Official Title: **A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITHOUT INHIBITORS**

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STUDY DRUG: Emicizumab (RO5534262)

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

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CONFIDENTIAL

*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.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF APPENDICES

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).

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 the disease roughly correlates with the residual endogenous level of FVIII activity. Approximately 68% of people with hemophilia A have moderate (25%) or severe (43%) forms, characterized by FVIII activity levels $<5\%$ or $<1\%$, respectively, leading to frequent bleeding events with the sequelae of musculoskeletal complications (e.g., arthropathy), local functional deficits, hemorrhagic shock, neurocognitive defects, or even death (World Federation of Hemophilia 2013).

Prophylactic FVIII replacement therapy (i.e., administered on a scheduled basis with the intent to prevent bleeds) has been proven to minimize bleeding events and complications (Manco-Johnson et al. 2007). Since the 1990s, recombinant FVIII (rFVIII) concentrates have been standard-of-care treatment options for patients with hemophilia A (Kingdon and Lundblad 2002). Current prophylactic regimens commonly use infusion therapy administered three times weekly; other regimens use every other day administration (Shapiro 2013).

Prophylactic FVIII replacement therapy has been recognized as superior to episodic treatment of symptomatic bleeds for several decades (Khawaji et al. 2012) and was adopted by national and international organizations as the desired treatment approach. However, the burden of treatment (Eton et al. 2013, Mair and May 2014) is extraordinarily onerous, as adequate prophylaxis requires a lifetime of self-administered intravenous (IV) infusion of FVIII 3–4 times each week. In addition to the obvious toll on the quality of patients' life (Teal et al. 2014), this burden results in suboptimal care for many who elect to avoid routine prophylaxis, despite its medical advantage (Geraghty et al. 2006; Lindvall et al. 2006; De Moerloose et al. 2008; Collins et al. 2014; Oldenburg 2015). Thus, episodic therapy is a standard-of-care for many patients with hemophilia in developed countries, where approximately one-third to one-half of the patients use FVIII on-demand and avoid continuous prophylaxis.

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, as 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 the pharmacokinetic properties of this antibody are expected to enable marked extension of the dosing interval to once weekly, every other week, 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 low burden prophylactic therapy.

Initial experience with emicizumab in humans was generated from one Phase I study (ACE001JP) and its ongoing extension, a Phase I/II study (ACE002JP). See the RO5543262 [Emicizumab] Investigator's Brochure for additional details on clinical studies with emicizumab. The results have also been published (Shima et al. 2016; Uchida et al. 2016). Based on these compelling data, the Phase III development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) was initiated. Studies BH29884 (adults and adolescents) and BH29992 (pediatric) in hemophilia A patients with FVIII inhibitors had a first data readout at the end of 2016 when this study was already ongoing.

Consequently it was decided that a minimum of 40 patients with prophylactic FVIII replacement therapy should come from a separate non-interventional study (NIS; BH29768) and have at least 6 months of data in the NIS before enrolling into Arm D of Study BH30071 (see Section 2).

2. STUDY DESIGN

Study BH30071 is a randomized, multicenter, open-label, Phase III clinical study will enroll patients aged 12 years or older with severe hemophilia A (intrinsic FVIII level < 1%)

without inhibitors against FVIII. Approximately 85 patients who received episodic treatment with FVIII prior to study entry and experience at least 5 bleeds over the prior 24 weeks (annual bleed rate [ABR] ≥ 10) will be randomized in a 2:2:1 ratio to the following regimens:

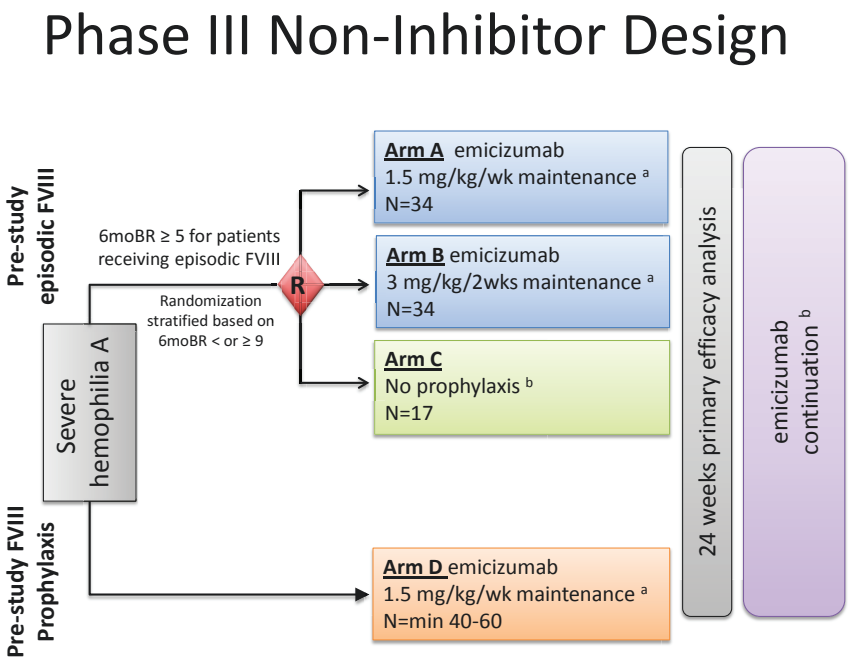
- Emicizumab prophylaxis at 3 mg/kg/week (wk) subcutaneously for 4 weeks, followed by 1.5 mg/kg/wk subcutaneously (Arm A)
- Emicizumab prophylaxis at 3 mg/kg/wk subcutaneously for 4 weeks, followed by 3 mg/kg/every 2 weeks (2wks) subcutaneously (Arm B), or
- No prophylaxis control arm (Arm C)

Randomization will be stratified according to the number of bleeds patients experienced over the last 24 weeks prior to study entry, < 9 versus ≥ 9 (or ABR 18), to ensure a balance of patients with lower versus higher number of bleeds in all arms. All patients will continue usual episodic treatment with FVIII in case of a breakthrough bleeding event.

In addition, 40–60 patients with severe hemophilia A who received FVIII prophylaxis prior to study entry will be enrolled and receive emicizumab prophylaxis at 3 mg/kg/wk subcutaneously for 4 weeks, followed by 1.5 mg/kg/wk subcutaneously (Arm D). To improve the validity of historical comparison in this group, at least 40 patients will be observed on FVIII prophylaxis in NIS BH29768 for a period of at least 24 weeks before enrolling in Arm D of this study.

The study schema is shown Figure 1.

Figure 1 Study Schema for Study BH30071



2wks = every 2 weeks; 6moBR = 6 months bleed rate; BR = bleed rate; FVIII = factor VIII; mo = month; R = randomization; wk = week.

[a] All patients will receive loading with four weekly doses of emicizumab 3 mg/kg/wk prior to starting maintenance.

[b] Arm C patients during the no prophylaxis period are designated $C_{control}$; whereas, after switch to emicizumab (allowed per protocol after 24 weeks), they are designated Arm C_{emi}.

The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic emicizumab versus no prophylaxis will be conducted after reaching the clinical cutoff, which occurs at the earliest timepoint when all randomized patients (Arms A, B, and C) and a minimum of 40 patients from Arm D have either completed 24 weeks in the study or discontinued from the study.

To obtain additional safety and efficacy data on emicizumab, patients who are randomized to the no prophylaxis arm (control arm, Arm $C_{control}$) will have the opportunity to switch after 24 weeks to receive emicizumab prophylaxis at 3 mg/kg/2wks maintenance dose after 4 weeks of 3 mg/kg/wk loading dose. For clarity, Arm C patients during the no prophylaxis period are designated $C_{control}$; whereas, after switch to emicizumab they are designated Arm C_{emi}. After completing at least 24 weeks of treatment with prophylactic emicizumab, patients who receive emicizumab prophylaxis (Arms A, B, D, or Arm C_{emi} after treatment switch) and derive clinical benefit will be allowed to continue emicizumab until marketing authorization as part of this study or a

separate extension study, as long as they continue to derive clinical benefit and emicizumab is still in clinical development.

Patients may be allowed to up-titrate their emicizumab dose if they meet the pre-specified criteria as described in the protocol. Patients in the randomized arms can escalate after at least 24 weeks on emicizumab prophylaxis, while dose increase is permitted at any time after the second qualifying bleed for patients in Arm D.

[redacted].

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 an electronic bleed and medication questionnaire (BMQ), which was developed by the Sponsor given that no standard questionnaire for collection of these data exists.

