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

NCT Number: NCT03315455

Document Date: Statistical Analysis Plan (SAP) Amendment Version 2: 22-July-2019

STATISTICAL ANALYSIS PLAN AMENDMENT

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**

PROTOCOL NUMBER: YO39309

STUDY DRUG: Emicizumab (RO5534262)

VERSION NUMBER: 2.0

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]

DATE FINAL: 12 May 2019

DATE AMENDED: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Date and Time(UTC)	Reason for Signing	Name
22-Jul-2019 12:54:28	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The following changes have been made:

- The non-interventional study (NIS) population has been added in order to evaluate patients who previously participated in the NIS BH29768.
- Intra-patient comparisons were added to evaluate the change in the number of treated bleeds and all bleeds over time compared with the patient's historical bleed rate for patients who participated in the NIS BH29768.
- Subgroup analyses of efficacy endpoints by inhibitor status were removed because separate efficacy outputs for patients with inhibitors and without inhibitors are already planned.

Additional minor changes have been made to improve clarity and consistency.

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1. BACKGROUND

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

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 2015).

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 two-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. These studies are Study BH29884, which evaluates 1.5 mg/kg weekly (QW) dose in the adult and adolescent population with FVIII inhibitors; Study BH29992, which evaluates 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W in pediatric patients with inhibitors; Study BH30071, which evaluates a 1.5 mg/kg QW and 3 mg/kg every 2 weeks (Q2W) dose in the non-inhibitor population; and Study BO39182, which evaluates 6 mg/kg every 4 weeks (Q4W) in a mixed (inhibitor and non-inhibitor) population.

2. STUDY DESIGN

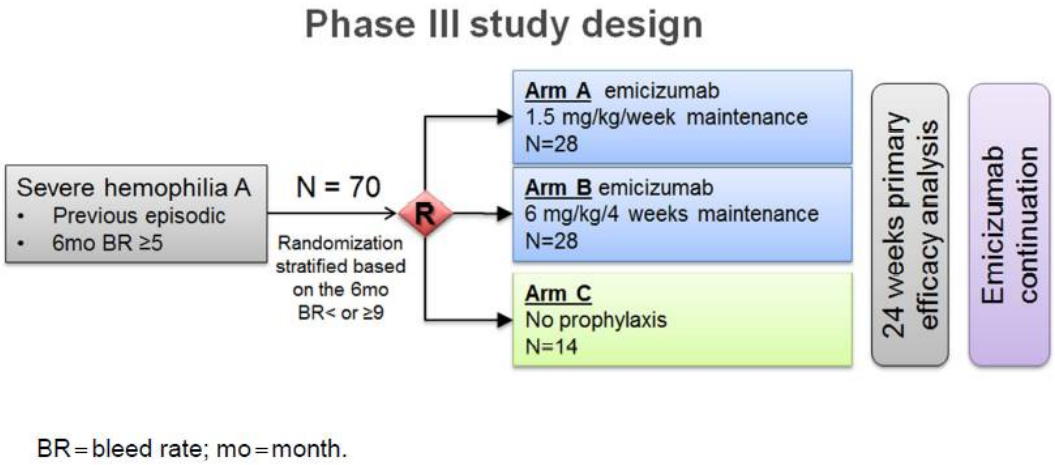
Study YO39309 is a randomized, multicenter, open-label, Phase III clinical study will enroll patients aged 12 years or older with hemophilia A regardless of FVIII inhibitor status. Approximately 70 patients who received episodic treatment with FVIII or bypassing agents prior to study entry and experience at least 5 bleeds over the prior 24 weeks will be randomized in a 2:2:1 ratio to the following regimens:

- Arm A: Emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 1.5 mg/kg QW subcutaneously
- Arm B: Emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg Q4W subcutaneously
- Arm C: No prophylaxis (control arm)

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 or bypassing agents in case of a breakthrough bleeding event.

