Official Title: **A MULTICENTER, OPEN-LABEL, PHASE III STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF EMICIZUMAB GIVEN EVERY 4 WEEKS (Q4W) IN PATIENTS WITH HEMOPHILIA A**

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STATISTICAL ANALYSIS PLAN

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SPONSOR: F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.*

PLAN PREPARED BY: [redacted]

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STATISTICAL ANALYSIS PLAN APPROVAL

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*Chugai will act as the Sponsor only in South Korea, Taiwan, and Japan. The specific details of the legal/regulatory entity within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

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1. BACKGROUND

Hemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with hemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (Mannucci and Tuddenham 2001; Franchini and Mannucci 2013).

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 men having one defective copy of the relevant gene on their X chromosome. The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical symptoms of hemophilia A include easy bruising prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage.

Recombinant FVIII (rFVIII) concentrates have been the standard-of-care treatment options for patients with hemophilia A (Kingdon and Lundblad 2002) since the 1990s. Prophylactic FVIII replacement therapy is recognized to be superior to episodic treatment of symptomatic bleeds for several decades (Khawaji et al. 2012) and has been adopted by national and international organizations as the desired treatment approach. Existing prophylactic regimens, however, commonly use infusion therapy requiring administrations 3 times a week, every other day, or even daily, depending on the patient's needs (Shapiro 2013). Combined with the fact that the regimen requires intravenous (IV) administration, the need for high frequency administration negatively impacts patient compliance as both the disease and the treatment tend to affect the health-related quality-of-life (HRQoL).

In addition up to 30% of patients with hemophilia A develop inhibitors against FVIII, thereby, requiring treatment with bypassing agents, which have a suboptimal hemostatic effect and require more frequent administrations.

The development of effective prophylactic treatment options with decreased immunogenicity and reduced treatment burden is thus a high, unmet medical need in the population of patients with hemophilia A.

Emicizumab (also known as ACE910 and RO5534262) is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Emicizumab bridges activated factor IX (FIXa) and factor X (FX) to restore the function of missing activated factor VIII (FVIIIa) that is needed for effective hemostasis. In patients with hemophilia A, hemostasis can be restored irrespectively of the presence of FVIII inhibitors because emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because of the pharmacokinetic (PK)

properties of this antibody, markedly extending the dosing interval to once weekly or even less frequently, this novel compound has the potential to dramatically change the treatment of patients with hemophilia A with or without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

Currently available experience with emicizumab in humans includes data from one Phase I study (ACE001JP) and its ongoing extension, a Phase I/II study (ACE002JP). Details of the results of this study are presented in Section 1.2 of the protocol and published in Shima et al. (2016; see also Uchida et al. 2016). Based on the Phase I/II data, a clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) has been initiated. Four Phase III studies are currently ongoing and are aimed at evaluating the efficacy and safety of emicizumab at various doses and in different populations. The studies are Study BH29884, which evaluates 1.5 mg/kg weekly (QW) dose in the adult and adolescent population with FVIII inhibitors; Study BH29992, which evaluates 1.5 mg/kg QW in pediatric patients with inhibitors; Study BH30071, which evaluates a 1.5 mg/kg QW and 3 mg/kg every 2 weeks (Q2W) dose in the non-inhibitor population; and Study BO39182, which evaluates 6 mg/kg every 4 weeks (Q4W) in a mixed (inhibitor and non-inhibitor) population.

2. STUDY DESIGN

Study BO39182 is a multicenter, open-label, single-arm, Phase III clinical study that will enroll patients aged 12 years or older with severe hemophilia A, irrespective of their inhibitor status. The study consists of a PK run-in cohort and an expansion cohort (see Figure 1) and will investigate a Q4W dosing regimen that would provide patients with a treatment option that requires less frequent dosing while providing an exposure similar to 1.5 mg/kg QW and 3 mg/kg Q2W emicizumab regimens that are also currently under investigation.

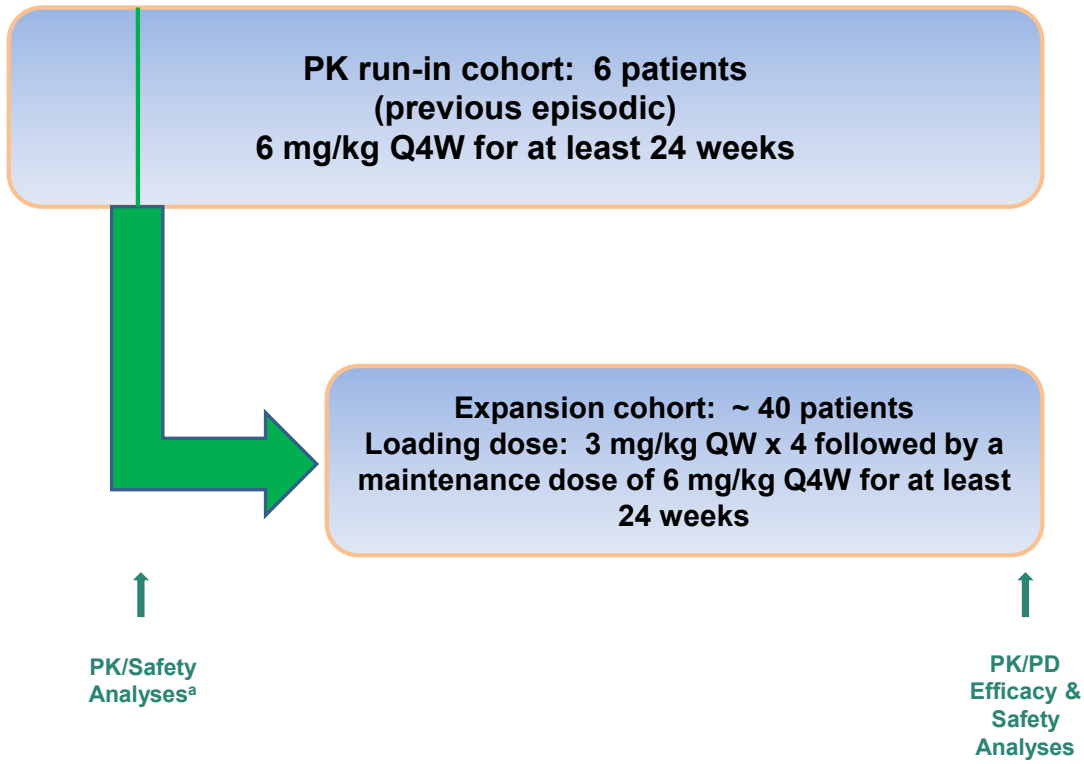
The PK run-in cohort plans to enroll 6 patients, previously on episodic treatment, to receive 6 mg/kg Q4W subcutaneously. This cohort will provide substantial knowledge on the pharmacokinetics (e.g., linearity and SC absorption) and will inform about preliminary safety and efficacy, prior to opening of the expansion cohort. Given that the main objective in this cohort is to investigate the pharmacokinetics of emicizumab after single and multiple administrations of 6 mg/kg Q4W, patients in this cohort will not receive any loading dose.

An interim analysis will be carried out on the PK run-in cohort after all the patients have been followed for at least 6 weeks. This analysis will constitute characterization of the PK profile (to assess whether the mean PK profile is as predicted [i.e., $\geq$ lower limit of 95% CI of the predicted mean PK profile]) and assessment of safety to inform the decision on whether or not to open the expansion cohort.

This analysis will be conducted by a Roche internal group of representatives from Clinical Pharmacology, Clinical Science, Clinical Safety and Statistics; no formal Internal Monitoring Committee (IMC) will be set up.

The expansion cohort will enroll 40 patients previously receiving either episodic or prophylactic hemophilia A treatment. Patients in this cohort will receive a loading dose of 3 mg/kg QW×4 subcutaneously followed by a maintenance dose of 6 mg/kg Q4W. Study objectives other than PK (i.e., efficacy and safety) will primarily be evaluated based on this cohort.

Figure 1 Study Schema for Study BO39182



PD=pharmacodynamic; PK=pharmacokinetic; Q4W=every 4 weeks; QW=every week.

[a] Analysis will occur when last patient enrolled in the PK run-in cohort has been in the study for 6 weeks.

The primary efficacy analysis will be conducted after all enrolled patients complete the 24-week treatment period, are lost to follow-up, or have withdrawn. The primary analysis will only consist of descriptive analyses of the objectives with no formal hypothesis testing.

An interim analysis for Study BO39182 may be conducted to support regulatory submissions and an interim clinical study report (CSR) may be written.

After 24 weeks of prophylactic treatment with emicizumab, all patients will be provided with the option to up-titrate their dose to 3 mg/kg QW, if they meet protocol-defined criteria of suboptimal response (see Section 4.3.2.1 of the protocol). Thereafter, the patient may choose to down-titrate to 6 mg/kg Q4W, 3 mg/kg Q2W, or 1.5 mg/kg QW; subsequent up-titration would again be allowed if protocol-defined criteria were met.