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. The draft questions were developed following review of the hemophilia A literature and discussions with medical professionals regarding what information on related bleeds was most important to capture. Prior to use in this study, qualitative interviews with patients with hemophilia A were conducted in order to evaluate the measure's content validity and to test the understanding and usability of the BMQ on an electronic, handheld device. Cognitive interviews were conducted in person with a total of 20 patients aged 12 years and older with hemophilia A; the results demonstrated that the BMQ was comprehensive and relevant to patients' experiences with bleeds and treatments.

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 (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

At specified visits, patients will complete health-related quality-of-life (HRQoL), health status, and satisfaction/preference questionnaires on a tablet device that will remain at study sites. The instructions for completing the patient-reported outcome (PRO) questionnaires electronically will be provided by the investigator staff during the Week 1 visit at the site. The data will be transmitted automatically after entry to a centralized secure database at the vendor.

2.2.3 [redacted]

[redacted]

[redacted]

2.3 ENDPOINTS

2.3.1 Primary Efficacy Endpoint

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 following rules as outlined in the sections below are applied.

2.3.1.1 Efficacy Period

The start of the efficacy period for each individual patient is defined as the first day when there is data in the BMQ. For patients starting the study on emicizumab (Arms A, B, and D) this is expected to coincide with the Week 1 visit, and the day of their first emicizumab dose. For patients who do not start the study on emicizumab (Arm C), the start of the efficacy period should coincide with the Week 1 visit.

Of note, the first day when there is data in the BMQ, includes the first day for which data is reported via the handheld device, a DCR, or the day of device activation.

A second efficacy period is defined for patients in Arm C who switch to emicizumab starting on the day of their first emicizumab dose.

For patients randomized or enrolled on emicizumab, 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), whichever is earlier. For patients randomized to no prophylaxis (Arm C), the end of the first efficacy period is defined as the day before the first emicizumab dose or the date of withdrawal from the initial study period (i.e., treatment phase according to eCRF) or the date of the clinical cutoff if

neither of the aforementioned events has taken place. For patients whose dose is up-titrated, the efficacy period on the initial dose (the initial period for patients randomized/enrolled to Arms A, B, and D; the second efficacy period, starting at first emicizumab dose for patients randomized to Arm C) ends 1 day prior to the first day on the up-titrated dose.

For patients who withdraw from the study before reaching the Week 1 visit, the duration of the efficacy period is set to 1 day, and it starts and ends on the day of randomization/enrollment.

For patients whose dose is up-titrated, the bleeds on the up-titrated dose are analyzed separately. The efficacy period on a given up-titrated dose (second efficacy period for patients randomized/enrolled to Arms A, B, and D; third efficacy period for patient randomized to Arm C) starts with the first day on this dose and ends on the day of the clinical cutoff or the date of withdrawal.

2.3.1.2 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 a hemophilia medication reported to be a “treatment for bleed,” irrespective of the time between the treatment and the preceding bleed. A bleed and the first treatment thereafter 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 (which are, however, counted as separate bleeds).

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

72-Hour Rule

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

2.3.2 Secondary Efficacy Endpoints

The same definition of the efficacy period applies to all bleed-related secondary efficacy endpoints.

2.3.2.1 All Bleeds

“All bleeds” 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 as for the primary analysis.

The endpoint of all bleeds fulfills the adapted ISTH criteria, as described in the protocol for the primary endpoint and the 72-hour rule, in particular. For treated bleeds, it is implemented exactly as defined for the primary endpoint. For non-treated bleeds (not followed by any treatments with coagulation factors before the recording of a subsequent bleed), it is implemented by calculating a treatment-free period of 72 hours from the bleed itself.

2.3.2.2 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.

2.3.2.3 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 using the joint compared with baseline.

2.3.2.4 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.

2.3.2.5 Intra-Patient Comparison

In the intra-patient comparison (on All Bleeds and on Treated Bleeds as defined in Section 2.3.2.1 and Section 2.3.2.2, respectively), only patients who participated in NIS BH29768 are included. This is because it is possible to apply the detailed bleed definitions only if the data are collected with the same granularity for both time periods. Of note, for some episodic patients who participated in NIS BH29768, the total time in that study prior to enrollment in Study BH30071 may be less than 24 weeks.

The efficacy period in NIS BH29768 is defined as the time from the first entry on the electronic, handheld device or site data entry system to the day the patient completed the study, which may occur between 1 day and a few days prior to

enrollment/randomization in Study BH30071. Usually, the date of the first BMQ entry in NIS BH29768 is the date the Training Module on the electronic, handheld device is completed. The end of the efficacy period in NIS BH29768 is defined as the date of withdrawal or date of study completion or on the day of the clinical cutoff, whichever occurs earlier.

2.3.2.6 Haem-A-QoL at 24 Weeks

The Haem-A-QoL and the Haemo-QoL-SF will be used to measure HRQoL in adults and adolescents, respectively. Therefore, all calculations and analyses will be conducted separately for these two measures. Total score and physical health subscale score for the Haem-A-QoL will be evaluated at 24 weeks in the study and formally analyzed as described in the efficacy analysis section. However, only the physical health subscale will be part of the hierarchical testing procedure highlighted in this analysis section. Other subscale scores will be analyzed in a descriptive way.

The number of adolescent patients in the randomized portion of the study will be too small to provide meaningful statistical analyses of the Haemo-QoL-SF and therefore the analysis of this endpoint will be descriptive.

2.3.2.7 EQ-5D-5L at 24 Weeks

The European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) index utility score using the U.K. value set and visual analogue scale (VAS) will be evaluated at 24 weeks in the study. These two endpoints will be analyzed as described in the efficacy analysis section but will not be part of the hierarchical testing procedure.

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- Patient satisfaction with treatment [redacted]
- Treatment preference for emicizumab prophylaxis versus FVIII prophylaxis or episodic therapy according to the preference survey
- Number of days away from school/work
- Number of days hospitalized
- [redacted]

2.3.4 Pharmacokinetic Endpoints

The pharmacokinetic (PK) endpoint for this study is the exposure (trough plasma concentration) to emicizumab at the following timepoints:

- Every week during Weeks 1–4 on emicizumab
- Every 2 weeks during weeks 5–8 on emicizumab
- Every 4 weeks during weeks 9–24 on emicizumab
- Every 8 weeks during weeks 25–48 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, anti-FVIII and anti-emicizumab antibodies), vital signs, ECG, and concomitant medication use.

2.3.6 Exploratory Biomarker Endpoints

Exploratory biomarker endpoints include

- Pharmacodynamic (PD) biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and FVIII activity
- [redacted]

2.4 DETERMINATION OF SAMPLE SIZE

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of patients with hemophilia A without inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the safety and efficacy of emicizumab.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a negative binomial (NB) distribution. With consideration of enrollment feasibility, a sample size of 75 patients, assuming an allocation ratio of 2:2:1 (30 patients in each randomized treatment group and 15 patients in control group), will achieve a power of more than 90% assuming a mean ABR of 4 and 14 bleeds (with variances $=$ mean $\times$ 10) for the emicizumab treatment and control arms respectively, representing an expected 71% reduction in the ABR compared to the control arm. Initial sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), assuming the patients from each treatment group are followed up to 0.5 units of time (i.e., 24 weeks).

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of an NB regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 90% power at the 2-sided 0.05 level of significance.

The analysis will include all enrolled patients regardless of their length of follow-up. Therefore, to ensure the analysis is based on sufficient follow-up data and with 2:2:1 treatment to control randomization, approximately 34 patients in each randomized

emicizumab treatment arm (68 in total) and 17 patients in the control arm (approximately 85 patients in total) will be enrolled.

With a minimum of 40 and a maximum of 60 patients enrolled in the open-label prophylactic emicizumab arm, and assuming a mean ABR of 4 and variance of 4×10, this number is considered sufficiently powered to evaluate the efficacy endpoint in this cohort; the treatment will be considered to provide adequate control if the upper limit of the one sided 97.5% CI around the mean ABR is less than or equal to 6.

The primary safety consideration in determining the sample size was the ability to sufficiently evaluate the safety profile of emicizumab as assessed by adverse events. Under the assumption that the occurrence of an adverse event can be adequately modeled using the binomial distribution, the planned sample size of 108–128 patients in the emicizumab treatment groups allows observation of adverse events having a true incidence rate of 1% with a probability of 0.66–0.72.

No sample size re-assessment of the initially specified sample size will be performed.

2.5 ANALYSIS TIMING

The primary efficacy analysis to assess the effect of emicizumab on bleed rate reduction will be performed at the earliest timepoint when all randomized patients (Arms A, B, and C) and a minimum of 40 patients from Arm D have either completed 24 weeks of study treatment or discontinued from the study.

