Official Title:	**A MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF SUBCUTANEOUS ADMINISTRATION OF EMICIZUMAB IN HEMOPHILIA A PEDIATRIC PATIENTS WITH INHIBITORS**
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STATISTICAL ANALYSIS PLAN

TITLE:	**A MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ONCE WEEKLY SUBCUTANEOUS ADMINISTRATION OF EMICIZUMAB IN HEMOPHILIA A PEDIATRIC PATIENTS WITH INHIBITORS**
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SPONSOR:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd.
PLAN PREPARED BY:	[redacted]
DATE FINAL:	Version 1: 15 July 2016
DATE AMENDED:	Version 2: 29 November 2016 Version 3: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	14-Mar-2018 10:33:43

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The Statistical Analysis Plan was amended because the study protocol was amended to add two additional cohorts to investigate less frequent emicizumab dosing schedules (every 2 weeks [Q2W] and every 4 weeks [Q4W]). The addition of these cohorts is reflected throughout the Statistical Analysis Plan.

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

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 5,000 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 (Franchini and Mannucci 2013).

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%–30% of patients with severe hemophilia A and in 3%–13% of those with moderate or mild disease (Franchini and Mannucci 2013). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with a history of high-titer (≥ 5 BU/mL) inhibitor following a re-challenge with FVIII administration (high-responding inhibitor), the only hemostatic options currently available are pro-thrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., “bypassing agents”).

Current standard prophylactic regimens commonly use infusion therapy administered three times a week; other regimens require daily or every other day administration, depending on the patient’s needs (Shapiro 2013). Major issues with current regimens are the need for adequate venous access and patient/family compliance with regular prophylaxis, especially in the very young pediatric population, in whom central venous access devices (CVADs) have been used to overcome technical difficulties. Thus, both the disease and its treatment have the potential to affect health-related quality of life (HRQoL), the latter through limitations on daily activities that treatment may impose.

The development of effective prophylactic treatment options with decreased immunogenicity and less frequent dosing requirements is a high unmet medical need in the population of hemophilia A patients with FVIII inhibitors. Given the significant unmet medical need among pediatric patients with hemophilia A with FVIII inhibitors and positive benefit-risk assessment for emicizumab, initiation of a pediatric Phase III study is appropriate.

Emicizumab is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of FVIII. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because of the expected pharmacokinetic properties of this antibody, markedly extending the dosing interval to once weekly or even less frequently, this novel compound has the potential to dramatically change the treatment of patients with hemophilia A with and without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

Currently available experience with emicizumab in humans includes data from one Phase I study (Study ACE001JP), its ongoing extension, a Phase I/II study (Study ACE002JP), and a site of injection and relative and absolute bioavailability study in healthy Japanese subjects (Study JP29574). See Protocol Section 1.2 for detailed description of the study results (Shima et al. 2016). On the basis of these compelling Phase I/II data, a clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) has been initiated. Four Phase III studies are currently ongoing and are aimed at evaluating the efficacy and safety of emicizumab at various dosing regimenses and in different populations. The studies are Study BH29884, which evaluates 1.5 mg/kg weekly (QW) in an adult and adolescent population with FVIII inhibitors; Study BH29992, which evaluates 1.5 mg/kg QW, 3mg/kg every 2 weeks (Q2W) and 6mg/kg every 4 weeks (Q4W) in pediatric patients with inhibitors; Study BH30071, which evaluates 1.5mg/kg QW and 3mg/kg Q2W in a population without inhibitors; and Study BO39182, which evaluates 6mg/kg Q4W in a population with or without inhibitors.

[redacted] meetings have been held with United States Food and Drug Administration (FDA) to discuss the development program of emicizumab. [redacted] The Paediatric Investigational Plan (PIP) was submitted to EMA/Paediatric Committee (PDCO) on 10 August 2015. On [redacted], the protocol for this study (plus the Informed Consent Form [ICF] and assent forms) was sent to the FDA, and the core Clinical Trial Application (CTA) was dispatched to the affiliates on [redacted].

On 16 November, 2017, the FDA approved the Biologics License Application (BLA) for HEMLIBRA (emicizumab-kxwh) for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in people with haemophilia A with factor VIII inhibitors (PwHAi). In addition, on 27 February, 2018, the European commissionapproved Hemlibra® (emicizumab) for routine prophylaxis of bleeding episodes in people with haemophilia A with factor VIII inhibitors.