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1.

2.2 COLLECTION OF PATIENT-REPORTED DATA

2.2.1 Collection of Bleed and Medication Data

Bleed and medication data are collected through a bleed and medication questionnaire (BMQ), which was developed by the Sponsor given that no standard questionnaire for collection of this data was available. The BMQ was developed as a patient-reported measure of bleeding episodes (including cause, type, location, and symptoms of bleeds) and hemophilia-related medication use. This questionnaire was initially used in the non-interventional study (NIS; BH29768), patients with inhibitors study (BH29884), and later in the studies for pediatric patients (Study BH29992) and the non-inhibitor patients (Study BH30071).

To capture bleed data, emicizumab use, and other hemophilia medication use during study treatment, patients will complete the BMQ on a handheld device that will be provided to them during the Week 1 visit at the study site. This device will remain with the patient for the duration of the study to enter bleed and medication data weekly at a minimum. In case a patient did not experience any bleeds or administer any treatments for a week, the patient is asked to log into the device and fill in the questionnaire to confirm this. These weekly entries, in addition to the bleeds and medication entries can also be used to assess compliance. Of note, the patient is able to enter bleeds and medications for the past 8 days, including the day the entries are made. This retrospective data entry window was considered acceptable in terms of recall bias and was added in order to optimize the completeness of data collection.

Patients who withdraw from emicizumab treatment will continue to record bleeds and hemophilia medication administration until they complete the safety follow-up visit.

The patient is able to edit and delete bleeds and medications for 24 hours after they are entered. Furthermore, the investigator and patient are instructed to review the data together at every clinic visit. If the patient has been unable to enter data for any reason, the investigator is able to do so using a data clarification request (Data Change Request [DCR]; not subject to the previous 8-day data entry window). Note, the symptoms of joint and muscle bleeds are not collected in this case because the patient may not be

able to reliably remember them. In addition, the investigator is able to request a change be made to the vendor's database by submitting a DCR.

Furthermore, the Sponsor's data manager and Medical Monitor review the patient entered data for clear inconsistencies against data collected on the electronic Case Report Form (eCRF) or to identify obvious data points to be clarified (e.g., missing entry of the weekly emicizumab injection). These requests are sent to the investigator, who reviews them with the patient and may enter the data via the site data entry system or request a change to be made in the vendor's database via a DCR, if necessary.

2.2.2 Collection of Health-Related Quality-of-Life Data

The Haem-A-QoL, Haemo-QoL-SF, and European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) questionnaires; data regarding days away from school/work; and patient preference questionnaire at Study Week 17 that asks which treatment they would prefer to continue to receive after having been treated with IV FVIII or bypassing agents (episodic or prophylactic) prior to study entry and SC emicizumab during the study, are filled in by the patients using a separate electronic, handheld device that is different from the BMQ device. While the BMQ device is kept by the patient, the HRQoL questionnaire device is kept at the site and is available to the patient at the scheduled visits according to the schedule of assessments (see Appendix 2).

2.3 OBJECTIVES AND ENDPOINTS

2.3.1 Efficacy Period for All Endpoints

The start of the efficacy period for each individual patient is defined as the date of first emicizumab administration.

The end of the efficacy period is defined as the date of the clinical cutoff or the date of withdrawal from the initial study period (i.e., treatment phase according to eCRF-Subject Disposition page), whichever is earlier. For patients whose dose is up-titrated, the efficacy period ends a day prior to the first day on the up-titrated dose.

The efficacy period on a given up-titrated/down-titrated dose starts with the first day on this dose and ends on the date of the clinical cutoff or the date of withdrawal or date preceding the next up-titration/down-titration. Bleeds on the up-titrated/down-titrated dose are analyzed separately (see Section 4.1).

Bleed rate is defined as the number of bleeds over the efficacy period. A bleed is counted in the primary analysis if it was treated with coagulation factors and fulfills the adapted International Society on Thrombosis and Haemostasis (ISTH; Blanchette et al. 2014) criteria, as described in Section 4.5.8 of the protocol. More specifically, the rules outlined in the sections below are applied.

2.3.2 Bleed-Related Efficacy Objectives and Endpoints

The key efficacy objective is to characterize the efficacy of 6 mg/kg emicizumab Q4W based on the number of bleeds over time for patients in the expansion cohort.

The bleed-related efficacy objectives are as follows:

- To evaluate the efficacy of prophylactic emicizumab in maintaining adequate control of bleeding based on treated bleeds over time
- To evaluate the clinical effect of prophylactic emicizumab on the number of joint bleeds over time
- To evaluate the clinical effect of prophylactic emicizumab on the number of target joint bleeds over time (target joints are defined as joints with ≥ 3 bleeds occurring in the same joint over the last 24 weeks prior to study entry; see Section 2.3.2.5)
- To evaluate the clinical effect of prophylactic emicizumab on the number of all bleeds (i.e., those treated and untreated with coagulation factors) over time
- To evaluate the clinical effect of prophylactic emicizumab on the number of spontaneous bleeds over time (spontaneous bleed rate)

2.3.2.1 Treated Bleed

A bleed is considered to be a "treated bleed" if it is directly followed (i.e., there is not an intervening bleed) by at least one hemophilia medication reported to be a "treatment for bleed" as specified in the BMQ, irrespective of the time between the treatment and the preceding bleed. A bleed and the first treatment thereafter and before a new bleed starts, are considered to be pairs (i.e., one treatment belongs to one bleed only), with the following exception: if multiple bleeds occur on the same calendar day, the subsequent treatment is considered to apply for each of these multiple bleeds.

Bleeds due to surgery/procedure are not included in the analysis. Only treatments that were recorded as "treatment for bleed" are included in the determination of a treated bleed. Note that a bleed can be treated with more than one treatment.

72-Hour Rule:

Two bleeds of the same type (e.g., "joint," "muscle," or "other") and at the same anatomical location are counted as one bleed if the second bleed occurs within 72 hours from the last treatment for the first bleed. The last treatment is defined as the last treatment associated with the bleed before a new bleed occurs, either in the same or in a different location.

2.3.2.2 All Bleeds

In addition to treated bleeds, "all bleeds" will be analyzed as an additional endpoint. This definition comprises both treated and non-treated bleeds. In this definition, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded from analysis—similar as in the analysis of treated bleeds.

The endpoint of “all bleeds” fulfills the adapted ISTH criteria, as described in the protocol and the 72-hour rule, in particular. This applies to the “all bleeds” definition as well. As “all bleeds” comprises treated and non-treated bleeds, the 72-hour rule will be implemented separately for the treated and non-treated bleeds.

For treated bleeds, the 72-hour rule is implemented exactly as defined for the “treated bleeds” endpoint (see Section 2.3.2.1).

For non-treated bleeds, the 72-hour rule is implemented by calculating a treatment-free period of 72 hours from the bleed itself. That is, a non-treated bleed is counted as a new bleed if it occurs more than 72 hours after the first sign of the preceding non-treated bleed or after the last treatment for a bleed.

2.3.2.3 Treated Spontaneous Bleeds

In the analysis of spontaneous bleeds, only treated bleeds that fulfill the 72-hour rule are included.

Bleeds are classified as “spontaneous” if there is no other known contributing factor such as trauma or procedure/surgery.

2.3.2.4 Treated Joint Bleeds

In the analysis of joint bleeds, only treated bleeds that fulfill the 72-hour rule are included. Bleeds due to procedure/surgery are again excluded.

Joint bleeds are defined as bleeds where the bleed type is “joint” as reported in the BMQ and is reported with at least one of the following symptoms: increasing swelling or warmth of the skin over the joint and/or increasing pain, decreased range of motion, or difficulty in using the joint compared with baseline.

2.3.2.5 Treated Target Joint Bleeds

Target joints are joints into which repeated bleeds occur (i.e., ≥ 3 bleeds into the same joint over the last 24 weeks prior to study entry). The target joints prior to study entry are identified through the eCRF. The bleeds in target joints during the efficacy period are defined by first selecting the bleeds that fulfill the definition of a treated joint bleed and then counting how many of these occurred in a target joint as defined prior to study entry. The locations to be taken into account are shoulder, elbow, wrist, fingers/thumb, hip, knee, ankle, sole/heel, and toes. Left and right sides of the same joint type are considered to be separate joints.

2.3.3 Health-Related Quality-of-Life (HRQoL) Endpoints

The EQ-5D-5L index utility score using the U.K. value set and visual analog scale (VAS) will be evaluated.