The final analysis will occur at the end of the study, as defined in the protocol. No interim analysis is planned for the study.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients who received episodic treatment with FVIII prior to study entry will be randomized in a 2:2:1 ratio to receive either emicizumab prophylaxis at 3 mg/kg/wk subcutaneously for 4 weeks, followed by 1.5 mg/kg/wk (Arm A) or 3 mg/kg/2wks (Arm B) subcutaneously, or to the control arm (no prophylaxis; Arm C). The time between screening and enrollment of eligible patients should be ≤ 6 weeks; otherwise, patients must be re-screened to determine if they continue to meet the inclusion and exclusion criteria. A central randomization procedure will be used for all patients who fulfill the

entry criteria at screening. A block based randomization method will be used, stratified by the number of bleeds in the last 24 weeks (<9 or ≥ 9). The proposed randomization method is designed to balance treatment group assignment within the prognostic stratification factor.

Patients on FVIII prophylaxis prior to study entry will be enrolled in a separate therapeutic arm to receive emicizumab prophylaxis (Arm D).

3.2 DATA MONITORING

An independent Data Monitoring Committee (iDMC) has been assembled to review the safety data collected during the study. The iDMC members consist of, at a minimum, independent hemostasis/thrombosis experts and a statistician, none of whom are otherwise involved in the conduct of study. All analyses for review by the iDMC are prepared by an independent Data Coordinating Committee (iDCC) that is independent of the Sponsor.

An iDCC performs unblinded analyses and provides tables and listings to support the iDMC reviews of safety data. The safety data include demographic data, adverse events, serious adverse events, and laboratory abnormalities (coagulation, hematology, and chemistry). Further information will be given by the iDCC to the iDMC 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 or closing a treatment arm for safety reasons. The iDMC will monitor the incidence of the anticipated adverse events, as well as the overall safety of patients, during the study.

The first safety review was conducted after 25 episodic patients (i.e., randomized to Arms A, B, or C) had been in the study for at least 2 months, and the iDMC recommended to continue. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor according to the emerging safety profile.

Further details are provided in a separate iDMC Charter.

4. STATISTICAL METHODS

4.1 OUTPUT LAYOUTS

The key output layouts are designed to address the study objectives in a flexible manner and provide an overall view of the efficacy and safety of emicizumab. In particular, patients in Arm C are allowed to switch to receive emicizumab after the first 24 weeks in the study, yielding two “study periods” (i.e., when they receive no prophylaxis for the first 24 weeks [no prophylaxis period, designated Arm $C_{control}$] and emicizumab prophylaxis thereafter [emicizumab period, designated Arm C_{emi}]). These two periods are analyzed

separately, and either period can be displayed on outputs together with the other treatment arms.

The four key output layouts are:

- **Randomized patients**: comparison of either emicizumab 1.5 mg/kg/wk (Arm A) versus no prophylaxis (control arm [Arm $C_{control}$] prior to switch to emicizumab) or emicizumab 3 mg/kg/2wks (Arm B) versus no prophylaxis (Arm $C_{control}$), within a single output produced for all comparisons involving arms A, B, and C prior to switch (Arm A versus Arm $C_{control}$ and Arm B versus Arm $C_{control}$); these outputs form the core set of the efficacy comparisons and will be supported by a corresponding safety analysis
- **All patients**: these outputs will be used to describe the baseline characteristics and study conduct
- **All emicizumab patients**: these outputs will provide an overall view of all data collected under emicizumab prophylaxis (including control arm patients after switch [Arm C_{emi}]) and will include analyses of safety and descriptive efficacy
- **Intra-patient comparisons**: Arm D is displayed separately with its own historical control (for Arms A and B, the patients are combined; see Section 4.5.2.6); for evaluations of the secondary endpoint with intra-patient comparisons, only patients who participated in the NIS BH29768 are included

Of note, patients may be allowed to up-titrate their emicizumab dose as described in Section 2. The data under the new, higher dose are 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). Note, with longer follow-up or in case up-titration occurs more frequently than expected, outputs on all data may form the core analysis and additional summaries will be produced by dose.

4.2 ANALYSIS POPULATIONS

4.2.1 Randomized Population (ITT)

The randomized population (intent-to-treat [ITT]) is defined as all randomized patients. The ITT population will be the primary analysis population for efficacy. Patients are analyzed according to their randomized treatment arm. Note that this population only includes patients in Arms A, B, and C.

4.2.2 All Patients

The All Patients population includes all patients in their originally assigned treatment arms (including patients in Arm D previously treated with prophylactic FVIII), according to the interactive voice or Web Response System (IxRS).

4.2.3 All Emicizumab Patients

The All Emicizumab Patients population is the same as the All Patients population for Arms A, B, and D. For Arm C, only patients who switch to receive emicizumab are included.

4.2.4 Pharmacokinetic-Evaluable Population

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

4.2.5 Safety Population

Two safety analysis populations are defined below:

- Safety Population 1 (SAF1) includes all patients in Arms A, B, and D who received at least one dose of emicizumab and patients in Arm C who started the study period, defined as having a Week 1 visit. For safety analysis of randomized patients, a subset of the SAF1 population (SAF1ND) will be used, which excludes patients in Arm D.
- Safety Population 2 (SAF2) is exactly the same as SAF1 for patients in Arms A, B, and D. For patients in Arm C, SAF2 includes all patients who switched to emicizumab and received at least one dose of emicizumab.

4.2.6 Up-titrated Population

The Up-Titrated population (UPT) includes patients whose emicizumab dose was up-titrated to 3 mg/kg/wk.

4.2.7 Non-Interventional Study (NIS) Population

The NIS population includes all patients who participated in NIS BH29768 prior enrollment to this study. The NIS population includes two subpopulations:

- The NISE population consisting in all the above NIS population previously treated with episodic FVIII
- The NISP population consisting in all the above NIS population previously treated with prophylactic FVIII

4.2.8 [redacted]

[redacted]

4.3 ANALYSIS OF STUDY CONDUCT

Flow of patients through the study will be displayed in a "CONSORT" diagram. A clear account of all patients who entered the study, who were enrolled and randomized, and who entered and completed each phase of the study will be displayed. In addition, reasons for premature discontinuations from study treatment and reasons for withdrawing from the study (e.g., during follow-up) will be described.

Major protocol deviations will be summarized.

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

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Comparisons between the treatment arms of demographic data (e.g. age, sex, race/ethnicity, weight, and height) and baseline disease characteristics (e.g., number of bleeds in the past 24 weeks, previous hemophilia treatments, and number of target joints) will be conducted to establish if any observed differences between the treatment arms are not due to imbalances in patient characteristics at baseline. Only descriptive analyses are planned, and no formal statistical tests will be applied.

4.5 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will be based on the All Patients population (see section 4.2.2).

4.5.1 Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in Section 2.3.1. The primary endpoint is based on treated bleeds.

The comparison of the number of bleeds over time between the randomized treatment arms will be performed using an NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study (the length of the efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9 according to the eCRF data) in the last 24 weeks prior to study entry as a stratification factor. This analytic model estimates the rate ratio, λ_t/λ_c, which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level.

Of note, hierarchical testing is used to account for multiple testing and the first test to be included in the hierarchy is the emicizumab 1.5 mg/kg/wk maintenance dose versus

control. The second test will be 3 mg/kg/2wks maintenance dose versus control. A global approach using a model statement (within GENMOD) with a 3-level categorical effect for treatment ("1.5 mg/kg/wk," "3 mg/kg/2wks," or "no prophylaxis") and an appropriate contrast statement will allow both tests to be performed via the following hypothesis

H_0 (null hypothesis): Rate Ratio $= 1$ versus H_1 (alternative hypothesis): Rate Ratio $\neq 1$.

Statistical significance at the prespecified α level will be based on a Wald testing procedure. Bleed rates for prophylactic emicizumab and no prophylaxis and the rate ratio will be presented and include 95% CIs.

The number of bleeds can also be annualized for each patient using the following formula:

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

Both the model-based method (estimated ABR from the NB model) and the method using the above formula (calculated ABR) will be used to describe the study results.

If the NB model converges, the Van Elteren test to compare the mean ABR between the randomized arms will be provided as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable or no bleeds at all were observed in one of the treatment arms, the primary efficacy analysis will be based on the Van Elteren test of ABR, according to the above formula.

Of note, the Van Elteren test will be applied separately for the Arm A versus Arm $C_{control}$ (using only patients randomized to Arms A and $C_{control}$) and for the Arm B versus Arm $C_{control}$ comparisons.