To ensure a representative variety of patients with hemophilia A enrolled in this study to investigate the efficacy and safety profile of emicizumab in both inhibitor and non-inhibitor populations, enrollment of up to 55 non-inhibitor patients will be permitted. Study patients will be enrolled globally from China and other Asia Pacific countries. At least 60 patients will be enrolled from China and Hong Kong. The study schema is shown Figure 1.

Figure 1 Study Schema for Study YO39309



BR = bleed rate; mo = month.

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) 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 the Arm B dosing regimen (emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg Q4W). 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, 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.

Those who are well controlled after 24 weeks on emicizumab (< 2 spontaneous and clinically significant bleeds) will continue treatment on their assigned emicizumab regimen; whereas, those who experience suboptimal control (≥ 2 spontaneous and

clinically significant bleeds) will have the option to escalate to 3 mg/kg QW after approval from the Medical Monitor.

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 start date and time, reason, type, location, and symptoms of bleeds) and hemophilia-related medication use (i.e. start date and time, reason, type, and dose of injection).

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 as soon as bleeding event occurs. In the event of no bleed or medication use, the patient should complete the questionnaire at least 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 and Health Status 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.

2.3 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 and B) 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 to Arms A and B; 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 same 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 to Arms A and B; 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 to have an unusual sensation ("aura") in the joint in combination with at least one of the following symptoms: increasing swelling or warmth of the skin over the joint; and/or increasing pain, progressive loss of range of motion or difficulty in using the limb 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, hip, knee, ankle. Left and right sides of the same joint type are considered to be separate joints.

2.3.2.5 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 of the study will likely to be too small to provide meaningful statistical analyses of the Haemo-QoL-SF and therefore the analysis of this endpoint may only be descriptive.

2.3.2.6 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:

- Number of days away from school/work
- Number of days hospitalized

2.3.4 Pharmacokinetic Endpoints

For patients treated on weekly dosing schedule, 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

For patients treated on every 4 weeks dosing schedule, the PK endpoint for this study is the exposure (trough plasma concentration) to emicizumab at the following timepoints:

- Every week during week 1–4 on emicizumab
- Every 4 weeks during weeks 5–24 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

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 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 70 patients, assuming an allocation ratio of 2:2:1 (28 patients in each randomized treatment group and 14 patients in control group), will achieve a power of more than 90% assuming a mean ABR of 4 and 18 bleeds (with variances $=$ mean $\times$ 10) for the emicizumab treatment and control arms respectively, representing an expected 78% 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.

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) 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 or bypassing agents 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 6 mg/kg/4wks (Arm B) subcutaneously, or to the control arm (no prophylaxis; Arm C). 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.

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 three 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 6 mg/kg/4wks (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. Randomized patients will be use 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**: for evaluations of the change in the number of treated bleeds and all bleeds over time compared with the patient's historical bleed rate, 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.

4.2.2 All Emicizumab Patients

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

4.2.3 Non-Interventional Study (NIS) Population

The NIS population includes all patients who participated in NIS BH29768 prior enrollment to this study. It consists of patients previously treated with episodic FVIII or bypassing agents.

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 and B 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.
- Safety Population 2 (SAF2) is exactly the same as SAF1 for patients in Arms A and B. 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.

4.3 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 randomized population (see Section 4.2.1). Subgroup analyses by inhibitor status will be performed for primary and selected efficacy endpoints. Detail will be described in Data Analysis Plan.

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 6 mg/kg/4wks 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," "6 mg/kg/4wks," 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
- 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 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 (ANCOVA). 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, 6 mg/kg/4wks, or no prophylaxis) will be produced for the comparisons of Arm A versus Arm C and Arm B versus Arm C.

4.5.2.5 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).

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 ANCOVA).

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

Given the small number of NIS episodic patients that were randomized to Arm A or B, the change in number of treated bleeds and all bleeds will be listed only.

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 Heam-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.

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 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 (ANCOVA)
- 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: 12-$<18, \geq 18$
- Age: $<65, \geq 65$
- 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.

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.

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) and markers related to bone and joint health 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.

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**
PROTOCOL NUMBER:	YO39309
VERSION NUMBER:	3
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase III
INDICATION:	Hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A. Specific objectives and corresponding endpoints for the study are outlined below.

