 2014; Wyrwich et al. 2015). Paired t-tests will be used to compare the on-treatment scores with the baseline scale scores for each HRQoL measure. Within-patient changes from baseline for the different HRQoL scale scores will also be calculated for each of the on-treatment timepoints. The proportion of patients who report changes that exceed clinically meaningful thresholds will be reported.

For each of the EQ-5D-5L assessments, the number and percentage of patients in each of the five categories for each question will be evaluated. Changes in the EQ-5D-5L index utility score from baseline will also be *reported*. In addition, summary statistics including mean, standard deviation, median, minimum, and maximum will be calculated according to the patients' health state using the EuroQoL visual analogue scale (EQ-VAS). The proportion of patients who report changes that exceed the clinically meaningful threshold on the EQ-5D-5L index and the EQ-VAS scores will be reported.

Summary statistics on patient preference for the emicizumab regimen compared with the previous regimen used will be presented.

A detailed description of the statistical methods that will be used for the secondary analyses will be provided in the SAP.

6.6 IMMUNOGENICITY ANALYSES

Data on the impact of immunogenicity (anti-emicizumab antibodies) on safety, efficacy, and/or PK will be summarized using standard language/terminology (Shankar et al. 2014).

The immunogenicity analyses will include patients with at least one pre-dose and one post-dose anti-emicizumab antibody assessment. The numbers and proportions of antibody-positive patients and antibody-negative patients during the treatment period will be summarized. Patients are considered to be antibody-positive if they are negative at baseline but develop an anti-emicizumab antibody response following *emicizumab* administration (treatment-induced antibody response), or if they are positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥ 0.60 titer units) than the titer of the baseline sample (treatment-enhanced antibody response). Patients are considered to be antibody-negative if they are negative at baseline and all post-baseline samples are negative, or if they are positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected). The relationship between anti-emicizumab antibody status and safety, efficacy, and PK endpoints will be analyzed and reported descriptively via subgroup analyses.

A detailed description of the statistical methods that will be used for the secondary analyses will be provided in the SAP.

6.7 PHARMACOKINETIC ANALYSES

For all patients, pre-dose (concentration at the end of the dosage interval [C_{trough}]) plasma concentrations of emicizumab will be presented descriptively for each timepoint. Data presented will include arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data for emicizumab following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as AUC, will be derived from individual post-hoc predictions. Results may be pooled with data from previous Phase I-III studies. If conducted, these analyses will be presented in a dedicated report.

6.8 BIOMARKER ANALYSES

Data from PD, safety biomarker, safety coagulation system biomarker, and bone and joint biomarker assessments will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analyses

The first *interim* analysis will be performed once *approximately* 100 patients have received treatment with emicizumab for at least 24 weeks. A second *interim* analysis will be performed when *approximately* 100 patients have received treatment with emicizumab for at least 52 weeks. The data from these analyses will subsequently be presented to the iDMC in order to enable them to effectively monitor the study (see Section 0).

Details regarding the planned interim analyses will be provided in the SAP and iDMC charter.

6.9.2 Optional Interim Analysis

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two additional interim efficacy analyses (i.e., beyond what is specified in Section 0). The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. Any interim analyses will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of

the data. Data entered manually will be collected using EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data and ePRO data will be sent directly to the either the Sponsor or the vendor using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

PRO data will be collected electronically through the use of electronic devices provided by an ePRO vendor *(HRQoL and EQ-5D-5L) or using a paper questionnaire (EmiPref). Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.* The electronic device is designed for entry of data in a manner that is attributable, secure, and accurate, in compliance with electronic records: 21 Code of Federal Regulations, Part 11. The *PRO* data *from the device* will be transmitted electronically *to the eCRF* in real time. Only identified and trained users may view the data, and their actions *(if any)* will become part of the audit trail. The Sponsor will have view-only access *to PRO data*. The Sponsor will receive all data (including requested meta-data) entered by the patients on the ePRO devices and all relevant study documentation.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required.

In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 0.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the U.S. or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the E.U. or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent

Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The IxRS system will be used to confirm the shipment condition and content of the IMP (see Section 0). A central laboratory will be used to conduct all laboratory assessments (see Section 0). A CRO will be responsible for data management of this trial (see Section 7.1). An iDMC will review the safety, efficacy, immunogenicity, and PK data collected during the study (see Section 0). The procedures that will be used by the iDMC will be detailed in an iDMC charter.