4.5.2 Secondary Efficacy Endpoints

Type I error for secondary endpoints is controlled through a hierarchical testing framework. The α level is 0.05. Following the two statistical comparisons described in Section 4.5.1 for the primary endpoint (Arm A versus Arm $C_{control}$ and Arm B versus Arm $C_{control}$) the secondary endpoints are included in the hierarchy in the following order:

- A versus C randomized comparison: all bleeds
- B versus C randomized comparison: all bleeds
- A versus C randomized comparison: treated joint bleeds
- B versus C randomized comparison: treated joint bleeds
- A versus C randomized comparison: treated spontaneous bleeds
- B versus C randomized comparison: treated spontaneous bleeds
- D intra-patient: all bleeds
- D intra-patient: treated bleeds

- A versus C randomized comparison: Haem-A-QoL physical health at 24 weeks
- B versus C randomized comparison: Haem-A-QoL physical health at 24 weeks

4.5.2.1 All Bleeds

The definition of all bleeds is described in Section 2.3.2.1. The analysis methodology is the NB regression model or the Van Elteren test, as described for the primary endpoint in Section 4.5.1.

4.5.2.2 Treated Spontaneous Bleeds

The definition of treated spontaneous bleeds is described in Section 2.3.2.2. The analysis methodology is the NB regression model or the Van Elteren test, the same as for the primary endpoint.

4.5.2.3 Treated Joint Bleeds

The definition of treated joint bleeds is described in Section 2.3.2.3. The analysis methodology is the NB regression model or the Van Elteren test, the same as for the primary endpoint.

4.5.2.4 Intra-Patient Comparison—Previous Prophylactic Patients

The definition of treated bleeds and all bleeds for the intra-patient comparison (Section 4.1) is the same as described for the primary and secondary endpoints. The analysis methodology will be applied for Arm D (previous prophylactic patients) using the same NB regression model as for the primary endpoint with the exception that the SAS GENMOD procedure will include a REPEATED statement, to account for the intra-patient comparison. For intra-patient analysis of Arms A and B, see Section 4.5.2.6.

4.5.2.5 Haem-A-QoL at 24 Weeks

The physical health subscore of the Haem-A-QoL at 24 weeks will be analyzed using analysis of variance (ANOVA). The model will include the treatment group together with the baseline score and treatment by baseline interaction as covariates. As for the primary analysis, a global approach with a 3-level categorical effect for treatment (1.5 mg/kg/wk, 3 mg/kg/2wks, or no prophylaxis) will be produced for the comparisons of Arm A versus Arm C and Arm B versus Arm C.

4.5.2.6 Secondary Efficacy Endpoints Not Included in the Hierarchy

Treated target joint bleeds (defined according to Section 2.3.2.4) on emicizumab will be compared with no prophylaxis and will be analyzed using the same methodology as for the primary endpoint (i.e., using the NB regression model or the Van Elteren test).

[redacted]

[redacted]

The Haem-A-QoL total score, the EQ-5D-5L index utility score based on the U.K. value set, and the VAS at 24 weeks will be analyzed using the same analysis methodology as the Haem-A-QoL physical health subscore (i.e., via ANOVA).

The same analysis methodology for the intra-patient comparison within Arm D for treated bleeds and all bleeds will be applied for the pooled Arms A and B (episodic patients randomized to emicizumab). Of note: given the small number of NIS episodic patients that were randomized to either Arm A or B, it was considered that a pooled analysis was considered as more appropriate than two separate analyses.

Only a descriptive summary of the Haemo-QoL-SF will be provided because of the small number of adolescents randomized to the study.

4.5.3 Exploratory Efficacy Endpoints

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 be calculated.

For EQ-5D-5L, Haem-A-QoL, and Haemo-QoL-SF, exploratory analyses include descriptive analyses of change from baseline and between group comparisons over time for each individual subscale and the overall score. In addition, a paired t-test will be conducted to compare the 24-week with the baseline score for the EQ-5D-5L and Haem-A-QoL questionnaires by treatment arm separately. Due to the limited number of adolescent patients, paired t-tests will not be conducted on the Haemo-QoL-SF scales. For EQ-5D-5L and Haem-A-QoL, the number of patients who reported a clinically meaningful change from baseline to Week 24 will be reported. For EQ-VAS, a meaningful change is 7 points and for the index scale it is 0.07 points (Walters et al. 2005; Pickard et al. 2007). For Haem-A-QoL a meaningful change is 7 points for the total score and 10 points for the physical health score (Wyrwich et al. 2015).

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

[redacted]

[redacted]

Regarding the preference survey that is given to patients in Arms A, B, and D at Week 17, the proportion of patients preferring the older hemophilia IV treatment prior to enrollment in the study, emicizumab, and without treatment preference will be computed along with 95% CIs. For patients who have a preference to emicizumab, the factors influencing the preference will be treated like ordered categorical variables (e.g., from "had no influence in my treatment preference" to "was the most important factor in my treatment preference") and will be summarized accordingly. The same approach will be applied for patients who have a preference to the old hemophilia treatment. Bar charts by preference factors may be produced to characterize the preference profile of each treatment ("emicizumab" or "old hemophilia treatment").

[redacted]

4.5.4 Sensitivity Analyses

The sensitivity analyses will include different methods to define bleeds or eligible bleed data and different statistical models.

Different ways to define bleeds or eligible bleed data for A versus C and B versus C randomized comparisons:

- Include all bleeds recorded by patients in the electronic patient-reported outcomes device (i.e., without the 72-hour rule)
- Include treated joint bleeds defined as treated bleeds where the bleed type is "joint," regardless whether any symptoms have been observed
- Include only patients who received at least 12 weeks of emicizumab treatment (if needed)
- Count days when treatment for bleeds was administered instead of the bleeds themselves
- Include only the first 24 weeks of efficacy period in the analysis. Patients who withdraw from study treatment are included up to the point of study treatment withdrawal.

Different ways to analyze secondary endpoints with intra-patient comparison:

- D intra-patient: include also period after up-titration
- A intra-patient and B intra-patient: provide also analyses separately by arm (i.e., without grouping Arm A and Arm B)

Different statistical models for the bleed rate:

- An alternative NB modeling approach (using the GENMOD procedure) for the primary endpoint in which the A versus C and B versus C randomized comparisons are tested using separate models, including in the first model only the data for patients randomized into arms A and C and in the second model only the data for patients randomized into arms B and C.
- Analysis of variance (ANOVA)
- Van Elteren test (calculated ABR)

4.5.5 Subgroup Analyses

Comparative subgroup analyses describing the primary endpoint, treated bleed rate, will be conducted for the randomized portion of the study. In addition, estimated ABR including 95% CI will be calculated for all treatment arms in each subgroup. Note, due to the small sample size, all subgroup analyses will be highly sensitive to variability caused by individual patients and need to be interpreted with caution. No p-values will be calculated.

The pre-specified subgroups are:

- Age: $< 18, \geq 18$
- Age: $< 65, \geq 65$
- Race: Asian, Black or African American, White, Other
- Number of bleeds during 24 weeks prior to study entry: $\leq 9, > 9$

- Number of target joints: no target joint, any target joint

Subgroup analyses are subject to having sufficient patients in a subgroup to provide meaningful results.

In addition, region- and/or country-specific analyses will be performed to support regulatory submissions as needed.

4.6 PHARMACOKINETIC ANALYSES

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively by treatment arm, 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, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the concentration-time curve (AUC), will be derived from individual post-hoc predictions. Data may be pooled with data from other studies. These analyses will be reported in a dedicated report.

In addition, region- and/or country-specific analyses will be performed to support regulatory submission as needed.

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), ECGs, vital signs, and antibodies to emicizumab and FVIII.

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.

Patient withdrawals from study treatment will be reported in patient 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) for each treatment arm. 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 in International System of Units (SI) will be presented by treatment arm. 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 by treatment arm using mean change from baseline tables over time. Measurements consist of heart and respiratory rate, temperature, and systolic and diastolic blood pressures.

4.7.5 Electrocardiogram

ECG results and corresponding changes from baseline will be summarized by treatment arm 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, parameters derived from thrombin generation, FVIII activity) [redacted] will be presented using summary statistics over time, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. Summary and individual patient plots will also be produced, if applicable. [redacted]

[redacted].

4.9 MISSING DATA

On the electronic handheld devices, including the tablet on which the HRQoL endpoints are reported, it is not possible to leave questions unanswered or to enter partial data. Therefore the data for the primary and secondary bleed related endpoints and the HRQoL questionnaires are considered complete.

In the site data entry system, the symptoms of joint and muscle bleed are not collected. Therefore, bleeds with an anatomical location in a joint are considered joint bleeds.

4.10 INTERIM ANALYSES

No efficacy interim analyses are planned.

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Appendix 1
Protocol Synopsis

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITHOUT INHIBITORS**
PROTOCOL NUMBER:	BH30071
VERSION NUMBER:	3
EUDRACT NUMBER:	2016-000072-17
IND NUMBER:	122,954
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase III
INDICATION:	Hemophilia A without inhibitors
SPONSOR:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.