Because different measures, Haem-A-QoL and Haemo-QoL-SF, are used for the adult and adolescent patients, respectively, all calculations and analyses will be conducted

separately for these two measures. For either questionnaire, descriptive analyses including summaries and 95% CIs of change from baseline for each individual subscale and the overall score will be performed.

Proportion of patients preferring emicizumab after 17 weeks of treatment will be presented along with ranked reasons for that choice.

Summary statistics of the number of days away from school/work and days hospitalized will be presented. Number of days of missed daycare/school and days hospitalized will be analyzed using descriptive statistics and 95% CIs.

2.3.4 Pharmacokinetic Endpoints

The PK endpoint for this study is the exposure (C_{trough}) of emicizumab prior to drug administration at the following timepoints:

PK Run-In Cohort

- Week 1 (predose Day 1; 8 hours post-injection on Day 1; then Day 3, Day 5); Week 2 (Day 8, Day 11); Week 3 (Day 15, Day 18); Week 4 (Day 22); Week 5 (Day 29 predose); Week 6 (Day 36); Week 7 (Day 43); and Week 8 (Day 50)
- Week 9 (Day 57); Week 13 (Day 85); Week 17 (Day 113); and Week 21 (Day 141) and additionally, once between two emicizumab administrations occurring between Week 9 and Week 21
- Week 22 (Day 148); Week 23 (Day 155); Week 24 (Day 162); and Week 25 (Day 169)
- Every 12 weeks, thereafter, while on emicizumab, until the end of the study.

Expansion Cohort

- Every week during Weeks 1−4 on emicizumab
- Every 4 weeks during Weeks 5−25 on emicizumab
- Every 12 weeks, thereafter, while on emicizumab, until the end of the study.

2.3.5 Safety Endpoints

Safety parameters to be measured include exposure, adverse events (including serious adverse events, adverse events of special interest, adverse events leading to drug discontinuation, and deaths), clinical laboratory results (hematology, chemistry, and anti-emicizumab antibodies), vital signs, ECG, concomitant medication use, and incidence of de novo development of FVIII inhibitors (in the non-inhibitor population).

2.3.6 Biomarker Endpoints

Biomarker endpoints include standard aPTT, modified aPTT, PT and prothrombin time international normalized ratio, D-Dimer, peak height thrombin generation, FIX antigen, FXIII activity, FVIII inhibitor titer, FVIII activity, fibrinogen, and pro-thrombin fragment 1.2 vWF antigen.

2.4 DETERMINATION OF SAMPLE SIZE

The sample size of 6 patients for the PK run-in cohort is considered appropriate to assess pharmacokinetics and safety to allow for an informed decision to open the subsequent expansion cohort with 40 additional patients. One additional patient was recruited in the run-in cohort to ensure that the predefined number of patients (6) complete 6-weeks treatment for required PK data in order to enable a decision for opening the expansion cohort, in case of withdrawal.

The overall sample size of 40 patients in the expansion cohort is based primarily on clinical considerations taking into account the limited number of patients with hemophilia A. It is expected that a sample size of 40 patients would, nonetheless, provide statistically robust point estimates with meaningfully narrow CIs.

2.5 ANALYSIS TIMING

Analysis on the PK run-in cohort will be conducted 6 weeks after the first 6 patients have completed 6 weeks in the study. This analysis will focus on pharmacokinetics and safety to inform on the opening of the expansion cohort.

The primary analysis will take place at the earliest time when all enrolled patients in the expansion cohort complete 24 weeks in the study or have withdrawn. These analyses will be carried out separately for patients in the expansion cohort and the PK run-in cohort.

The final analysis will occur at the end of the study as defined in the protocol. Additional updates may be performed between the primary and final analyses, as requested by Health Authorities or deemed necessary by the Sponsor.

Additional analyses for Study BO39182 may be conducted to support regulatory submissions.

3. STUDY CONDUCT

Study BO39182 is a single-arm study implemented in two parts. The first part enrolled 6 patients to receive 6 mg/kg Q4W of SC emicizumab and will provide pharmacokinetic and safety information for opening of the expansion cohort. An additional seventh patient was enrolled to ensure sufficient patients (6) to complete 6 weeks of treatment for required PK data to make the decision for opening the expansion cohort, in case of a patient withdrawal. Since patients in the run-in cohort do not receive a loading dose and therefore reach steady state concentrations later, their bleeding may not be fully controlled by emicizumab; this cohort is restricted to patients who were previously on episodic treatment.

Forty patients will be enrolled in the expansion cohort to receive prophylactic emicizumab at 3 mg/kg QW loading dose for 4 weeks, followed by 6 mg/kg Q4W.

Patients with either prior episodic or prophylactic treatment regimen are eligible for the expansion cohort.

After 24 weeks in the study, all patients are eligible to up-titrate to 3 mg/kg QW with approval from the Medical Monitor if they fulfill the protocol requirements for up-titration (see Section 4.3.2.1 of the protocol). Subsequently, up-titrated patients may decide to down-titrate to 6 mg/kg Q4W, 3 mg/kg Q2W, or 1.5 mg/kg QW. This process of up- and down-titration may repeat more than once.

3.1 DATA MONITORING

After 6 enrolled patients in the PK run-in cohort have each completed 6 weeks in the study, an analysis will be performed to evaluate PK and preliminary efficacy and safety of prophylactic emicizumab administered subcutaneously at 6 mg/kg/Q4W. This analysis will include data collected from all patients at the time. An internal Roche group will be constituted to evaluate whether or not to open the expansion cohort given the available data. There will not be an independent Data Monitoring Committee (iDMC) or a formal IMC for this study.

4. STATISTICAL METHODS

4.1 OUTPUT LAYOUTS

While the efficacy and safety objectives will primarily be evaluated on the expansion cohort, the same will also be evaluated on the PK run-in cohort at the time of the clinical cutoff to complement the data from the expansion cohort, as applicable. The two key output layouts will therefore be:

- **PK Run-In Cohort:** Includes data from patients enrolled in the PK run-in cohort. This cohort receives 6 mg/kg Q4W without any loading dose.
- **Expansion Cohort:** Includes data from the planned 40 patients who receive 3 mg/kg QW loading dose for 4 weeks followed by 6 mg/kg Q4W.

The output results will be presented in separate tables as below:

Parameter	Run-In Cohort Total

Parameter	Expansion Cohort Total

The data under the new, up-titrated or down-titrated dose is analyzed and reported separately. Additional summaries will be produced for key safety and exposure on all data (i.e., data before and after up-titration).

4.2 ANALYSIS POPULATIONS

4.2.1 Treated Patient Population

This population includes all enrolled patients who received at least one dose of emicizumab. This will be the primary efficacy and safety analysis population separately for PK run-in and expansion cohorts as described above.

4.2.2 All Patient Population

This population includes all patients enrolled into the study.

4.2.3 Pharmacokinetic-Evaluable Population

This population includes all patients who have received at least one dose of emicizumab and have at least one post-dose emicizumab concentration result.

4.2.4 Up-Titrated/Down-Titrated Population

This population includes patients whose dose was changed at least once during the study.

4.3 ANALYSIS OF STUDY CONDUCT

The flow of patients through the study will be displayed in a “CONSORT” diagram. A clear account of all patients who entered the study, were enrolled, and completed the study will be displayed. In addition, reasons for premature discontinuation from study treatment and reasons for withdrawing from the study will be described.

Major protocol deviations will be summarized.

Observation time and duration of follow-up, as well as adherence to schedule of assessments and compliance with data entry into the electronic, handheld device will also be evaluated.

4.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic data (e.g., age, race/ethnicity, height, weight) and baseline disease characteristics (e.g., inhibitor status, previous hemophilia treatment, number of target joints) will be summarized for all patients.

4.5 EFFICACY ANALYSIS

Efficacy objectives in this study will be assessed descriptively without any formal hypothesis testing.

4.5.1 Bleed Rate Endpoints

The number of bleeds will be analyzed using the negative binomial regression model with efficacy period as an offset in the model to account for the difference in follow-up times. Annualized Bleeding Rate (ABR) will be estimated from the model and presented with 95% CI.

In addition to the model based approach, individual patient ABR will also be calculated based on the formula:

$$\text{ABR} = \left(\frac{\text{Number of bleeds the during efficacy period}}{\text{Number of days during the efficacy period}}\right) \times 365.25$$

Should the negative binomial not converge, then only the formula-based ABR will be presented.

All bleeds will be characterized descriptively, including the type, location, and cause of bleed (surgery/procedure, traumatic, spontaneous). Bleed rates for spontaneous and traumatic bleeds will also be calculated.

The number of bleeds, types, and locations of bleed will be summarized for all patients and listed for each patient individually. Exploratory analyses will be conducted to characterize the type, location, frequency, and pattern of bleeds.