9.4.1 Independent Data Monitoring Committee

An iDMC will be assembled to review the safety data collected during the study. The iDMC members will consist of, at minimum, independent hemostasis/thrombosis experts and a statistician, none of whom will be otherwise involved in the conduct of study. All analyses for review by the iDMC will be prepared by the SMT statistician. Monitoring and analysis of all

significant safety events will be performed on a continuous basis. A first interim analysis of the study data will be performed once approximately 100 patients have received treatment with emicizumab for at least 24 weeks (see Section 0), and a second interim analysis will be performed when approximately 100 patients have received treatment with emicizumab for at least 52 weeks. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor according to the emerging data.

The SMT statistician will perform analyses and provide tables and listings to support the study reviews by the iDMC. The safety data that will be provided will include demographic data, adverse events (the incidence and severity of all adverse events, including thromboembolic events, microangiopathic hemolytic anemia or TMA, systemic hypersensitivity, anaphylaxis, and anaphylactoid events), medication dose information, physical examination findings, vital sign data, and laboratory abnormalities (hematology and chemistry). If available, the efficacy data that will provided will include the number of bleeds over time, ABR data, the HRQoL of patients, the health status of patients according to EQ-5D-5L scores, and patient preference for the emicizumab regimen compared with the previous regimen used. Further information will be provided on request.

Following each meeting, the iDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the iDMC may recommend stopping the study for safety reasons.

The meeting schedule and all other iDMC-related activities will be specified in a separate iDMC charter. All closed meetings will be summarized in written minutes available only to iDMC members. These minutes will be kept by the iDMC chair until the end of the study. The recommendations can be communicated to the Sponsor verbally but have to be confirmed in writing according to a pre-defined timeframe.

The final decision of acting upon the recommendations from the iDMC will rest with the Sponsor.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information.

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

9.7 STUDY PARTICIPANT SURVEY

Consenting patients may be asked about their study experience via a short study-specific survey.

Survey questions will ask the patient to rate their study experience on a scale of 1-5 on topics that include the following: information provided prior to the study, the consent and enrolment process, study participation, study results and feeling appreciated as a study patient.

Patients will be asked to complete the survey at the end of the study. The goal of this survey is to identify areas where Roche is performing well and areas where improvement may be required.

Information will be provided to the Sponsor securely and on an anonymous basis and consent to the survey is totally voluntary and does not affect patient's enrolment to the study.

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Appendix 1
Schedule of Activities

	Screening	Treatment											Early Termination / Study Completion	Safety Follow-up Visit [a]
Visits	**Wk -4 to Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**3 m**	**6 m**	**9 m**	**12 m**	**15 m [b]**	**18 m**	**21 m [b]**	**Unscheduled visit**	**2 years**	
Time Window, days			± 2	± 2	± 2	± 7	± 7	± 7	± 14	± 14	± 30	± 30		± 30	
Informed consent [c]	x														
Inclusion / exclusion criteria	x														
Medical history and demographics [d]	x														
Physical examination [e]	x	x	x	x	x	x	x	x	x		x		x	x	x
Vital signs [f]	x	x	x	x	x	x	x	x	x		x		x	x	x
Concomitant medications [g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology and *blood* chemistry [h,*r*]	x	x	x	x	x	x	x	x	x		x		x	x	x
Pregnancy test [*i*,*r*]	x	x			x	x	x	x	x		x		x	x	
HIV and hepatitis serology [j]	x														
Anti-FVIII antibodies [k,*r*]		*x*			x	x	x		x		x			x	x
Anti-emicizumab antibodies [l,*r*]		x			x	x	x		x		x			x	x

Appendix 1
Schedule of Activities (cont.)

	Screening	Treatment												Early Termination / Study Completion	Safety Follow-up Visit [a]
Visits	**Wk -4 to Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**3 m**	**6 m**	**9 m**	**12 m**	**15 m [b]**	**18 m**	**21 m [b]**	**Unscheduled visit**	**2 years**	
Time Window, days			± 2	± 2	± 2	± 7	± 7	± 7	± 14	± 14	± 30	± 30		± 30	
ePRO bleed / medication recording [m]		x	x	x	x	x	x	x	x	x	x	x	x	x	
Surgical events [n]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Adverse events [o]	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Management *of emicizumab* [p]		x	x	x	x	x	x	x	x	x	x	x	x	x	
HRQoL [q]		x				x	x		x		x			x	
Health status (EQ-5D-5L) [q]		x				x	x		x		x			x	
Treatment preference questionnaire (EmiPref) [r]						x									
PK assessment [s,t]		x	x	x	x	x	x		x		x			x	x
Safety biomarkers assessment [s,u]		x			x	x	x		x		x			x	x
Safety coagulation system biomarkers assessment [s,v]		x			x										
PD biomarkers assessment [s,w]		x			x	x	x		x		x			x	

Appendix 1
Schedule of Activities (cont.)