2. STUDY DESIGN

This non-randomized, multicenter, open-label, Phase III clinical study will enroll children with hemophilia A who have inhibitors against FVIII. Children with hemophilia A and documented historical FVIII inhibitor titer ($\geq$ 5 BU) must currently be receiving treatment with bypassing agents. At least 40 patients younger than 12 years of age and up to approximately 80 patients are planned for enrolment, with allowance for patients 12-17 years of age who weigh $<$ 40 kg at the time of informed consent. Patients will receive weekly SC doses of emicizumab at 1.5 mg/kg QW (Cohort A) for a minimum of 52 weeks or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first (see Figure 1). After 52

weeks of treatment, an individual patient who continues to derive clinical benefit may continue receiving prophylactic emicizumab as part of this study or a future separate emicizumab extension study.

Because of the uncertainty of the dosing regimen needed in patients < 12 years of age or < 40 kg to achieve similar exposure as in adults and adolescents, this study will first evaluate the appropriate dosing regimen in children by starting with the same weekly dosing regimen (1.5mg/kg QW) being evaluated in the Phase III study (Study BH29884) in adult and adolescent patients with hemophilia A with inhibitors. Emicizumab will be administered with a weekly loading dose of 3.0 mg/kg QW for the first 4 weeks (Day 1 of each week) followed by a maintenance dose of 1.5 mg/kg QW (Cohort A) for the remainder of the treatment period (Day 1 of each week). Individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab. Investigators will monitor patients regularly with the guidance of an up-titration algorithm. If patients meet protocol-defined criteria for efficacy-guided up-titration, the investigator will contact the Medical Monitor to initiate a discussion about possible up-titration.

In a first interim data review, the appropriateness of the initial dosing regimen will be evaluated (maintenance dose of 1.5 mg/kg QW) after the first 3-5 patients (≥ 2 to < 12 years of age) have been dosed for a minimum of 12 weeks. A Joint Monitoring Committee (JMC) will review all cumulative data (e.g., safety, efficacy, and pharmacokinetics) at the first interim data review and provide recommendations on increasing the starting maintenance dose if a majority of the first 3-5 patients fail to achieve optimal control of bleeds after the first 12 weeks of treatment or their plasma emicizumab trough concentration is lower than the one being targeted in adolescents and adults (i.e., 45 µg/mL). All patients enrolled following the first interim data review will receive the starting maintenance dose selected/confirmed by the JMC. Patients enrolled prior to the first interim data review will remain on their current maintenance dose unless they meet eligibility for up-titration based on protocol-defined criteria.

In order to include and safely treat the youngest patients (birth to < 2 years of age), this study will include a staggered approach to enrolment by age. Patients ≥ 2 to < 12 years of age and patients 12-17 years of age who weigh < 40 kg will enroll first. A second interim data review will occur once at least 10 patients between ≥ 2 and < 12 years of age have been dosed for a minimum of 12 weeks, at which time all cumulative data (e.g., safety, efficacy, and pharmacokinetics) will be evaluated by the JMC to provide recommendations for enrolment of children < 2 years of age, as well as recommendations on any additional adaptations of the maintenance dose, if necessary.

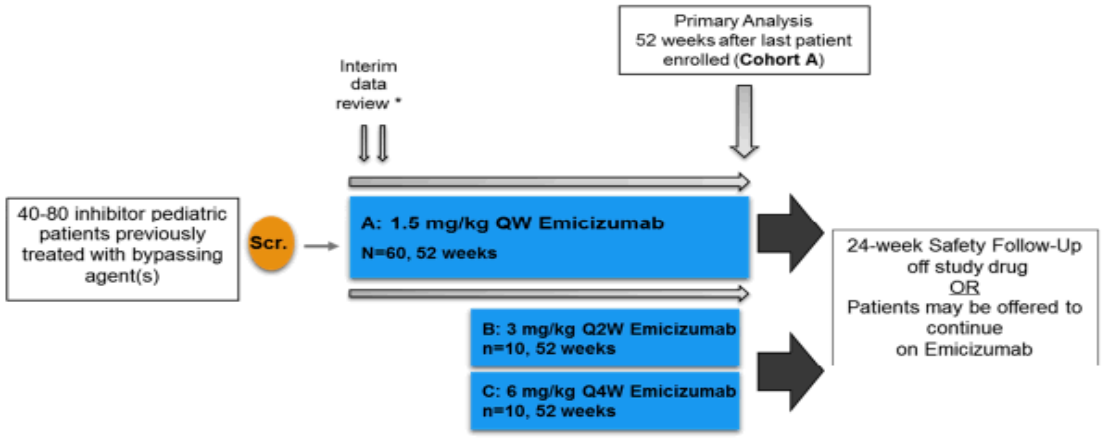
If patient recruitment is faster than anticipated, enrolment will be placed on a temporary hold following the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose (Cohort A). After the JMC recommendations