Objectives and Endpoints

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of prophylactic emicizumab (i.e., administered on a scheduled basis with the intent to prevent bleeds) compared with no prophylaxis in patients with hemophilia A without factor VIII (FVIII) inhibitors on the basis of the following endpoint:

- The number of bleeds over time (i.e., bleed rate)

The endpoint will be analyzed separately for the two emicizumab arms: 1.5 mg/kg/week (wk) and 3 mg/kg/every 2 weeks (2wks). The primary endpoint is based on treated bleeds.

Secondary Efficacy Objective

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of prophylactic emicizumab (in each individual emicizumab arms) on the basis of the following endpoint:

  Change in the number of bleeds over time compared with the patient's historical bleed rate *
- To evaluate the efficacy of prophylactic emicizumab administered at 1.5 mg/kg/wk or 3 mg/kg/2wks subcutaneously compared with no prophylaxis for patients previously treated with episodic FVIII on the basis of the following endpoints:

  All bleeds over time

  Spontaneous bleeds over time (spontaneous bleed rate)

  Joint bleeds over time

Appendix 1

Protocol Synopsis (cont.)

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)

HRQoL of patients according to Haem-A-QoL (aged ≥18) or Haemo-QoL-Short Form (aged 12–17) scores after 24 weeks

Health status of patients according to EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) scores after 24 weeks

- To evaluate the efficacy of prophylactic emicizumab administered at 1.5 mg/kg/wk subcutaneously for patients previously treated with prophylactic FVIII on the basis of the following endpoint:

  Maintaining adequate control of bleeding by evaluation of the bleed rate *

* Analyses will be performed for treated bleeds and all bleeds.

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To assess satisfaction regarding treatment with emicizumab prophylaxis [redacted]
- To assess treatment preference for emicizumab prophylaxis versus FVIII prophylaxis or episodic therapy according to the preference survey
- To assess changes in number of days away from school/work during treatment with prophylactic emicizumab compared with no prophylaxis
- To assess changes in number of hospitalization days during treatment with prophylactic emicizumab compared with no prophylaxis
- To assess potential pharmacodynamic (PD) biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and FVIII activity
- [redacted]
- [redacted]
- [redacted]

Safety Objective

The safety objective for this study is to evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A without inhibitors on the basis of the following endpoints:

- Incidence and severity of adverse events
- 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, or anaphylactoid reactions
- *Incidence and severity of thrombotic microangiopathy*
- Incidence and clinical significance of anti-emicizumab antibodies
- Incidence of de novo development of FVIII inhibitors in patients receiving emicizumab prophylaxis

Appendix 1

Protocol Synopsis (cont.)

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the exposure (trough plasma concentration) to emicizumab in patients treated on weekly or every 2 weeks dosing schedule at the following timepoints:

- Every week during Weeks 1–4 on emicizumab
- Every 2 weeks during Weeks 5–8 on emicizumab
- Every 4 weeks during Weeks 9–24 on emicizumab
- Every 8 weeks during Weeks 25–48 on emicizumab
- Every 12 weeks thereafter while on emicizumab, until the end of the study

Study Design

Description of Study

This randomized, multicenter, open-label, Phase III clinical study will enroll patients aged 12 years or older with severe hemophilia A (intrinsic FVIII level $< 1\%$) without inhibitors against FVIII. Eighty-five patients who received episodic treatment with FVIII prior to study entry and experience at least 5 bleeds over the prior 24 weeks (annual bleed rate [ABR] ≥ 10) will be randomized in a 2:2:1 ratio (see protocol) to the following regimens:

- Emicizumab prophylaxis at 3 mg/kg/wk subcutaneously for 4 weeks, followed by 1.5 mg/kg/wk subcutaneously (Arm A),
- Emicizumab prophylaxis at 3 mg/kg/wk subcutaneously for 4 weeks, followed by 3 mg/kg/2wks subcutaneously (Arm B), or
- No prophylaxis control arm (Arm C).

Randomization will be stratified according to the number of bleeds patients experienced over the last 24 weeks prior to study entry—less than versus greater than or equal to 9 (or ABR 18)—to ensure a balance of patients with lower versus higher number of bleeds in all arms. All patients will *use* episodic treatment with FVIII *at the lowest expected dose to achieve hemostasis* in case of a breakthrough bleeding event *(see below)*.

In addition, 40–60 patients with severe hemophilia A who received FVIII prophylaxis prior to study entry will be enrolled and will receive emicizumab prophylaxis at 3 mg/kg/wk subcutaneously for 4 weeks, followed by 1.5 mg/kg/wk subcutaneously (Arm D; see protocol). A minimum of 40 patients in this group will complete at least 24 weeks of observation in an ongoing non-interventional study (BH29768) prior to enrollment in this study. Eligibility for all patients in Arm D will be based on investigator's attestation of adequate prophylaxis regimen in the 24 weeks prior to study entry.

To avoid bleeds before adequate emicizumab plasma concentration is reached, these patients will continue their regular FVIII prophylaxis until the second emicizumab loading dose. At the end of the first week of treatment, 95% of patients are expected to achieve emicizumab level of 8 µg/mL, which is projected to have FVIII activity equivalent to approximately $> 2\%$. Thrombotic events were not found in the Japanese Phase I/II study where doses of FVIII were administered to treat breakthrough bleeds while patients had higher emicizumab steady-state level, supporting the safety of this approach. Importantly, routine prophylaxis will be prohibited for all patients enrolled in Arms A, B, or C and for patients in Arm D immediately after the second emicizumab dose.

Study enrollment will take place at the Week 1 visit. A patient who fulfills the inclusion and exclusion criteria should be enrolled and assigned to a treatment arm at the Week 1 visit, the same day when the first dose of emicizumab is due for patients in Arms A, B, and D.

Emicizumab is intended for prophylactic use only (i.e., not to treat bleeds that have already occurred). The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic emicizumab versus no prophylaxis will be

Appendix 1

Protocol Synopsis (cont.)

conducted at the earliest timepoint when all randomized patients (Arms A, B, or C) and a minimum of 40 patients from Arm D have either completed 24 weeks in the study or discontinued from the study. Therefore, there will be a range of observation periods from 6 to approximately 12 months, or longer. Study patients will be enrolled globally from the Americas, Europe, Africa, and Asia-Pacific region.

To obtain additional safety and efficacy data on emicizumab, patients who are randomized to the no prophylaxis arm (control arm, Arm C) will be expected to switch after 24 weeks to receive emicizumab prophylaxis at 3 mg/kg/2wks maintenance dose after 4 weeks of 3 mg/kg/wk loading dose. This dose was chosen to enhance the safety and efficacy data obtained with Arm B patients.

After completing at least 24 weeks of treatment with prophylactic emicizumab, patients who receive emicizumab prophylaxis (Arms A, B, D, or Arm C after treatment switch) and derive clinical benefit will be allowed to continue emicizumab until marketing authorization as part of this study or a separate extension study, as long as they continue to derive clinical benefit and emicizumab is still in clinical development (see protocol). Those who are well controlled (ABR < 4) will continue treatment on their assigned emicizumab regimen; whereas, patients in Arms A, B, or C (after 24 weeks on emicizumab) who experience suboptimal control (ABR ≥ 4) will be offered the option to escalate to 3 mg/kg/wk after approval from the Medical Monitor. Patients in Arm D who experience suboptimal control while on emicizumab prophylaxis at the maintenance dose, will have the opportunity to escalate to 3 mg/kg/wk immediately after the second qualifying bleed. Criteria and details of dose escalation are described in the protocol.

During the study, individual bleeds will be captured as they occur, while HRQoL, health status, patient safety, patient preference and satisfaction, [redacted], and days of school or work missed will be assessed as outlined in the schedule of assessments. Patients (or their caregiver) will be asked to record on an electronic, handheld device their bleeds (i.e., start date and time, reason, type, location, and associated symptoms of each bleed) and hemophilia-related medication use (i.e., start date and time, reason, type, dose of injection, and number of doses) at least weekly, when a bleed occurs, or when a hemophilia medication was taken at home or in the clinic.

Throughout the study, biomarkers related to thromboembolism (e.g., D-dimer, prothrombin 1.2 fragment) and emicizumab trough concentrations will be collected as per the schedule of assessments. Immunologic biomarkers (i.e., anti-emicizumab antibodies and anti-FVIII antibodies) will also be measured as per the schedule of assessments (see protocol).