	Screening	Treatment												Early Termination / Study Completion	Safety Follow-up Visit [a]
Visits	**Wk -4 to Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**3 m**	**6 m**	**9 m**	**12 m**	**15 m [b]**	**18 m**	**21 m [b]**	**Unscheduled visit**	**2 years**	
Time Window, days			± 2	± 2	± 2	± 7	± 7	± 7	± 14	± 14	± 30	± 30		± 30	
Bone and joint biomarker assessment *(fasting)* [s,x]		x					x				x			x	
Additional laboratory assessments [y]		*For breakthrough bleeds treated with bypassing agents*													
Emicizumab administration		Weekly subcutaneous injection													

d=day; eCRF=electronic Case Report Form; EQ-5D-5L=EuroQoL Five-Dimension-Five Levels Questionnaire; FVIII=Factor VIII; Haem-A-QoL=Hemophilia Adult Quality of Life Questionnaire; Haemo-QoL-SF=Hemophilia Quality of Life Short Form; HIV=human immunodeficiency virus; HRQoL=Health-Related Quality of Life; m=months *(based on calendar months)*; PD=pharmacodynamic; PK=pharmacokinetic; Wk=week

Notes: the maximum allowable time between Screening and enrollment is 4 weeks; if the elapsed time between Screening and enrollment is more than 4 weeks, Screening must be repeated.

Except for the bleed/medication records, all other patient data will be collected during clinic visits.

b. *Patients who discontinue emicizumab prior to the completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first.*

c. Optional visits, as per the investigator's discretion.

d. **Written informed consent** must be obtained before any study-specific screening *tests or evaluations are* performed. *For adolescents (i.e., patients who are 12–17 years of age), an Informed Assent Form will be completed instead. Parents or caregivers of adolescents will also complete an Informed Consent Form.* The enrollment form will be completed after informed consent and/or assent is obtained. *All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.*

e. ***Medical history and demographics*** data will be collected from patient medical records and documented in the eCRF. *Medical history includes hemophilia-related history, clinically significant diseases, procedures (including prior surgeries), use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior ITI, anaphylaxis, or known thrombophilia. It should also include all medication taken in the*

4 weeks prior to screening (including prescription drugs, over-the-counter drugs, and herbal/homeopathic remedies and therapies). Any hemostatic medications (e.g. bypassing agents) and other medications used to treat or prevent bleeds in the 6-month period prior to starting emicizumab treatment will also be collected. Demographic data will include age, sex, and self-reported race and ethnicity.

f. A complete **physical examination** will be performed *during* Screening *and should include, but not necessarily be limited to, an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF.* Targeted physical examinations *(i.e.,* joints for bleeds, evidence of arthropathy; skin for bruises, hematomas and *ISRs;* other organ systems *as clinically indicated)* should be *conducted at subsequent visits or* as clinically indicated. *New or worsened clinically significant abnormalities from screening should be recorded as adverse events, if appropriate, on the Adverse Event eCRF.*

g. ***Vital signs*** *include measurement of* body temperature (oral, rectal, axillary, or tympanic), *heart and respiratory rates,* blood pressure and weight. *On treatment days, measurement should occur* prior to emicizumab *administration*. Height will be measured and recorded only *during* Screening and 6 and 12 months after starting emicizumab. *Additional vital signs assessments may also be taken anytime as unscheduled assessments as judged by the investigator. In addition,* vital signs may be taken to help monitor for hypersensitivity reactions during or after injections *at the investigator's discretion, although these data* should not be entered into the eCRF.