4.5.2 Health-Related Quality-of-Life (HRQoL) Endpoint

The Health Utilities Index (HUI) score and VAS score at each assessment and change from baseline will be calculated from the EQ-5D-5L. In addition, the number of patients who report a clinically meaningful change from baseline to Week 24 on the HUI and VAS will be reported. A meaningful change in the VAS is 7 points and for the HUI it is 0.7 points (Walters et al. 2005; Pickard et al. 2007).

The Haem-A-QoL, and Haemo-QoL-SF will be analyzed descriptively for each individual subscale and in overall score. Summaries of change from baseline will be provided with 95% CIs. In addition, the proportion of patients reporting a clinically meaningful change from baseline to Week 24 on the physical health and total scores will be reported. A meaningful change on the physical health scale is 10 points and for the total score it is 7 points (Wyrwich et al. 2015).

The proportion of patients preferring either emicizumab or previous hemophilia treatment regimen will be calculated and presented with 95% CIs based on the patient preference questionnaire. The proportion of patients selecting each reason for their preference and the top three preferred reasons affecting the patient preference will also be summarized.

The number of days away from school/work and days hospitalized will be analyzed using descriptive statistics and 95% CIs.

4.5.3 Subgroup Analyses

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

- Age: $< 18, \geq 18$
- Age: $< 65, \geq 65$

- Race: Asian, Black or African American, White, Other
- Hemophilia severity: mild, moderate, severe
- Number of target joints at study entry: no target joint, any target joint
- FVIII Inhibitor status: with FVIII inhibitor, without FVIII inhibitors
- Previous treatment regimen: prior episodic, prior prophylactic
- Number of bleeds in the 24 weeks prior to entry: $<9, \geq 9$ for patients being on prior episodic treatment

Note that due to the likely small sample sizes, subgroup analyses will be highly susceptible to variability and should therefore be interpreted with caution.

Additional region- and/or country-specific analyses may be performed to support regulatory submissions as needed.

4.6 PHARMACOKINETIC ANALYSES

4.6.1 PK Run-In Cohort

PK parameters of emicizumab will be estimated using non-compartmental methods after the first and the sixth injection and include:

- T_{max}: Time to maximum observed plasma concentration
- C_{max}: Maximum observed plasma concentration
- AUC_{τ}: Area under the plasma concentration-time curve over a dosing interval
- $AUC_{0\text{-}inf}$: Area under the plasma concentration-time curve between time zero (predose) extrapolated to infinity (only for the first injection)
- $t_{½}$: Apparent terminal half-life
- CL/F and CLss/F: Apparent Clearance

Concentration data and calculated PK parameters for emicizumab will be presented in individual listings, summary tables (including descriptive statistics: mean, geometric means, medians, ranges, standard deviations, and coefficients of variation) and graphs (including concentration versus time plots on linear and semi-logarithmic scales) as appropriate.

4.6.2 Expansion Cohort

For all patients, predose (trough) plasma concentrations of emicizumab will be presented descriptively at each timepoint by dose group, including 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 of emicizumab following SC administration. Population PK parameters, such as clearance (CL/F) and volume of distribution (V/F), will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be

investigated. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from other emicizumab studies and completed Phase III studies. These analyses will be reported in a dedicated report.

4.7 SAFETY ANALYSES

Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential and platelet counts), ECGs, vital signs, anti-drug antibodies (ADAs), and de novo anti-FVIII inhibitors.

4.7.1 Exposure to Study Medication

Information on study drug administration will be summarized by duration and cumulative dose. In addition, treatment exposure will be summarized, including delays and interruptions. The number of patients whose dose was up-titrated will be summarized. A similar summary will be generated for patients who down-titrate back to 6 mg/kg Q4W, 1.5 mg/kg/QW, or 3 mg/kg Q2W.

Patient withdrawals from study treatment will be reported as listings and summary tables.

4.7.2 Adverse Events

Adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade (WHO Criteria). All adverse events will be coded using the current version of MedDRA at time of database closure. The total number and percentage of patients with at least one adverse event and total number of adverse events will be summarized. Separate adverse event summaries for serious adverse events, adverse events of special interest, severity, relatedness, and discontinuation/modification will be provided.

4.7.3 Laboratory Data

For clinical laboratory data that were collected from local laboratories, summary statistics will be presented in International System of Units (SI). Laboratory data not collected in SI units will be converted to SI units as applicable. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

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

4.7.4 Vital Signs

Vital signs will be summarized using mean change from baseline tables over time. Measurements consist of heart and respiratory rate, temperature, and systolic and diastolic blood pressure.

4.7.5 Electrocardiogram

ECG results and corresponding changes from baseline will be summarized by cohort and visit for QT, RR, HR, QTcB, QTcF, PR and QRS and T- and U-wave morphology.

4.8 EXPLORATORY BIOMARKER ANALYSES

PD parameters (e.g., aPTT, PT, FVIII activity, thrombin generation, FIX:Ag, FX:Ag) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

All other exploratory biomarkers will be analyzed and reported descriptively.

4.9 MISSING DATA

On the electronic, handheld device, it is not possible to leave questions unanswered or to enter partial data. Therefore, the data for bleed-related endpoints coming from the electronic, handheld device are complete.

In the site data entry system (Gather), it is possible to leave the time of a treatment or a bleed blank because the patient might not be able to reliably remember these.

4.10 INTERIM ANALYSES

4.10.1 PK Run-In Analysis

An analysis of the PK run-in cohort data will be performed after the sixth patient has been on treatment for 6 weeks, to support the decision to open the expansion cohort. This analysis will constitute characterization of the PK profile (to assess whether the mean PK profile is as predicted [i.e., $\geq$ lower limit of 95% CI of the predicted mean PK profile]) and assessment of safety to inform the decision on whether or not to open the expansion cohort. This analysis will be carried out internally and there will be no formal IMC.

4.10.2 Additional Interim Analysis

Additional interim analyses may be performed to support regulatory submissions. The results of these analyses will be documented in interim CSRs and would include patients from both the run-in and expansion cohorts.

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Appendix 1
Protocol Synopsis

TITLE:	**A MULTICENTER, OPEN-LABEL, PHASE III STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF EMICIZUMAB GIVEN EVERY 4 WEEKS (Q4W) IN PATIENTS WITH HEMOPHILIA A**
PROTOCOL NUMBER:	BO39182
VERSION NUMBER:	2
EUDRACT NUMBER:	2016-001094-33
IND NUMBER:	122954
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase III
INDICATION:	Hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd.

Objectives and Endpoints

Pharmacokinetic Run-In Phase Objectives

The objectives of the pharmacokinetic run-in are as follows:

- To investigate the pharmacokinetics of emicizumab after single and multiple (every 4 weeks [Q4W]) subcutaneous (SC) administration of 6 mg/kg
- To assess the safety and tolerability of emicizumab after Q4W SC administration of 6 mg/kg
- To explore the prophylactic effect of emicizumab in maintaining adequate control of bleeding
- To investigate the effect of emicizumab on pharmacodynamic (PD) markers including (but not limited to) aPTT, thrombin generation, and factor VIII (FVIII) activity

Expansion Phase

Efficacy Objectives

The efficacy objectives are as follows:

- To evaluate the efficacy of prophylactic emicizumab in maintaining adequate control of bleeding
- To evaluate *the clinical effect of prophylactic emicizumab on* the number of joint bleeds over time
- To evaluate *the clinical effect of prophylactic emicizumab on* the number of target joint bleeds over time (target joints are defined as joints with ≥ 3 bleeds occurring in the same joint over the last 24 weeks prior to study entry)
- To evaluate *the clinical effect of prophylactic emicizumab on* the number of all bleeds (i.e., those treated and untreated with coagulation factors) over time
- *To evaluate the clinical effect of prophylactic emicizumab on the number of spontaneous bleeds over time (spontaneous bleed rate)*

Appendix 1
Protocol Synopsis (cont.)

- To evaluate the health-related quality of life (HRQoL) of patients according to Haem-A-QoL (≥ 18y) or Haemo-QoL_SF (ages 12–17) scores after 24 weeks
- To evaluate the health status of patients according to EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) scores after 24 weeks
- To assess preference for emicizumab regimen compared with previous regimen used
- To assess the number of days away from school/work
- To assess the number of days hospitalized

Safety Objectives

The safety objectives of this study are to evaluate the overall safety of emicizumab given Q4W in patients with hemophilia A based on the following endpoints:

- The incidence and severity of adverse events
- The incidence and severity of thromboembolic events
- Changes in physical examination findings and vital signs
- Incidence of laboratory abnormalities
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to drug discontinuation
- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events
- *Incidence of thrombotic microangiopathy*
- The incidence and clinical significance of anti-emicizumab antibodies
- The incidence of de novo development of FVIII inhibitors (non-inhibitor population)

Pharmacokinetic Objective

The pharmacokinetic (PK) objective of this study is as follows:

- To characterize the pharmacokinetics of multiple Q4W SC doses of 6 mg/kg emicizumab

Exploratory Pharmacodynamic Biomarker Objective

The exploratory PD biomarker objective is as follows:

- To investigate the effect of Q4W doses of emicizumab on PD parameters, including but not limited to aPTT, thrombin generation and FVIII activity at timepoints throughout the study

Study Design

Description of Study

Study BO39182 is a multicenter, open-label, non-randomized study designed to investigate the efficacy, pharmacokinetics, safety, and pharmacodynamics of emicizumab (6 mg/kg) administered in a Q4W dosing regimen. Patients with hemophilia A with or without inhibitors against FVIII will be enrolled. The study consists of two parts: a PK run-in part followed by an expansion part.