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for some of these tests are normalized by low plasma concentrations of emicizumab, a variety of assay formats (one stage, chromogenic) and modifications (predilution of patient plasma) will be investigated for assessment of PD response at higher emicizumab plasma concentrations. [redacted] In addition, FIX and FX antigen levels will be measured.

Physical examinations, [redacted], vital signs assessments, ECGs, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients, with the exception that emicizumab PK and ADAs will not be measured in patients in Arm C prior to the switch to emicizumab treatment. Adverse events will be captured as they occur for the duration of the study.

All patients who receive emicizumab in the study will undergo PK assessments. A washout period from FVIII therapy is not required prior to inclusion because FVIII replacement does not interfere with emicizumab PK assessments, and some patients with hemophilia A require frequent dosing with FVIII to treat bleeds or for prophylaxis.

An independent Data Monitoring Committee (iDMC) composed of at minimum hemostasis/thrombosis experts and a statistician will be in place for the duration of the study

Appendix 1

Protocol Synopsis (cont.)

and will monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study (to be described in the iDMC charter).

Breakthrough bleeds for patients receiving emicizumab will be treated with FVIII *at the lowest FVIII dose expected* to *achieve hemostasis* and captured as they occur on the handheld device. Patients (or their caregiver) will report bleed information, including site of bleed, type of bleed, category of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed. During the study patients will enter bleed and medication data at least weekly. Of note, the clinical experience in the ongoing Phase I and I/II clinical studies includes the treatment of breakthrough bleeds with FVIII or bypassing agents in patients receiving emicizumab (over [redacted] bleeds treated) without any related safety concerns reported. *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 on emicizumab who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds (see protocol). Although FVIII and aPCC are fundamentally different in their potential interaction with emicizumab, investigators should keep in mind that circulating emicizumab increases patients' coagulation potential. Therefore, it is recommended that:*

- *Breakthrough bleeds should be treated with the lowest FVIII dose expected to achieve hemostasis, which may be lower than the patients' prior FVIII dose. Investigators should review with patients the dose to be used to treat breakthrough bleeds.*
- *If breakthrough bleeding does not resolve after the first dose of FVIII, patients should be instructed to contact the treatment center before infusing multiple FVIII doses.*
- *Investigators and patients should consider objective verification of bleeds.*

*I*nvestigators will contact the Medical Monitor in the event of suspected lack or loss of efficacy of emicizumab in order to discuss potential laboratory evaluations (e.g., anti-emicizumab antibodies, coagulation tests) to be performed as well as to re-evaluate their patient's benefit-risk of continued treatment.

The reason for the use of FVIII products will be documented (e.g., bleeding, one time prophylaxis, etc.). A thorough documentation of the treatments for bleeds will be required, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed.

A non-interventional study (BH29768) has been initiated to document the number and types of bleeds and current treatment with episodic or prophylactic FVIII agents, as well as to collect information on HRQoL, health status, and safety in patients with hemophilia A. The assessments in the non-interventional study will mitigate the risk of underreporting of bleeds that likely occurs in the real world, and the resulting data will serve as a source of comparator information for some analyses conducted in the Phase III clinical studies, including this study. In addition, the non-interventional study will enable earlier identification and confirmation of patients who may qualify for the Phase III clinical study. It is anticipated that a significant number of patients participating in Study BH29768 will enroll in this study, as long as they meet the inclusion and exclusion criteria and are able to enroll at a participating site while the study is open for enrollment.

[redacted]

Appendix 1

Protocol Synopsis (cont.)

Number of Patients

A total of 125–145 patients with severe hemophilia A will be enrolled, including 85 patients who received episodic treatment with FVIII and 40–60 who received FVIII prophylaxis prior to study entry.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by the patient or a legal guardian
- Able to comply with the study protocol, in the investigator's judgment
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of patient-reported outcome questionnaires and bleed and medication diary through the use of an electronic device
- Aged 12 years or older at the time of informed consent
- Body weight $\geq$ 40 kg at the time of screening
- Diagnosis of severe congenital hemophilia A (intrinsic FVIII level $<$ 1%)
- A negative test for inhibitor (i.e., $<$ 0.6 BU) within 8 weeks of enrollment
- No documented inhibitor (i.e., $<$ 0.6 BU), FVIII half-life $<$ 6 hours, or FVIII recovery $<$ 66% in the last 5 years
- Patients who completed successful immune tolerance induction (ITI) at least 5 years before screening are eligible, provided they have had no evidence of inhibitor recurrence (permanent or temporary) as may be indicated by detection of an inhibitor, FVIII half-life $<$ 6 hours, or FVIII recovery $<$ 66% since completing ITI.
- Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks
- For patients on no prophylaxis (episodic treatment) pre-study, $\geq$ 5 bleeds in the last 24 weeks prior to study entry.
- Patients who were on FVIII prophylaxis for at least the last 24 weeks, can be enrolled regardless of the number of bleeds during this period. Eligibility will be based on investigator's attestation of adequate prophylaxis regimen.
- At least 40 patients who were on FVIII prophylaxis pre-enrollment will have been enrolled for a minimum of 24 weeks in Study BH29768 (non-interventional)
- Adequate hematologic function, defined as platelet count $\geq$ 100,000/μL and hemoglobin $\geq$ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN) (excluding Gilbert's syndrome) and both AST and ALT $\leq 3 \times$ ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine $\leq 2.5 \times$ ULN and creatinine clearance by Cockcroft-Gault formula $\geq$ 30 mL/min
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$ 1% per year and are approved by local health authorities and ethics committees 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).

Appendix 1

Protocol Synopsis (cont.)

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.

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 of 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
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous (in the past 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 increase risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known HIV infection with CD4 count < 200 cells/μL within 24 weeks prior to screening. Patients with HIV infection who has CD4 > 200 and meet all other criteria are eligible.
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- Patients who are at high risk for TMA *(e.g., have a previous medical or family history of TMA)*, in the investigator's judgment.
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of:
  - 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 concurrently, within last 30 days or 5 half-lives, whichever is shorter
- Inability to comply with the study protocol in the opinion of the investigator
- Pregnant or lactating, or intending to become pregnant during the study
- Women who are not postmenopausal (≥ 48 weeks of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

End of Study

The primary analysis will take place at the earliest timepoint when all randomized patients (Arms A, B, and C) and a minimum of 40 patients from Arm D have either completed 24 weeks of treatment or discontinued from the study.

Appendix 1

Protocol Synopsis (cont.)

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., LPLV), as defined below:

- Completed 24 weeks of emicizumab and either transferred to a separate extension study to receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products or to commercial product

OR

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

OR

- Consent has been withdrawn

OR

- Lost to follow-up

Length of Study

The approximate length of the entire study from the first patient enrolled to the last patient last visit (LPLV [last patient, last visit]; *see below*) is 2 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Emicizumab, the only investigational medicinal product (IMP) in Study BH30071, is required for completion of this study and will be provided by the Sponsor, and accountability for each vial is required throughout the study. The study site will acknowledge receipt of IMPs using the interactive voice or Web response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

Used and unused IMP vials will be returned by study patients to the site and appropriately accounted for. Used vials will then be disposed of at the study site according to the study site's institutional standard operating procedure. Instructions regarding how to handle unused vials should be obtained from the Sponsor. 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.

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. In addition, use of long-acting medications taken infrequently (e.g., zoledronic acid, Denosumab) will be recorded as well. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

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

- To avoid bleeds before adequate emicizumab level is reached, patients in Arm D will continue their regular FVIII prophylaxis until the second emicizumab loading dose. Concomitant routine FVIII prophylaxis is not permissible otherwise during the study.
- Drugs intended to control bleeds, including FVIII as standard of care/episodic treatment. Specific dosages of FVIII will not be mandated in the study but rather should be administered according to the respective prescribing information or as previously used per each individual patient (for information on the formulation, packaging, and handling of agents, see the local prescribing information for the marketed drug in question).
- 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.)

Statistical Methods

Efficacy Analysis

The primary and secondary efficacy analyses to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis will include all randomized patients, with patients grouped according to the treatment assigned at randomization. For patients previously treated with prophylactic FVIII, the efficacy analysis will include all enrolled patients.

Safety Analysis

The safety analyses population will be based on all enrolled patients grouped according to the actual treatment received. For Arm C patients, all safety data reported up to the day prior to switching will be included in the 'control arm' safety summaries, and all safety data reported on or after the date of switching to active treatment will be reported separately.

Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to emicizumab and FVIII.

To evaluate the overall safety of prophylactic emicizumab compared to no prophylaxis, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade for each treatment arm.

For clinical laboratory data, summary statistics will be presented by treatment arm. 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 PK will be summarized adopting standard language/terminology.

Pharmacokinetic Analyses

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively by treatment 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 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. Data may be pooled with data from other studies. These analyses will be reported in a dedicated report.