h. *The definition of* ***concomitant medications****, as well as permitted and prohibited medications is described in Section 4.4. Concomitant medications used by a patient from 4 weeks prior to initiation of emicizumab to the Study Completion/Early Termination Visit (or to the Safety Follow-up Visit, if applicable) should be reported to the investigator and recorded on the Concomitant Medications eCRF. Treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), will be collected in the bleed records.*

i. ***Hematology and blood chemistry*** assessments will include a complete blood count with differential and serum chemistries *(see Section 4.5.6.1). L*aboratory assessments completed *during* Screening do not have to be repeated at Week 1, if the period between Screening and Week 1 is ≤ 5 days and there has been no change in the patient's health status as assessed by the investigator. *Samples will be sent to the central laboratory for analysis.*

j. ***Pregnancy tests:*** Female patients of childbearing potential (including those who have had a tubal ligation) will be required to have a negative serum pregnancy test result *during* Screening and again within 7 days prior to the first dose of emicizumab. *U*rine pregnancy tests *will be* performed *throughout the study treatment period.* Pregnancy testing will be *conducted* at the local laboratory.

k. *The specific tests utilized for* ***hepatitis and HIV serology*** *testing are per local standard of care. As this patient population is at high risk for HIV, hepatitis A, B and C, sites should consider testing for these. While the specific serological tests used is at the discretion of the Investigator, this is with the understanding that the status of that participants' hepatitis or HIV is confidently known at time at enrollment. HIV and hepatitis serology tests will be conducted at the local laboratory.*

l. *For the assessment of* ***anti-FVIII antibodies*** *(inhibitors), functional assays that utilize a clotting readout (classic Bethesda or Nijmegen assay) cannot be used for patients on emicizumab therapy as emicizumab drives clotting even in the presence of FVIII inhibitors, causing a false-negative test result (see Section 5.1.3). After the first dose, local measurement of FVIII inhibitors, if indicated, requires use of an ELISA-based test or a chromogenic Bethesda assay. At the discretion of the local investigator, any additional urgent request to assess FVIII inhibitors will need to be sent to the central laboratory (see Appendix 2 for additional information). Plasma samples for anti-FVIII antibodies will be analysed at the central laboratory*

m. *Plasma* samples *are required for immunogenicity assessments* to detect **anti-emicizumab antibodies**. *Additional* samples to detect anti-emicizumab antibodies may also be drawn at the time of hypersensitivity events or following suspected loss of efficacy. *Samples will be analysed* at *the* central laboratory.

Appendix 1
Schedule of Activities (cont.)

n. ***ePRO bleed / medication recording:*** At the Week 1 visit, patients will be trained on how to record their bleeds and hemophilia medication use *on the ePRO device where possible*. Data that need to be recorded will include the site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. *At least once a week, patients will need to record any hemophilia medication use (including emicizumab) and information regarding any bleeding events*. Investigator review of patient-reported bleed/medication records with the patient/caregiver will occur for completeness and accuracy at all of the visits during the treatment period, at study completion, at any unscheduled visits (if required), and at the Early Termination Visit (if required).

*o. Thorough documentation on **surgical events** will be requested, including type of surgery or procedures, treatments, outcomes, etc.*

p. ***Adverse events:*** *After informed consent has been obtained but prior to initiation of emicizumab, only serious adverse events caused by a protocol-mandated intervention should be reported.* Injection-site reaction adverse events will be collected on *the injection site reaction form.*

q. ***Management of emicizumab:*** Drug dispensation will not occur at the Study Completion Visit or the Early Termination Visit (if required). Patients will only receive *emicizumab* during an unscheduled visit if drug dispensation is required at this time.

r. ***HRQoL and EQ-5D-5L:*** *P*atients will be *requested* to complete Haem-A-QoL (adults age: ≥ 18 years) or the Haemo-QoL-SF (adolescents ages: 12−17 years) questionnaire and the EQ-5D-5L questionnaire. *Questionnaires will be self-administered electronically before the patient/caregiver receives any information on disease status, prior to the performance of non-PRO assessments, and prior to emicizumab administration (if on a treatment day). Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.*

s. ***EmiPref:*** At the 3-month assessment, patients will be prompted to complete *a paper version of* the EmiPref questionnaire *(Appendix 3). The questionnaire will be self-administered before the patient/caregiver receives any information on disease status, prior to the performance of non-PRO assessments, and prior to emicizumab administration (if on a treatment day*).

t. *On treatment days, blood collection should occur within 2 hours prior to emicizumab administration unless otherwise specified. Unless otherwise specified, additional analysis will be performed at a local laboratory, as per the investigator's discretion. Any additional laboratory results which are required as part of the patient's safety assessment should be recorded in the unscheduled visit eCRFs. Central labs are part of the non-eCRF data which will be sent to the Sponsor directly by the central lab vendor.*

u. *Plasma samples are required for **PK assessments.** On days where samples are to be collected, the emicizumab injection will be performed in the clinical unit. One single pre-dose sample is required on the applicable visits. Samples will be analysed by the* central laboratory.