PK Run-In-Part

In the PK run-in part, a full PK profile will be measured in the first 6 enrolled patients during the first 4 weeks to characterize the pharmacokinetics of a single SC dose of 6 mg/kg emicizumab in patients with hemophilia A. After the first and second emicizumab administration, an intense PK sampling will occur. A reduced PK sampling schedule will be used to characterize repeated Q4W SC administration from Week 9 to Week 21. After the sixth injection at Week 21, PK sampling frequency will be increased to characterize steady-state pharmacokinetics (see protocol).

Appendix 1
Protocol Synopsis (cont.)

An analysis of the data collected when all 6 patients in the PK run-in cohort have been followed for at least 6 weeks will be performed to assess whether the mean PK profile is as predicted (i.e., ≥ lower limit of 95% CI of the predicted mean PK profile) after repeated 6 mg/kg SC administration Q4W. In addition to PK, safety will be assessed in order to establish whether the expansion cohort can be opened. This analysis will be conducted by a Roche internal group of representatives from Clinical Pharmacology, Clinical Science, Clinical Safety, and Statistics; no formal Internal Monitoring Committee (IMC) will be set up.

Expansion Part

An expansion phase will be conducted to further investigate the efficacy, pharmacokinetics, safety, and pharmacodynamics in a cohort of 40 patients. These patients will start with loading doses of 3 mg/kg QW×4, followed by a maintenance dose of 6 mg/kg Q4W for at least 24 weeks overall. These patients will undergo PK sampling to investigate trough concentrations (C_{trough}) and samples (predose) will be drawn as per the schedule of assessments (see protocol).

The primary analysis (descriptive analyses of the study objectives) will be conducted either after the last enrolled patient completes the 24-week treatment period, is lost to follow-up, or has withdrawn, whichever occurs first.

During the study, individual bleeds will be captured as they occur while HRQoL, health status, patients' preference and days of school or work missed will be assessed as outlined in the schedule of assessments in protocol. Patients (or their legally authorized representative) will be asked on a weekly basis to record via their electronic, handheld device whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a bleed has been given.

Physical examinations, vital signs, ECG, and laboratory assessments will be performed as detailed in the schedule of assessments (see protocol) and will be the same for all patients receiving emicizumab, regardless of whether they are enrolled in the PK run-in cohort or the expansion cohort. Adverse events will be captured on an ongoing basis, as they occur during the study.

Emicizumab is intended for prophylactic use only (i.e., not to treat bleeds that have already occurred). There is clinical experience in the ongoing Phase I/II clinical studies with the treatment of over 60 breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents. FVIII, aPCC, or recombinant activated factor VII (rFVIIa) do not interfere with emicizumab PK assessments and no safety signals have been observed when breakthrough bleeds were treated with standard-of-care regimens during Phase I/II studies. *However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), 2 events of TMA and 2 thromboembolic events were observed in patients who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds. Therefore, it is recommended that breakthrough bleeds in the inhibitor population are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided or limited.*

Therefore, *a* washout period *of 72 hours* prior to the first emicizumab dose in this study *is required for patients receiving prior aPCC or Byclot®. Also a washout period of 72 hours for* patients who were previously receiving ITI is required prior to the first emicizumab administration. Patients *may* require dosing with FVIII or for the treatment of potential breakthrough bleeds *(see protocol)*, especially for the time period until steady-state concentrations of emicizumab have been reached.

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation) will be collected as per the schedule of assessments and always coupled with a PK assessment *for days where PK and PD samples are to be drawn*. As values for many tests are normalized by even low plasma concentrations of emicizumab, a variety of assay formats (one-stage, chromogenic) and modifications (pre-dilution of patient plasma) will be investigated for assessment of PD response at higher emicizumab plasma concentrations. It is not expected that these biomarkers will be used to guide the selection of patients to be treated with emicizumab. However, these biomarkers may be used to identify a future assay for the monitoring of emicizumab activity. In addition, factor IX (FIX) and factor X (FX) antigen levels will be monitored.

Appendix 1
Protocol Synopsis (cont.)

Biomarkers related to thromboembolism (e.g., D-dimer, prothrombin fragment 1.2) and immunologic biomarkers (i.e., anti-emicizumab antibodies and anti-FVIII antibodies) will be measured as per the schedule of assessments (see protocol).

Breakthrough bleeds will be treated with appropriate coagulation products *with either FVIII (non-inhibitor patients) or rFVIIa (inhibitor patients) at the lowest expected dose* to *achieve hemostasis* and captured as they occur. When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed (e.g., other than emicizumab in case of breakthrough bleeds). The reason for the use of coagulation products (e.g., FVIII or rFVIIa) will be documented (e.g., bleeding*, preventative dose before activity*). Thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. *For patients with inhibitors against FVIII who experience a breakthrough bleed that requires treatment with bypassing agents, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments.*

*All p*atients*, irrespective of the cohort assigned,* who continue to derive clinical benefit will be given the opportunity to continue receiving prophylactic emicizumab either within this study or as part of a future extension study according to Roche policy on post-study drug access. After 24 weeks on prophylactic emicizumab, all patients will be able to continue on their 6 mg/kg Q4W maintenance dose or may be provided the option to increase their dose to 3 mg/kg QW if they meet protocol-defined criteria of suboptimal response. *Suboptimal response is defined as follows:*

- *≥*2 *qualifying* bleeds *within 24 weeks* while on *prophylactic* emicizumab

Qualifying bleeds are defined as spontaneous, verified by investigator (e.g., by imaging or physical examination), and *occurring while on prophylactic emicizumab at steady state (after the Week 5 visit for expansion cohort/after Week 17 visit for PK run-in cohort). These patients must* receive approval from the Medical Monitor to *increase their dose to 3 mg/kg QW.*

Patients who discontinue emicizumab will be followed for 24 weeks after the last emicizumab dose.

Number of Patients

Approximately 46 patients with congenital hemophilia A previously treated with either FVIII or bypassing agents will be enrolled in the study (6 patients in the PK run-in phase and 40 patients in the expansion phase).

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (consent/assent will be taken as appropriate)
- Aged ≥ 12 years
- Willingness 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
- Body weight ≥ 40 kg at screening
- Diagnosis of severe congenital hemophilia A or hemophilia A with FVIII inhibitors
- *Patients using rFVIIa or willing to switch to rFVIIa as primary bypassing agent for the treatment of breakthrough bleeds*
- *FVIII inhibitor test during screening with titer results available prior to first administration of study drug*

Appendix 1
Protocol Synopsis (cont.)

- Patients without FVIII inhibitors (<0.6 BU/mL) who completed successful ITI must have done so at least 5 years before screening and must have no evidence of inhibitor recurrence (permanent or temporary) indicated by detection of an inhibitor >0.6 BU/mL since ITI
- For patients to be enrolled into PK run-in cohort:

  Current episodic treatment (FVIII or bypassing agents) at the time of entry into this study and documentation of details of episodic treatment for at least 24 weeks prior to entry into this study
- For patients to be enrolled into the expansion cohort:

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

  For patients on an episodic regimen, ≥ 5 bleeds in the prior 24 weeks, regardless of inhibitor status
- Adequate hematologic function, defined as a platelet count $\geq 100{,}000/\mu L$ and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin $\leq 1.5\times$ age-adapted upper limit of normal (ULN) (excluding Gilbert's syndrome) and $both$ AST and ALT $\leq 3\times$ age-adapted ULN at the time of screening, and no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine $\leq 2.5\times$ age-adapted ULN and creatinine clearance $\geq$ 30 mL/min by Cockcroft-Gault formula
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 1 year 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 study 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 for contraception.

Exclusion Criteria

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

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing or planned ITI therapy; patients in whom ITI has failed will be eligible with a 72-hour washout period prior to the first emicizumab administration.
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment

Appendix 1
Protocol Synopsis (cont.)