1. Objectives	2. Corresponding Endpoints
3. Primary Efficacy Objective:	**4. Primary Efficacy Endpoint**
• 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 The primary definition of a bleed is a bleed for which coagulation factors are administered *(i.e., treated blood)*.	• 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 QW and 6 mg/kg Q4W
5. Secondary Efficacy Objective:	**6. Secondary Efficacy Endpoints**
• To evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis • Change over time compared with historical bleed rate prior to study entry will be conducted within each treatment arm.	• To evaluate the efficacy in reducing the number of all bleeds over time • Change in the number of treated bleeds and all bleeds over time compared with the patient's historical bleed rate • To evaluate the efficacy in reducing the number of joint bleeds over time • To evaluate the efficacy in reducing the number of target joint bleeds over time • Change in HRQoL of patients according to Haem-A-QoL (aged ≥ 18 years) or Haemo-QoL-Short Form (aged 12–17 years) scores after 24 weeks • Change in health status of patients according to European Quality of Life Five-Dimension-Five Levels (EQ-5D-5L) Questionnaire scores after 24 weeks

Appendix 1
Protocol Synopsis (cont.)

7. Exploratory Objective:	8. Exploratory Endpoints
• To assess the number of days away from school/work • To assess the number of days hospitalized • To assess potential PD biomarkers of emicizumab	• Changes in number of days away from school/work during treatment • Changes in number of hospitalization days during treatment • PD Biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and FVIII activity
9. Safety Objective:	**10. Safety Endpoints**
• To evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A	• The incidence and severity of adverse events • The incidence and severity of thromboembolic events • *Incidence and severity of thrombotic microangiopathy* • 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 • The incidence of severe hypersensitivity, anaphylaxis, or anaphylactoid reactions • The incidence and clinical significance of anti-emicizumab antibodies

Appendix 1
Protocol Synopsis (cont.)

11. Pharmacokinetic Objective:	12. Pharmacokinetic Endpoints
To characterize the exposure (trough plasma concentration) to emicizumab in patients treated on QW or Q4W dosing	• Trough plasma concentration • The plasma samples will be collected at the scheduled timepoints below: For patients treated on weekly dosing schedule: – 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 or after the last patient completes 24 weeks treatment of emicizumab, whichever occurs first For patients treated on every 4 weeks dosing schedule: – Every week during Weeks 1–4 on emicizumab – Every 4 weeks during Weeks 5–24 on emicizumab – Every 12 weeks thereafter while on emicizumab, until the end of the study or after the last patient completes 24 weeks treatment of emicizumab, whichever occurs first

FVIII = factor VIII; HRQoL = health-related quality of life; PD = pharmacodynamic; Q4W = every 4 weeks; QW = every week.

Study Design

– **Description of Study**

Study YO39309 is a randomized, multicenter, open-label, Phase III clinical study designed to investigate the efficacy, safety, and pharmacokinetics of emicizumab in patients with hemophilia A regardless of factor VIII (FVIII) inhibitor status. Seventy patients who received episodic therapy with FVIII or bypassing agents prior to study entry and experienced at least 5 bleeds over the prior 24 weeks (annualized bleeding rate [ABR] ≥ 10) will be randomized in a 2:2:1 ratio to the following regimens:

Arm A: Emicizumab prophylaxis at 3 mg/kg weekly (QW) subcutaneously for 4 weeks, followed by 1.5 mg/kg QW subcutaneously

Arm B: Emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg every 4 weeks (Q4W) subcutaneously

Arm C: No prophylaxis control arm

– **Number of Patients**

Seventy patients will be enrolled and enrollment of up to 55 non-inhibitor patients will be permitted. Study patients will be enrolled from China and other countries. At least 60 patients will be enrolled from China.

– **Target Population**

Patients with severe hemophilia A who previously received episodic therapy with either FVIII or bypassing agents will be enrolled.

Appendix 1
Protocol Synopsis (cont.)