v. *Plasma samples for **safety biomarkers** must be citrate plasma. Tests may include, but are not limited to, D-dimer. Samples will be analysed by the central laboratory. See Appendix 2.*

w. Plasma samples for **safety coagulation system biomarker** assessments *must be citrate plasma. Tests include* FVIII:Ag, FIX:Ag and FX:Ag. *Samples will be analysed by the central laboratory. See Appendix 2.*

x. *Plasma samples for **PD biomarker assessments** must be citrate plasma. Tests will include, but are not limited to,* FVIII activity and modified aPTT (one stage). *Time windows for sample collection are specified in Appendix 2*
Schedule of Biomarker Samples

y. . Additional plasma samples will be collected for future exploratory research, which may include tests such as clot waveform analysis (CWA) and others (see Appendix 2
Schedule of Biomarker Samples

z.). *Samples will be analysed by the central laboratory.*

Appendix 1
Schedule of Activities (cont.)

aa. Serum and plasma EDTA samples *for* ***bone and joint biomarkers*** must be collected after fasting (no food or drink other than water for at least 8 hours prior to the blood draw). Ideally these samples should be collected in the morning (before noon), in order to control for diurnal variation. Please consult the Central Laboratory Services Manual for details. The selection of exploratory bone and joint biomarkers to be tested will build on findings from biomarker analyses in other emicizumab trials and may include CTX-1, OPG, P1NP, and soluble RANK-L (see Appendix 2 Schedule of Biomarker Samples

bb.). *Samples will be analysed by the central laboratory.*

cc. ***Additional laboratory assessments****: In the event of a breakthrough bleed that is treated with bypassing agents, it is recommended that the following laboratory tests will be performed within 24–48 hours of initial bypassing agent use (these tests will be conducted so that the investigator can monitor the patient for potential thromboembolic events and microangiopathic hemolytic anemia or TMA). These tests include platelet count, serum creatinine, LDH and schistocytes. A plasma sample should also be provided for central laboratory monitoring of prothrombin fragment F1+2, fibrinogen and D-dimer.* Samples for these tests should ideally be analysed at the central laboratory. *Exceptionally in urgent situations where results are required quickly, local laboratory testing can be used, with results recorded in the eCRF. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours until 24–48 hours after the last dose of bypassing agents is administered to treat a specific bleed. If applicable, laboratory results should be recorded in the unscheduled visit eCRFs.*

Appendix 2
Schedule of Biomarker Samples

Sample	Visit [a]	*Time window*	Biomarker assays [b]
Safety biomarkers [c]	*Week 1*	*Day 1*	*May include, but are not limited to, D-dimer*
	Week 5	*± 2 days*	
	3 months	*± 7 days*	
	6 months	*± 7 days*	
	12 months	*± 14 days*	
	18 months	*± 30 days*	
	Study completion	*± 30 days*	
	Safety Follow-up Visit (if applicable)		
Safety coagulation system biomarkers [c]	*Week 1*	*Day 1*	*FVIII:Ag, FIX:Ag and FX:Ag*
	Week 5	*± 2 days*	
PD *biomarkers* [c]	Week 1	*Day 1*	*Will include, but are not limited to:* *FVIII inhibitor titer,* Modified aPTT (one-stage), FVIII activity
	Week 5	*± 2 days*	
	3 months	*± 7 days*	
	6 months	*± 7 days*	
	12 months	*± 14 days*	
	18 months	*± 30 days*	
	Study completion	*± 30 days*	
Bone and joint *biomarkers (fasting)* [d]	Week 1	*Day 1*	Exploratory biomarkers of bone turnover and joint health *[e]*
	6 months	*± 7 days*	
	18 months	*± 30 days*	
	Study completion	*± 30 days*	

aPTT=activated partial thromboplastin time; CTX-1=C-terminal telopeptide of collagen 1; CWA=clot waveform analysis; EDTA=ethylenediaminetetraacetic acid; OPG=osteoprotegerin; P1NP=procollagen type 1 amino-terminal propeptide; PD=pharmacodynamic; RANK-L=receptor activator of nuclear factor kappa-B ligand

a. All samples are to be collected *within 2 hours* prior to emicizumab injection (if applicable) *unless otherwise specified.*

b. Assays that will be tested are listed. Blood volumes and processing procedures will be specified in the *Central* Laboratory *Services* Manual. *Biomarker assessments will be conducted at the central laboratory. Additional analysis will be performed at a local laboratory, as per the investigator's discretion.*

c. Samples are required to be citrate plasma. Additional plasma will be collected for future exploratory research, which may include tests such as CWA and others.