- *Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment*
- Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Known HIV infection with CD4 counts $<$200 cells/μL

  HIV infection with CD4 counts $\geq$200 cell/μL permitted
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- Concomitant disease, condition, significant abnormality on screening evaluations or laboratory tests, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the investigator/co-investigator, pose an additional unacceptable risk in administering study drug to the patient
- Receipt of any of the following:

  Emicizumab in a prior investigational study

  An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration

  A non–hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter

  Any other investigational drug currently being administered or planned to be administered
- Inability to comply with the study protocol in the opinion of the investigator
- Pregnancy or lactation or intention to become pregnant during the study
- Women with a positive serum pregnancy test result within 7 days prior to initiation of study drug

End of Study

The end of this study is defined as the date when the last remaining patient has completed the last visit (last patient last visit [LPLV]), as defined by any of the following criteria:

- Completion of *at least* 24 weeks of emicizumab treatment and *either* transfer to a *separate* extension study to receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products

OR

- Completion of the end-of-study safety follow-up visit 24 weeks after discontinuing emicizumab

OR

- Withdrawal of consent

OR

- Lost to follow-up

Appendix 1
Protocol Synopsis (cont.)

Length of Study

The length of the study for an individual patient will be:

- Screening period up to 4 weeks
- Treatment and observation period at least 24 weeks
- Safety follow-up visit 24 weeks after discontinuing emicizumab unless patient transfers to a *separate* emicizumab extension study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 20 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

The emicizumab regimen being tested is 3 mg/kg QW for 4 weeks followed by 6 mg/kg Q4W subcutaneously for 24 weeks. All patients with suboptimal control may have the option to increase the dose to 3 mg/kg QW after 24 weeks, with approval from the Medical Monitor

Non-Investigational Medicinal Products

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF page.

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

- For patients in the expansion cohort who are on FVIII prophylaxis, they may continue their regular FVIII prophylaxis until the second emicizumab loading dose in order to avoid bleeds before adequate emicizumab level is reached. Concomitant routine FVIII prophylaxis is not otherwise permissible during the study.
- Drugs intended to control bleeds, including FVIII *concentrates (non-inhibitor patients) or rFVIIa (inhibitor patients), should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase 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 taken for patients who are using rFVIIa (e.g., consideration of using no more than 90 μg/kg rFVIIa as an initial dose).

  In the event that aPCC is the only available bypassing agent, 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. For patients receiving aPCC prior to study entry, a washout period of 72 hours prior to first emicizumab dosing is required.

  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 μg/kg of Byclot®). For patients receiving Byclot® prior to study entry, a washout period of 72 hours prior to first emicizumab dosing is required.

  Exact dose and schedule of FVIII or bypassing agents should be discussed with patients at the beginning 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 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 assessments.
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to result in systemic exposure

Appendix 1
Protocol Synopsis (cont.)

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

Statistical Methods

Primary Analysis

The efficacy objective is to evaluate the clinical effect of 6 mg/kg emicizumab Q4W based on the number of bleeds over time.

The analyses will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of the time that each patient stays in the study included as an offset in the model.

The number of bleeds will be also annualized (Annualized Bleeding Rate—ABR) for each patient using the following formula:

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

In case the negative binomial model does not converge the above formula will be used as the sole method of analysis.

The clinical effect of prophylactic emicizumab on the number of bleeds, joint bleeds, target joint bleeds, spontaneous bleeds and all bleeds (i.e., those treated and untreated with coagulation factors) over time will be evaluated.

The number of bleeds, sites of bleeds, and types of bleeds will be summarized for all patients and listed for each patient individually. Several exploratory analyses will be conducted to characterize the type, location, duration, frequency, and pattern of bleeds. For continuous endpoints, descriptive statistics will be calculated and categorical endpoints will be characterized through frequency tables.

The primary final analysis will be performed 24 weeks after the last enrolled patient started treatment or has withdrawn prematurely, whichever occurs first.

Safety Analyses

The safety analyses population will be based on all patients who received at least one administration of emicizumab. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology including complete blood count with differential and platelet counts), ECGs, vital signs, anti-drug antibodies (ADAs), and de novo anti-FVIII inhibitors.

To evaluate the overall safety of emicizumab, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade.

For clinical laboratory data, summary statistics will be presented. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Pharmacokinetic Analyses

PK Run-In Cohort

PK parameters of emicizumab will be estimated using non-compartmental methods after the first and the sixth injections and include:

- T_{max}: Time to maximum observed plasma concentration
- C_{max}: Maximum observed plasma concentration
- AUC_{τ}: Area under the plasma concentration-time curve over a dosing interval
- $AUC_{0\text{-inf}}$: Area under the plasma concentration-time curve between time zero (predose) extrapolated to infinity (only for the first injection)
- $t_{½}$: Apparent terminal half-life

Appendix 1
Protocol Synopsis (cont.)

- CL/F and CLss/F: Apparent Clearance

Concentration data and calculated PK parameters for emicizumab will be presented in individual listings, summary tables (including descriptive statistics: mean, geometric means, medians, ranges, standard deviations, and coefficients of variation) and graphs (including concentration versus time plots on linear and semi-logarithmic scales) as appropriate.

Expansion Cohort

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively, including 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 of 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 area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies and completed Phase III studies. These analyses will be reported in a dedicated report.

Immunogenicity Analyses

The immunogenicity analyses will include patients with at least one predose and one postdose ADA assessment.

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized. Patients are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA 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 ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

Exploratory Analyses

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Determination of Sample Size

The sample size of 6 patients for the PK run-in cohort is considered appropriate to assess pharmacokinetics and safety to allow for an informed decision to open the subsequent expansion cohort with 40 additional patients.

The overall sample size of 40 patients in the expansion cohort is based primarily on clinical considerations taking into account the limited number of patients with hemophilia A.

Planned Interim Analysis

An analysis of pharmacokinetics and safety will occur when the first 6 patients have been on treatment for 6 weeks. On the basis of the results for pharmacokinetics and safety (e.g., $\geq$ lower limit of 95% CI of the predicted mean PK profile, no severe unexpected safety findings), the study will proceed with the expansion cohort.

This analysis will be conducted by a Roche internal group of representatives from Clinical Pharmacology, Clinical Science, Clinical Safety and Statistics; no formal IMC will be set up.

Appendix 2
Schedule of Assessments

PK RUN-IN COHORT															
	Screening		Treatment Period										From Week 25 to Study Completion	Study Completion or Early Termination [a]	Safety F/U Visit
Week	—	—	1	2	3	4	5	9	13	17	21	25			
Day [b]	–28 to –1	–7 to –1	1	8	15	22	29	57	85	113	141	169			
Informed consent [c]	x														
Inclusion/exclusion criteria	x														
Demographics and medical history [d]	x														
Physical examination including height and weight [e]	x		x [f]		x [f]		x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	Q12W [f]	x [f]	x
Vital signs [g]	x		x	x		x	x	x	x	x	x	x	Q12W	x	x
Concomitant medications [h]			x		x		x	x	x	x	x	x	Q12W	x	x
Adverse events [i]			Ongoing												
12-lead ECG [j]	x						x [k]					x	x [l]	x	
Hematology [m]		x	x	x	*x*		x	x	x	x	x	x	Q12W	x	x
Blood chemistry [n]		x	x	x	*x*		x	x	x	x	x	x	Q12W	x	x
Pregnancy test [o]	x	x	x	x	*x*		x	x	x	x	x	x	Q12W	x	x
Emicizumab administration [p]			x				x	x	x	x	x	x	Q4W		
PK, PD, and ADA	See protocol														
Bleed /medication questionnaire [q]			Weekly and on days of bleeds											x	*x*

Appendix 2
Schedule of Assessments (cont.)

PK RUN-IN COHORT															
	Screening		Treatment Period										From Week 25 to Study Completion	Study Completion or Early Termination [a]	Safety F/U Visit
Week	—	—	1	2	3	4	5	9	13	17	21	25			
Day [b]	–28 to –1	–7 to –1	1	8	15	22	29	57	85	113	141	169			
Bleed/medication review [r]			x				x	x	x	x	x	x	Q4W	x	*x*
Following treatment with bypassing agents [s]			*Monitoring for thromboembolic events and thrombotic microangiopathy.* [s]												

ADA = anti-drug antibody; eCRF = electronic Case Report Form; EQ-5D-5L = European Quality of Life-5 Dimensions-5 Levels; F/U = follow-up; HRQoL = health-related quality of life; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcome; Q4W = every 4 weeks; Q12W = every 12 weeks.

[a] Study completion visit when either the patient completed 24 weeks' study duration and transferred to an emicizumab extension study OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation OR patient is lost to follow-up. If study completion occurs after 24 weeks in the study, the completion assessments displayed in the schedule of assessments are similar with the Week 25 visit.