Exploratory Analyses

Summary statistics of the number of work/school days missed and days hospitalized will be presented by treatment arm. Summary statistics will also be presented for the [redacted] emicizumab Preference Survey. PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) [redacted] will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

[redacted]

Appendix 1

Protocol Synopsis (cont.)

[redacted]

Determination of Sample Size

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of patients with hemophilia A without inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the safety and efficacy of emicizumab.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a negative binomial (NB) distribution. With consideration of enrollment feasibility, a sample size of 75 patients, assuming an allocation ratio of 2:2:1 (30 patients in each randomized treatment group and 15 patients in control group), will achieve a power of more than 90% assuming a mean ABR of 4 and 14 bleeds (with variances = mean $\times$ 10) for the emicizumab treatment and control arms respectively, representing an expected 71% reduction in the ABR compared to the control arm. Initial sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), assuming the patients from each treatment group are followed up to 0.5 units of time (i.e., 24 weeks).

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of an NB regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 90% power at the 2-sided 0.05 level of significance.

The analysis will include all enrolled patients regardless of their length of follow-up. Therefore, to ensure the analysis is based on sufficient follow-up data and with 2:2:1 treatment to control randomization, approximately 34 patients in each randomized emicizumab treatment arm (68 in total) and 17 patients in the control arm (approximately 85 patients in total) will be enrolled.

With a minimum of 40 and a maximum of 60 patients enrolled in the open-label prophylactic emicizumab arm, and assuming a mean ABR of 4 and variance of 4×10, this number is considered sufficiently powered to evaluate the efficacy endpoint in this cohort; the treatment will be considered to provide adequate control if the upper limit of the one-sided 97.5% CI around the mean ABR is less than or equal to 6.

The primary safety consideration in determining the sample size was the ability to sufficiently evaluate the safety profile of emicizumab as assessed by adverse events. Under the assumption that the occurrence of an adverse event can be adequately modeled using the binomial distribution, the planned sample size of 108–128 patients in the emicizumab treatment groups allows observation of adverse events having a true incidence rate of 1% with a probability of 0.66–0.72.

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) data to-date (and potentially from the non-interventional study [BH29768] findings) may be performed. This may result in an increase in sample size, if necessary, to maintain adequate power without affecting the type 1 error rate. Study integrity will be upheld, as access to information via aggregated analyses and their results will be minimized to limit operational bias.

Appendix 1

Protocol Synopsis (cont.)

[redacted]

Interim Analyses

No interim analysis for efficacy is planned.

Appendix 2
Schedule of Assessments

Schedule of Assessments–Arms A, B, and D																			
	Screen-ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Every 8 Wks from Wk 33	Wk 49	Every 12 Wks from Wk 61	*Wk 73*	Daily/ weekly[a]	Study Com-pletion/ ET	Safety F/U Visit [b]
Informed consent [c]	x																		
Inclusion/exclusion criteria	x																		
Medical history and demographics [d]	x																		
Physical examination (including weight) [e]	x	x				x						x		x	*x*	*x*		x	x
Height	x											x		x					
Vital signs *(including weight)* [f]	x	x [f]	x	x	x	x	x	x	x	x	x	x [f]	x	x [f]	x	*x*		x [f]	x
Serum pregnancy test [h]	x	x																	
Concomitant medications [i]	x	x				x		x	x	x	x	x	x	x	x	*x*		x	x
ECG [j]	x	x [j]				x						x						x	
Safety laboratory assessments [h]	x [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	x
Anti-FVIII antibodies [k]	x [k]	x		x					x			x	x	x	x	*x*		x	x
Anti-emicizumab antibodies [l]		x [l]				x		x [l]	x	x [l]	x	x [l]	x [l]	x [l]	x [l]	*x* [l]		x	x [l]

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments–Arms A, B, and D																			
	Screen-ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Every 8 Wks from Wk 33	Wk 49	Every 12 Wks from Wk 61	*Wk 73*	Daily/ weekly[a]	Study Com-pletion/ ET	Safety F/U Visit [b]
Bleed/medication questionnaire [m]																	x		
Bleed/medication data review [n]		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*		x	x
IMP management [p]		x	x	x	x	x	X	x	x	x	x	x	x	x	x	*x*		x	
HRQoL and health status (EQ-5D-5L) [q]		x							x			x		x		*x* [q]		x	
PK assessment [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	x
PD biomarkers [s]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	x
[redacted]																			
Patient preference survey										x									
[redacted]																			
RCR blood DNA sample (optional) [w]			x [w]	x [w]	x [w]	x [w]													

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments–Arm C (Screening to Switch to Emicizumab)								
	Screen-ing	Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Daily/ weekly [a]
Informed consent [c]	x							
Inclusion/exclusion criteria	x							
Medical history and demographics [d]	x							
Physical examination (including weight) [e]	x	x						
Vital signs *(including weight)* [f]	x	x [f]	x	x	x	x	x	
Height	x							
Serum pregnancy test [h]	x							
[redacted]								
Concomitant medications [i]	x	x	x	x	x	x	x	
ECG [j]	x	x [j]						
Safety laboratory assessments [h]	x [h]	x						
Anti-FVIII antibodies [k]	x							
Bleed/injection questionnaire [m]								x
Bleed/injection data review [n]		x	x	x	x	x	x	
Adverse events [o]		x	x	x	x	x	x	
HRQoL and health status [q]		x			x			
[redacted]								
PD biomarkers assessment [s]		x						
[redacted]								
RCR blood DNA sample (optional) [w]			x					

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments–Arm C (Continued, at Time of Switch to Emicizumab)																		
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Every 8 Wks from Wk 57	Wk 73	Every 12 Wks from Wk 85	*Wk 97*	Daily/ weekly[a]	Study Compl-etion/ ET	Safety F/U Visit [b]
Physical examination (including weight) [e]	x				x						x		x	*x*	*x*		x	x
Vital signs *(including weight)* [f]	x [f]	x	x	x	x	x	x	x	x	x	x [f]	x	x [f]	x	*x*		x [f]	x
Height	x										x		x					
Serum pregnancy test [h]	x																	
Concomitant medications [i]	x				x		x	x	x	x	x	x	x	x	*x*		x	x
ECG [j]	x				x [j]						x						x	
Safety laboratory assessments [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	x
Anti-FVIII antibodies [k]	x		x					x			x	x	x	x	*x*		x	x
Anti-emicizumab antibodies [l]	x [l]				x		x [l]	x	x [l]	x	x [l]	x	x [l]	x	*x*		x	x [l]
Bleed/medication questionnaire [m]																x	*x*	*x*
Bleed/medication data review [n]	x				x		x	x	x	x	x	x	x	x	*x*		x	x

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments–Arm C (Continued, at Time of Switch to Emicizumab)																		
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Every 8 Wks from Wk 57	Wk 73	Every 12 Wks from Wk 85	*Wk 97*	Daily/ weekly[a]	Study Compl-etion/ ET	Safety F/U Visit [b]
Adverse events [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	x
IMP management [p]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	
HRQoL and health status [q]	x							x			x		x		*x* [q]		x	
PK assessment [r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	x
PD biomarkers [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	x
[redacted]																		

BMQ = bleed and medication questionnaire; eCRF = electronic Case Report Form; EQ-5D-5L = EuroQoL Five-Dimension-Five Levels Questionnaire; ET = early termination; F/U = follow-up; FVIII = factor VIII; HRQoL = health-related quality of life; [redacted]; IMP = investigational medicinal product, PD = pharmacodynamic; PK = pharmacokinetic; RCR = Roche Clinical Repository; [redacted]; wk = Week.

Notes: The maximum allowable time between screening and enrollment is 6 weeks; if the elapsed time between screening and enrollment is more than 6 weeks, screening must be repeated. All assessments should be performed within ± 2 days of the scheduled visit for the first 12 weeks and for Weeks 25–37 for Arm C patients who switch over, then ± 7 days thereafter. Clinic visits should coincide with the day of emicizumab dosing, and on those days the dose should be administered after blood draws and other assessments are conducted. Unscheduled assessments may be performed at the discretion of the investigator and as clinically indicated. Except for the bleed/injection questionnaire, HRQoL, and health status, all other patient data will be collected during office or nurse visits. Evaluation at Weeks 25 or 49 will occur after a full 24 or 48 weeks in the study. Study completion evaluation occurs when a patient discontinues emicizumab or transitions into another study.

[a] Patients will complete the Bleed/Medication Questionnaire at least weekly and at the time of a bleed, or when they take a hemophilia-related medication (including emicizumab). Arm B patients should indicate at least weekly whether or not they had a bleed.