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

d. Serum and plasma EDTA samples for bone markers must be collected after fasting (no food or drink other than water for at least 8 hours prior to the blood draw). Ideally these samples should be collected in the morning (before noon), in order to control for diurnal variation. Please consult the Central Laboratory Services Manual for details.

e. The selection of exploratory bone and joint biomarkers to be tested will build on findings from biomarker analyses in other emicizumab trials. Biomarkers that have been tested in these trials include CTX-1, OPG, P1NP, and soluble RANK-L.

Appendix *3*~~3~~
EmiPref Patient Preference Questionnaire

(Paper Version, United Kingdom / English)

Instructions: You have been treated with intravenous (IV) Factor VIII or bypassing agent (your old hemophilia treatment) and prophylactic subcutaneous (SC) emicizumab (the new study drug treatment). Please complete the following questions based on your experience with these treatments.

There are no right or wrong answers and your responses will not influence your continued participation in the study or treatment with emicizumab.

1. Which of the treatments would you prefer to take as the treatment for your hemophilia? (Mark ONLY one response)

	Prefer my old hemophilia treatment (IV)
	Prefer the new study drug treatment (SC)
	Have no preference

If you indicated a preference, please complete question 2.

If you did not have a preference, you do not need to complete questions 2.

Appendix *3*
EmiPref Patient Preference Questionnaire (cont.)

2. Below are some factors that may have influenced your treatment preference. Please indicate which factors had an influence on YOUR preference. Please indicate YES (this influenced my preference) or NO (this did not influence my preference) for each item.

   On those you said YES to, please rank the top 3 in order of importance (1 being the "most important" reason for your preference).

	Yes	No	Importance rank
Route of administration (IV or SC) was easier			
Pain associated with treatment was less			
Worry about finding a vein was less			
Concern over port use/infection was less			
Administration was easier			
Able to keep treatment at room temperature			
Time to administer treatment was shorter			
The frequency of treatments was lower			
Effect on other activities (work, school, sports, social interactions) was less			
Impact on family members and friends was less			
Worries about having a bleed were less			
Quality of life, in general, was better			
It was easier to take every dose my doctor recommended			
Made me feel more 'normal'			

3. Please add any additional information about your experience with the study drug (SC emicizumab).

Appendix 4*4*
Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network.[1] Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue/uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure [a]
- Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline.

[1] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

a. Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

Appendix 5

WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	< 6.5 g/dL
Absolute neutrophil count	1000–1500/mm^3	750–999/mm^3	500–749/mm^3	< 500/mm^3
Platelets	75000–99999/mm^3	50000–74999/mm^3	20000–49999/mm^3	< 20000/mm^3
PT	1.01–1.25 × ULN	1.26–1.5 × ULN	1.51–3.0 × ULN	> 3 × ULN
aPTT	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3 × ULN	> 3 × ULN
Fibrinogen	0.75–0.99 × LLN	0.50–0.74 × LLN	0.25–0.49 × LLN	< 0.25 × LLN
Fibrin split product	20–40 µg/mL	1–50 µg/mL	51–60 µg/mL	> 60 µg/mL
Methemoglobin	5%–9.9%	10.0%–14.9%	15.0%–19.9%	> 20%
LIVER ENZYMES				
AST (SGOT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
ALT (SGPT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
GGT	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Alkaline phosphatase	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	> 5.0 × ULN
CHEMISTRIES				
Hyponatremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	> 165 mEq/L or mental status changes or seizures

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	> 7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	< 30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116–160 mg/dL	161–250 mg/dL	251–500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	< 6.1 mg/dL or life-threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4–1.2 mEq/L	1.1–0.9 mEq/L	0.8–0.6 mEq/L	0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0–2.4 mg/dL	1.5–1.9 mg/dL or replacement Rx required	1.0–1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1–1.5 × ULN	1.6–2.5 × ULN	2.6–5 × ULN	> 5 × ULN
BUN	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Creatinine	1.1–1.5 × ULN	1.6–3.0 × ULN	3.1–6 × ULN	> 6 × ULN or required dialysis
URINALYSIS				
Proteinuria	1+or < 0.3% or < 3 g/L or 200 mg–1 g loss/day	2-3+ or 0.3-1.0% or 3-10 g/L 1-2 g loss/day	4+or > 1.0% or > 10 g/L 2–3.5 g loss/day	Nephrotic syndrome or > 3.5 g loss/day
Hematuria	Microscopic only	Gross, no clots	Gross + clots	Obstructive or required transfusion