[b] In order to characterize pharmacokinetics, it is mandatory assessments be performed on the exact visit day until Week 25; no deviation from visit day is acceptable *until Week 25, deviations of ±2 days are acceptable thereafter.*

[c] Obtain written informed consent (or patient written assent and parent written informed consent if patient is an adolescent) before performing any study related procedures. *If patient fulfils the inclusion criteria, the patient should be enrolled in the study on the same day when the first dose of emicizumab is administered (Day 1).*

[d] Collected from patient's medical record and documented in the eCRF.

[e] Height assessment at Day 1 only for adults and weight assessments Q4W for all patients.

[f] Height assessments for adolescents at Day 1 and ideally at all drug administration and PK sampling visits when the patients will be at the investigational site but at least every 12 weeks (repeated assessments).

[g] Body temperature (oral or tympanic), blood pressure, pulse rate, respiratory rate.

[h] Concomitant medication (e.g., extra pain medication to treat bleeds) will be recorded at the time of the visits, excluding treatments for bleeds, which will be collected in the bleeding questionnaire.

Appendix 2
Schedule of Assessments (cont.)

[i] Adverse events are collected on an ongoing basis throughout the study. Injection-site reactions will be collected on a separate form from the adverse event form. After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

[j] If screening ECG is abnormal, repeat at Week 1. *ECGs will also be performed: once during Weeks 4–8 after starting emicizumab or dose escalation (up-titration); once 24 weeks after starting emicizumab or dose escalation (up-titration); and at study completion/early termination.*

[k] *Once during Weeks 4–8 after starting emicizumab.*

[l] For any dose increase (i.e., 3 mg/kg QW), an ECG should be obtained after 4 weeks of starting the new dose at the next scheduled clinic visit.

[m] Predose (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width), performed locally. Laboratory assessments completed at the screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator.

[n] Predose (sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase), performed locally. Laboratory assessments completed at the screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator.

[o] Female patients with childbearing potential will be required to have a negative serum pregnancy test result at Screening and up to 7 days prior to enrollment (Day −7 to Day −1). If applicable, during the study, urine pregnancy tests will be performed at the scheduled visits.

[p] 6 mg/kg Q4W emicizumab.

[q] Bleed information (start date and time, reason, type, location, and associated symptoms of each bleed) and medication for bleeds (breakthrough bleeds) should be reported by the patient via an electronic handheld device when a bleed occurs or at least on a weekly basis (retrospective reporting for last 7 days). *If the patient discontinues study treatment, bleed and bleed medication data should be provided by the patient until the safety follow-up visit (24 weeks after last study drug administration).*

[r] Investigator review of bleed information.

[s] *Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed. If applicable, laboratory results should be recorded on the unscheduled visit eCRFs.*

Appendix 2
Schedule of Assessments (cont.)

Expansion Cohort															
	Screening		Treatment Period										From Week 25 to Study Completion	Study Completion or Early Termination [a]	Safety Follow-Up Visit
Week	—	—	1	2	3	4	5	9	13	17	21	25			
Day [b]	–28 to –1	–7 to –1	1	8	15	22	29	57	85	113	141	169			
Informed consent [c]	x														
Inclusion/exclusion criteria	x														
Demographics and medical history [d]	x														
Physical examination including height and weight [e]	x		x [f]		x [f]		x [f]	x [f]	x [f]	x [f]	x [f]	x [f]	Q12W [f]	x [f]	x
Vital signs [g]	x		x	x		x	x	x	x	x	x	x	Q12W	x	x
Concomitant medications [h]			x		x		x	x	x	x	x	x	Q12W	x	x
Adverse events [i]			Ongoing												
12-lead ECG [j]	x						x [k]					x	x [l]	x	
Hematology [m]		x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x
Blood chemistry [n]		x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x

Appendix 2
Schedule of Assessments (cont.)

Expansion Cohort															
	Screening		Treatment Period										From Week 25 to Study Completion	Study Completion or Early Termination [a]	Safety Follow-Up Visit
Week	—	—	1	2	3	4	5	9	13	17	21	25			
Day [b]	–28 to –1	–7 to –1	1	8	15	22	29	57	85	113	141	169			
Pregnancy test [o]	x	x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x
PRO (HRQoL) [p]			x						x			x	Q12W	x	
Days missed from school/work [q]			*x*						*x*			*x*	*Q12W*	*x*	
PRO (Preference)										x [r]					
Health status (EQ-5D-5L) [s]			x						x			x	Q12W	x	
Emicizumab administration [t]			x	x	x	x	x	x	x	x	x	x	Q4W		
PK, PD, ADA	See protocol														
Bleed/medication questionnaire [u]			Weekly and on days of bleed											x	*x*
Bleed/medication review [v]			x				x	x	x	x	x	x	Q4W	x	*x*
Following treatments with bypassing agents [w]			*Monitoring for thromboembolic events and thrombotic microangiopathy* [w]												

Appendix 2
Schedule of Assessments (cont.)

ADA = anti-drug antibody; eCRF = electronic Case Report Form; EQ-5D-5L = European Quality of Life-5 Dimensions-5 Levels; ET = early termination; F/U = follow-up; FIX = factor IX; FVIII = factor VIII; FX = factor X; FXIII = factor XIII; HRQoL = health-related quality of life; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcome; Q4W = every 4 weeks; Q12W = every 12 weeks.

[a] Study completion visit when either the patient completed 24 weeks' study duration and transferred to an emicizumab extension study OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation OR patient is lost to follow-up. If study completion occurs after 24 weeks in the study, the completion assessments displayed in the schedule of assessments are similar with the Week 25 visit.

[b] Assessments can deviate from planned schedule by ±2 days.

[c] Obtain written informed consent (or patient written assent and *legal representative* written informed consent if patient is an adolescent) before performing any study related procedures. *If patient fulfils the inclusion criteria, the patient should be enrolled in the study on the same day when the first dose of emicizumab is administered (Day 1).*

[d] Collected from patient's medical record and documented in the eCRF.

[e] Height assessment at Day 1 only for adults and weight assessments Q4W for all patients.

[f] Height assessments for adolescents at Day 1 and ideally at all drug administration and PK sampling visits that the patients will be at the investigational site, but at least every 12 weeks (repeated assessments).

[g] Body temperature (oral or tympanic), blood pressure, pulse rate, respiratory rate.

[h] Concomitant medication (e.g., extra pain medication to treat bleeds) will be recorded at the time of the visits, excluding treatments for bleeds, which will be collected in the bleeding questionnaire *starting from Day 1. FVIII taken in the week prior to starting emicizumab (week prior to Day 1) will also be collected on the Concomitant Medication eCRF page for patients without inhibitors to FVIII who will continue their prior FVIII prophylaxis during the first week of the study.*

[i] Adverse events are collected on an ongoing basis throughout the study. Injection-site reactions will be collected on a separate form from the adverse event form. After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

[j] If screening ECG is abnormal, repeat at Week 1. *ECGs will also be performed: once during Weeks 4–8 after starting emicizumab or dose escalation (up-titration); once 24 weeks after starting emicizumab or dose escalation (up-titration); and at study completion/early termination.*

[k] *Once during Weeks 4–8 after starting emicizumab.*

[l] For any dose increase (i.e., 3 mg/kg/wk), an ECG should be obtained after 4 weeks of starting the new dose at the next scheduled clinic visit.

[m] Predose: (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width), performed locally. Laboratory assessments completed at the Screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator.

Appendix 2
Schedule of Assessments (cont.)

[n] Predose (e.g., sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase), performed locally. Laboratory assessments completed at the Screening visit do not have to be repeated at Week 1, if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator.

[o] Female patients with childbearing potential will be required to have a negative serum pregnancy test result at Screening and up to 7 days prior to enrollment (Day −7 to Day −1). If applicable, during the study, urine pregnancy tests will be performed at the scheduled visits.

[p] Day 1 assessment predose (=baseline), followed by assessments at Week 13 predose and Week 25 predose by Haem-A-QoL (age >18 years) and Haemo-QoL-Short Form (ages 12−17 years).

[q] *Day 1 assessment predose (=baseline), followed by assessments at Week 13 predose and Week 25 predose.*

[r] Predose.

[s] Day 1 assessment predose (=baseline), followed by assessments at Week 13 predose and Week 25 predose by EQ-5D-5L questionnaire.

[t] 3 mg/kg Q4W emicizumab loading dose, followed by 6 mg/kg Q4W emicizumab maintenance dose.

[u] Bleed information (start date and time, reason, type, location, and associated symptoms of each bleed) and medication for bleeds (breakthrough bleeds) should be reported by the patient via an electronic, handheld device when a bleed occurs or at least on a weekly basis (retrospective reporting for last 7 days). *If the patient discontinues study treatment, bleed and bleed medication data should be provided by the patient until the safety follow-up visit (24 weeks after last study drug administration).*

[v] Investigator review of bleed information.