[b] A safety follow-up visit will occur 24 weeks after discontinuing emicizumab.

[c] Obtain written informed consent (or patient's assent and legal representative written informed consent if patient is an adolescent) before distribution of BMQ handheld device and collection of any data. Patients will be enrolled and randomized after giving informed consent and assent when appropriate. *A patient who fulfills the inclusion and exclusion criteria should be enrolled and assigned to a treatment arm on the same day when the first dose of emicizumab is due (Week 1 visit).*

[d] Collected from patient medical records and documented in the eCRF, including information on target joint(s).

[e] Calculation of dose based on weight is required. A complete physical examination will be performed at screening and at least a targeted physical examination will be performed at subsequent visits. Targeted physical examination of joints (for bleeds, evidence of arthropathy) and skin (for bruises, hematomas, and injection-site reactions) as clinically indicated and/or with report of new or worsening adverse event. [redacted]

[f] Body temperature, blood pressure, pulse rate, and respiratory rate only to be used to monitor during and after injection for hypersensitivity reactions and not to be entered into eCRF, except at Weeks 1, 25, 49, at study completion/early termination, and at the safety follow-up visit (i.e., 24 weeks after discontinuing emicizumab for patients in Arms A, B, and D and at Week 73 for patients in Arm C). *If Screening and Week 1 occur on the same date, the vital signs should be measured only once. If Screening and Week 1 occur on different dates, vital signs entry should be repeated for both assessments.* Height will be measured at screening and annually.

[g] See protocol.

[h] Laboratory data (performed locally) include: complete blood count with differential (i.e., neutrophils, hemoglobin, platelet count), serum chemistries (including sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid). 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. Female patients with childbearing potential will be required to have a negative serum pregnancy test result at Screening (and within 7 days of study drug initiation, if applicable) and urine pregnancy tests performed at every clinic visit, with the exception of Weeks 2–4 and 7. Patients in Arm C will have serum pregnancy test performed at Screening and before starting emicizumab (Week 25).

[i] Concomitant medications (e.g., extra pain medication with bleed) will be asked about at the time of the monthly assessment, excluding treatments for bleeds (i.e., FVIII and other medications to treat bleeds), which will be collected on the bleeding questionnaire. Hemostatic medications to treat or prevent bleeds in the week prior to starting emicizumab will also be collected and during Week 1 for patients in Arm D who continue their prior FVIII prophylaxis for the first week of the study.

[j] Performed locally. If screening ECG is abnormal, repeat at Week 1 (or Week 2 [or Week 5 for Arm C] if Screening and Week 1 occur on the same day), otherwise do not repeat. ECGs will also be performed 4–8 and 24 weeks after starting emicizumab or dose escalation (up-titration), as well as at study completion/early termination.

Appendix 2
Schedule of Assessments (cont.)

[k] Patient must have a documented local inhibitor test with negative result (< 0.6 BU) at screening or within the 8 weeks prior to enrollment. Starting at Week 1, all subsequent anti-FVIII antibodies will be measured at a central laboratory using an aliquot of the citrate plasma collected for PD biomarker assessments, so a separate blood draw is not necessary. Please consult the central laboratory services manual for details.

[l] Samples to detect anti-emicizumab antibodies will be collected prior to emicizumab administration at every clinic visit. However, only samples from the following visits will be analyzed initially: (Arms A, B, and D) immediately prior to the first injection at Week 1, every 8 weeks from Weeks 9–49, every 12 weeks starting from Week 61, and at the 24-week post-emicizumab safety follow-up visit following initiation of emicizumab; Arm C immediately prior to the first injection at Week 25, every 8 weeks from Weeks 33–73, every 12 weeks starting from Week 85, and at the 24-week post-emicizumab safety follow-up visit following initiation of emicizumab. If any of these samples are positive and/or if there is suboptimal clinical response or low pharmacokinetic exposure, the remaining collected samples may be analyzed for anti-emicizumab antibodies. Anti-emicizumab antibodies may also be drawn at the time of systemic hypersensitivity events.

[m] Reported by the patient, or the patient's legally authorized representative, and includes: start date and time, reason, type, location, and associated symptoms of each bleed, as well as start date and time, reason, type, number of injections, and dose of each *hemophilia medication* injection, *including* emicizumab. *Patients who stop taking emicizumab should continue reporting bleeds and hemophilia medication administration on the handheld device until the safety follow-up visit.*

[n] At the Week 1 visit, patients will be trained on how to use and be provided their own handheld device. At subsequent visits as marked, investigator review of patient-reported bleed/injection questionnaire information will be conducted for completeness and accuracy.

[o] Injection-site reaction adverse events will be collected on a separate form from the adverse event form. If there is unexpected worsening of the patient's hemophilia in terms of severity (e.g., increased number of doses of FVIII to stop bleeds compared with before study entry), frequency of bleeds, or nature at any time during the study, this should be documented as an adverse event on the Adverse Event eCRF, conveying that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia").

[p] Drug accountability will not be performed at the first visit that includes emicizumab receipt. Drug dispensation will not occur at the study completion/early termination visit.

[q] Haem-A-QoL questionnaire (age ≥ 18) and Haemo-QoL-Short Form (ages 12–17), health status questionnaire EQ-5D-5L. Patient-reported outcomes will be captured on-site by a device and transmitted to the database. After Week 49, HRQoLs will be captured every 24 weeks.

[r] Emicizumab concentration. Plasma samples for this assessment should be taken prior to injection. Patients will be dosed at the clinics (self-administration) on days where trough plasma samples are to be collected

[s] See protocol for detailed explanation of PD biomarker assessments (Sets 1 and 2). Blood samples will be banked for 5 years for future exploratory PD biomarker analyses. Blood samples may also be drawn to conduct biomarker assays at the central laboratory on an unscheduled basis (at the clinical judgment of the investigator) at any time.

[t] [redacted]

u [redacted]

v [redacted]

w Sample for the RCR is optional and requires an additional consent. This single sample may be drawn at Week 2, 3, 4, **or** 5 but is not drawn at Week 1 in order to avoid excessive blood draw.

Appendix 2
Schedule of Assessments (cont.)

SCHEDULE OF PHARMACODYNAMIC ASSESSMENTS		
Sample	Visit [a]	Biomarker assays [b]
PD Set 1	**Starting on emicizumab (Arms A, B, and D):** Every week during Weeks 1–4 Every 2 weeks during Weeks 5–7 Every 4 weeks during Weeks 9–25 Every 8 weeks during Weeks 33–49 Every 12 weeks thereafter, while on emicizumab (Week 61 and beyond) Study Completion/Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator), while on emicizumab [c] **Starting on no prophylaxis, switch to emicizumab after 24 weeks (Arm C):** Week 1 Every week during Weeks 25–28 Every 2 weeks during Weeks 29–32 Every 4 weeks during Weeks 33–48 Every 8 weeks during Weeks 49–73 Every 12 weeks thereafter, while on emicizumab (Week 85 and beyond) Study Completion/Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator), while on emicizumab [c]	Standard aPTT Modified aPTT PT FVIII activity Thrombin generation FIX antigen FX antigen D-dimer Prothrombin fragment 1.2

Appendix 2
Schedule of Assessments (cont.)

SCHEDULE OF PHARMACODYNAMIC ASSESSMENTS		
Sample	Visit [a]	Biomarker assays [b]
PD Set 2	**Starting on emicizumab (Arms A, B and D):** Week 1 Week 25 Study Completion/Early Termination Safety Follow-up Visit **Starting on no prophylaxis, switch to emicizumab after 24 weeks (Arm C):** Week 1 Week 25 Week 49 Study Completion/Early Termination Safety Follow-up Visit	FXIII activity VWF antigen Fibrinogen
[redacted]	[redacted]	[redacted]

Appendix 2
Schedule of Assessments (cont.)

SCHEDULE OF PHARMACODYNAMIC ASSESSMENTS		
Sample	Visit [a]	Biomarker assays [b]
	[redacted]	

Appendix 2
Schedule of Assessments (cont.)

[redacted]; [redacted]; FVIII = factor VIII; FIX = factor IX; FX = factor X; [redacted]; [redacted]; PD = pharmacodynamic; [redacted]; VWF = von Willebrand factor.

[a] All samples are to be collected on Day 1 of the indicated week, prior to emicizumab injection (if applicable). PD samples will be citrate plasma, EDTA plasma, or serum. Refer to protocol for exact study visits.

[b] Biomarker assays will include, but are not limited to, those listed. [redacted] Blood volumes and processing procedures will be specified in the Central Laboratory Services Manual.

[c] Reasons for unscheduled visits may include evaluation or treatment for bleeds or hypersensitivity reactions.

[d] [redacted].