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CARDIAC DYSFUNCTION				
Cardiac rhythm		Symptomatic, transient signs, no Rx required	Recurrent/persistent; no Rx required	Requires Rx
Hypertension	Transient inc. > 20 mm; no Rx	Recurrent, chronic, > 20 mm, Rx required	Requires acute Rx; no hospitalization	Requires hospitalization
Hypotension	Transient orthostatic hypotension, no Rx	Symptoms correctable with oral fluids Rx	Requires IV fluids; no hospitalization required	Requires hospitalization
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no Rx	Symptomatic effusion; pain; ECG changes	Tamponade; pericardiocentesis or surgery required
Hemorrhage, blood loss	Microscopic/occult	Mild, no transfusion	Gross blood loss; 1−2 units transfused	Massive blood loss; > 3 units transfused
RESPIRATORY				
Cough	Transient; no Rx	Treatment-associated cough local Rx	Uncontrolled	
Bronchospasm, acute	Transient; no Rx < 70%−79% FEV_1 (or peak flow)	Requires Rx normalizes with bronchodilator; FEV_1 50%−69% (or peak flow)	No normalization with bronchodilator; FEV_1 25%−49% (or peak flow retractions)	Cyanosis: FEV_1 < 25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	Mild discomfort; no limits on activity	Some limits on eating/drinking	Eating/talking very limited	Requires IV fluids
Nausea	Mild discomfort; maintains reasonable intake	Moderate discomfort; intake decreased significantly; some activity limited	Severe discomfort; no significant intake; activities limited	Minimal fluid intake
Vomiting	Transient emesis	Occasional/moderate vomiting	Orthostatic hypotension or IV fluids required	Hypotensive shock or hospitalization required for IV fluid therapy

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Constipation	Mild	Moderate	Severe	Distensions w/vomiting
Diarrhea	Transient 3−4 loose stools/day	5-7 loose stools/day	Orthostatic hypotension or > 7 loose stools/day or required IV fluids	Hypotensive shock or hospitalization for IV fluid therapy required
NEURO AND NEUROMUSCULAR				
Neuro-cerebellar	Slight incoordination dysdiadochokinesis	Intention tremor, dysmetria, slurred speech; nystagmus	Locomotor ataxia	Incapacitated
Mood	Mild anxiety or depression	Moderate anxiety or depression and therapy required	Severe anxiety or depression or mania; needs assistance	Acute psychosis; incapacitated, requires hospitalization
Neuro control	Mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	Moderate confusion/agitation some limitation of ADL; minimal Rx	Severe confusion/agitation needs assistance for ADL; therapy required	Toxic psychosis; hospitalization
Muscle strength	Subjective weakness no objective symptoms/signs	Mild objective signs/symptoms no decrease in function	Objective weakness function limited	Paralysis
OTHER PARAMETERS				
Fever: oral, > 12 hours	37.7−38.5°C or 99.9−101.3°F	38.6−39.5°C or 101.4−103.1°F	39.6−40.5°C or 103.2−104.9°F	> 40.5°C or > 104.9°F
Headache	Mild, no Rx therapy	Transient, moderate; Rx required	Severe; responds to initial narcotic therapy	Intractable; required repeated narcotic therapy
Fatigue	No decrease in ADL	Normal activity decreased 25−50%	Normal activity decreased > 50% can't work	Unable to care for self
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema	Anaphylaxis
Local Reaction	Tenderness or erythema	Induration < 10 cm or phlebitis or inflammation	Induration ≥ 10 cm or ulceration	Necrosis

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Mucocutaneous	Erythema; pruritus	Diffuse, maculo-papular rash, dry desquamation	Vesiculation, moist desquamation, or ulceration	Exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

ADL=activities of daily living; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; GGT=gamma glutamyl transferase; IV=intravenous; LLN=lower limit or normal; PT=prothrombin time; Rx=treatment; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; ULN=upper limit of normal; WHO=World H