[w] *Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and schistocytes within 24−48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24−48 hours thereafter until 24−48 hours following the last dose of bypassing agents administered to treat a given bleed. In the case that such local laboratory tests are performed, laboratory results should be recorded on the unscheduled visit eCRFs.*

Appendix 2
Schedule of Assessments (cont.)

SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES

PK RUN-IN																														
	Screen-ing	Treatment Period																										From Week 25 to Study Com-pletion	Study Com-pletion or ET [a]	Safety F/U visit
Week		1			2		3		4		5	6	7	8	9	10 to 12[b]	13	14 to 16[b]	17	18 to 20[b]	21	22	*23*	*24*	25			
Day	-28 to -1 days	1	3	5	8	11	15	18	22	25	29	36	43	50	57		85		113		141	148	*155*	*162*	169			
Emicizumab PK [b]		x	x [c,d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q12W	x	*x*
Emicizumab ADA[d]		x									x				x		x		x		x				x	Q12W	x	x
Emicizumab biomarker set 1 [e]		x									x		x		x	x [f]	x	x [f]	x	x [f]	x		x		x	Q12W	x	*x*
Emicizumab biomarker set 2[g]			x[c]	x	x	x	x	x	x	x																			
Anti-FVIII antibodies [h, i]	x	x													*x*				*x*						x	Q12W	x	x
Following treatments with bypassing agents		*Monitoring for thromboembolic events and thrombotic microangiopathy* [j]																										

Appendix 2
Schedule of Assessments (cont.)

ADA = anti-drug antibody; ET = early termination; F/U = follow-up; FIX = factor IX; FVIII = factor VIII; FX = factor X; FXIII = Factor XIII; PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; Q12W = every 12 weeks.

Note: Blood samples should always be drawn predose (if taken on days of emicizumab administration); consult the Sample Handling Manual for details. PD biomarker tests will include, but are not limited to those listed here. In order to characterize pharmacokinetics, it is mandatory that assessments are being performed on the exact visit day until Week 25; no deviation from visit day is acceptable *until Week 25. Deviations from the schedule of assessments of ± 2 days are acceptable after Week 25.*

[a] Study completion visit when either the patient completed 24 weeks' study duration and transferred to an emicizumab extension study OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation OR patient is lost to follow-up. If study completion occurs after 24 weeks in the study, the completion assessments displayed in the schedule of assessments are similar with the Week 25 visit.

[b] During the first 8 weeks, PK sampling will occur at the following timepoints: Week 1 (predose Day 1; 8 hours post-injection on Day 1; then Day 3, Day 5), Week 2 (Day 8, Day 11), Week 3 (Day 15, Day 18), Week 4 (Day 22), Week 5 (Day 29 predose), Week 6 (Day 36), Week 7 (Day 43), and Week 8 (Day 50). A reduced PK sampling schedule will follow to characterize repeated Q4W SC administration from Week 9 to Week 25. From Week 9 to Week 21, patient will have PK blood samples taken at Week 9 (Day 57), Week 13 (Day 85), Week 17 (Day 113), and Week 21 (Day 141). From Week 9 to Week 21, additionally the patient will return once between two emicizumab administrations for a blood sample to be drawn for PK analysis; patients can decide whether this sampling will be 1, 2, or 3 weeks after the latest injection. An individual patient may choose each of the specific intervals (1, 2, or 3 weeks after to the latest injection) at least once. After the sixth injection at Week 21, PK sampling frequency will be increased to characterize steady-state pharmacokinetics, with samples collected at Week *22* (Day 148), Week *23* (Day 155), and Week 24 (Day 162). Another sample will be taken at Week 25 (Day 169) followed by PK assessments every 12 weeks until study completion.

[c] 8 hours postdose on Day 1.

[d] Emicizumab ADA blood samples may also be drawn to if hypersensitivity event occur or on an unscheduled basis (at the clinical judgment of the investigator) at any time.

[e] Set 1 = Standard aPTT, modified aPTT, PT, FVIII activity, thrombin generation, FIX antigen, FX antigen, *FVIII antigen (baseline only),* D-dimer, prothrombin fragment 1.2*,* vWF antigen *(timepoints of Week 1 Day 1, Week 13, Week 25, study completion or ET, safety follow-up visit),* fibrinogen *(timepoints of Week 1 Day 1, Week 13, Week 25, study completion or ET, safety follow-up visit), and FXIII activity (baseline only).*

[f] PD assessments occurring once between two Q4W emicizumab administrations to be done on the same day the PK sample is taken (see footnote above).

[g] Set 2 = FVIII activity, D dimer, prothrombin fragment 1.2*, standard aPTT, modified aPTT, and PT.*

[h] A sample for inhibitor testing (anti-FVIII antibodies) must be obtained *during screening,* within *4* weeks *prior to* enrollment (i.e., before initiation of Week 1, Day 1 assessments). The results must be available before enrollment, and local testing will not replace the central laboratory inhibitor testing performed at Week1.

[i] Starting at Week 1, this and all subsequent anti-FVIII antibodies will be measured at a central laboratory. Anti-FVIII antibodies will be *tested by a central laboratory* at

Appendix 2
Schedule of Assessments (cont.)

Week 1, Week 25, *every 12 weeks thereafter,* at the completion visit, *and safety follow-up visit* for all patients. Testing at Week *9* (Day *57*) and Week *17* (Day *113*) for non-inhibitor patients only.

j *Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed. In the case that such local laboratory tests are performed, laboratory results should be recorded on the unscheduled visit eCRFs.*

Appendix 2
Schedule of Assessments (cont.)

EXPANSION COHORT														
	Screen-ing	Treatment Period										From Week 25 to Study Completion	Study Completion or Early Termination [a]	Safety F/U Visit
Week		1	2	3	4	5	9	13	17	21	25			
Day	-28 to -1 days	1	8	15	22	29	57	85	113	141	169			
Emicizumab PK		x	x	x	x	x	x	x	x	x	x	Q12W	*x*	*x*
Emicizumab ADA [b]		x				x	x	x	x	x	x	Q12W	x	x
Emicizumab biomarker set 3(EDTA) [c]			*x*	*x*	*x*						*x*	*Q12W*		
Emicizumab biomarker set 1[d]		x	x	x	x	x	x	x	x	x	x	Q12W	*x*	*x*
Anti-FVIII antibodies [e, f]	x	x					*x*		*x*		x	Q12W	x	x
Following treatments with bypassing agents		*Monitoring for thromboembolic events and thrombotic microangiopathy. [g]*												

Appendix 2
Schedule of Assessments (cont.)

ADA = anti-drug antibody; F/U = follow-up; FIX = factor IX; FVIII = factor VIII; FX = factor X; FXIII = Factor XIII; PK = pharmacokinetic; Q12W = every 12 weeks.

Note: Blood samples should always be drawn predose (if taken on days of emicizumab administration); consult the Sample Handling Manual for details. PD biomarker tests will include but are not limited to those listed here. In order to characterize pharmacokinetics, it is mandatory that assessments are being performed within ± 2 days of the scheduled visits.

[a] Study completion visit when either the patient completed 24 weeks' study duration and transferred to an emicizumab extension study OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation OR patient is lost to follow-up. If study completion occurs after 24 weeks in the study, the completion assessments displayed in the schedule of assessments are similar with the Week 25 visit.

[b] Emicizumab ADA blood samples may also be drawn if hypersensitivity event occurs or on an unscheduled basis (at the clinical judgment of the investigator) at any time.

[c] *Set 3 = Exploratory biomarker assay of emicizumab concentration that requires EDTA rather than citrate plasma.*

[d] Set 1 = Standard aPTT, modified aPTT, PT, FVIII activity, thrombin generation, FIX antigen, FX antigen, D-dimer, prothrombin fragment 1.2 vWF antigen *(timepoints of Week 1 Day 1, Week 13, Week 25, study completion or ET, safety follow-up visit)*, and fibrinogen *(timepoints of Week 1 Day 1, Week 13, Week 25, study completion or ET, safety follow-up visit)*.

[e] A sample inhibitor testing (anti-FVIII antibodies) must be obtained within 8 weeks *prior to* enrollment, (i.e., before initiation of Week 1, Day 1 assessments). The results must be available before enrollment, and local testing will not replace the central laboratory inhibitor testing performed at Week 1.

[f] Starting at Week 1, this and all subsequent anti-FVIII antibodies will be measured at a central laboratory. Anti-FVIII antibodies will be *tested by a central laboratory* at Week 1, Week 25, *every 12 weeks thereafter,* at the completion visit, *and safety follow-up visit* for all patients. Testing at Week *9* (Day *57*) and Week *17* (Day *113*) is for non-inhibitor patients only.

[g] *Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed. In the case that such local laboratory tests are performed, laboratory results should be recorded on the unscheduled visit eCRFs.*