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 (PRO) 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 or hemophilia A with FVIII inhibitors

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 episodic therapy (FVIII or bypassing agents) and of number of bleeding episodes for at least the last 24 weeks

$\geq$ 5 bleeds in the last 24 weeks prior to study entry

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 AST and/or 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 a contraceptive method with a failure rate of $<$ 1% per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 1 year of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of $<$ 1% per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $<$ 1% per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods 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

Patients who are at high risk for thrombotic microangiopathy (e.g., have a previous medical or family history of thrombotic microangiopathy), in the investigator's judgment

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 cells/μL 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

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 with positive 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) have either completed 24 weeks of treatment or discontinued from the study.

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

Completion of 24 weeks of emicizumab treatment and transfer to a future extension study to receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products

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

Withdrawal of consent

Lost to follow-up

- **Length of Study**

The approximate length of the entire study from screening of the first patient to the end of the study will be approximately 22 months.

Investigational Medicinal Products

The investigational medicinal product for this study is emicizumab.

Each single-use vial contains 150 mg (nominal) of emicizumab at pH 6.0. The Drug Product is formulated as 150 mg/mL emicizumab in 150 mmol/L arginine, 0.5 mg/mL poloxamer 188, 20 mmol/L histidine–aspartic acid buffer (pH 6.0).

Each patient starting on prophylactic emicizumab will receive 3 mg/kg QW subcutaneously for 4 weeks as loading doses, followed by 1.5 mg/kg QW (Arm A) or 6 mg/kg Q4W (Arm B)

subcutaneously, for a total of at least 24 weeks or as long as they continue to derive sufficient clinical benefit.

Non-Investigational Medicinal Products

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

Drugs intended to control bleeds, including FVIII products or bypassing agents as standard-of-care episodic treatment. Exact dosages will not be specified in the study but rather these agents should be administered according to the respective prescribing information or as previously used by each individual patient (for information on the formulation, packaging, and handling of FVIII or bypassing agents, refer to local prescribing information for the agent 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

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

Statistical Methods

A detailed description of the statistical methods for the primary and secondary efficacy analyses will be provided in the statistical analysis plan.

– **Primary Analysis**

The primary efficacy analysis will be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient yet to complete 24 weeks in the study discontinues study participation, whichever occurs first, and using an intent-to-treat principle. The separate comparison of the number of bleeds over time between each of the randomized emicizumab arms and control arm will be performed using a negative binomial (NB) regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (< 9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t / λ_c., which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level. 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 QW maintenance dose versus control. The second test will be 6 mg/kg Q4W maintenance dose versus control (or 3 mg/kg Q2W versus control, depending on global Study BO39182 data readout). The description below covers both hypotheses to be tested:

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

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha 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% confidence intervals.

The number of bleeds can also be annualized for each patient using the following formula: ABR $=$ (Number of bleeds during the efficacy period/Total number of days during the efficacy period) $\times$ 365.25. If the NB model converges, $van\ Elteren$ test to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable, the primary efficacy analysis will be based on the $van\ Elteren$ test of ABR.

– **Determination of Sample Size**

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 NB distribution. With consideration of enrollment feasibility, a sample size of 70 patients, assuming an allocation ratio of 2:2:1 (28 patients in each randomized treatment group and 14 patients in control group), will achieve a power of more than 90% assuming a mean ABR of 4 and 18 bleeds (with variances $=$ mean $\times$ 10) for the emicizumab treatment and control arms, respectively,

representing an expected 78% reduction in the ABR compared with the control arm. Initial sample size calculations were performed assuming the patients from each treatment group are followed up to 0.5 units of time (i.e., 24 weeks).

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.

Multiplicity will be accounted for by testing emicizumab QW arm versus no prophylaxis first, and upon successful testing, emicizumab Q4W versus no prophylaxis, each at 0.05 level.

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) global data to date 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.

Schedule of assessments and schedule of samples

The schedule of assessments and schedule of pharmacokinetic, immunogenicity, and biomarker samples are available in the Protocol version 3 (appendices 1 and 2, respectively).