are released following both interim data reviews, the study will continue to enrol in Cohort A up to a maximum of approximately 60 patients.

Once 1) the exposure at 1.5 mg/kg QW has been characterized in this pediatric population; 2) Cohort A is fully enrolled; and 3) review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifies no safety concerns, this study will open two additional non-randomized cohorts to investigate Q2W and Q4W regimens in pediatric patients. Parallel enrolment with alternate cohort allocation to Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W) will occur, for a total of approximately 10 patients per cohort. Of note, enrolment to Cohorts B and C will be limited to patients 2-11 years of age. Emicizumab will be administered with a loading dose of 3 mg/kg QW for the first 4 weeks followed by a maintenance dose of 3 mg/kg Q2W (Cohort B) and 6mg/kg Q4W (Cohort C) for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first (see Figure 1). Individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab. The entire study will enrol up to approximately 80 patients .

All patients will continue to receive prior therapy as prescribed by their treating physician with episodic bypassing agents to treat breakthrough bleeds as needed. However, prophylactic use of bypassing agents should be discontinued by the time the first dose of emicizumab is given.

Figure 1 Study Schema



JMC = Joint Monitoring Committee; Q2W = every 2 weeks; Q4W = every 4 weeks; QW = once weekly; Scr = screening.

* In a first interim data review, the starting maintenance dose will be re-evaluated after the first 3−5 patients (≥2 to <12 years of age) have been dosed for a minimum of 12 weeks. A JMC will review all cumulative data (e.g., safety, efficacy, and pharmacokinetics) to provide recommendations on increasing the starting maintenance dose. A second interim data review by the JMC will occur once at least 10 patients (≥ 2 to < 12 years of age) have been dosed for a minimum of 12 weeks, at which time all available cumulative data (e.g., safety, efficacy, and pharmacokinetics) will be evaluated to provide recommendations for the enrolment of children < 2 years of age, as well as on the maintenance dose. If patient recruitment is faster than anticipated, enrolment will be placed on a temporary hold after the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose. After the JMC recommendations are released following both interim data reviews, the study will continue to enroll up to a maximum of approximately 60 patients in Cohort A. Subsequently, should no safety concerns arise from review of adult/adolescent data at Q2W (BH30071) and Q4W (BO39182) dosing, parallel enrolment with alternate cohort allocation to Cohorts B and C (up to approximately 10 patients per cohort) will commence.

The primary analysis for all cohorts will be performed 52 weeks after all patients in the primary population of Cohort A have been enrolled or withdrawn prematurely, whichever occurs first (see Section 2.5). The primary population of Cohort A consists of all patients enrolled prior to the close of enrolment for patients ≥ 2 years of age (up to approximately 60 patients) and is used to define the timing of the primary analysis of the study. The efficacy analysis will evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate) and will characterize the efficacy of up-titration on an intra-patient and population level. If no patients < 2 years of age are included in the primary population of Cohort A, the primary analysis will still occur at the specified time; however, enrolment to Cohort A may be left open exclusively for patients < 2 years of age in order to enrol approximately 5 such patients. Note that these patients will be included in the primary analysis of Cohort A regardless of their follow-up time. Additionally, all available data from patients enrolled in Cohorts B and C (regardless of their follow-up time) will be included at the time of the primary analysis.

In order to complement the analysis of Study BH29884 in adult and adolescents with inhibitors an interim analysis will be performed for Study BH29992 at the same time as the primary analysis of Study BH29884. An interim clinical study report (CSR) will be written for Study BH29992, in which some analyses may differ from the final study analyses. These differences are outlined in this SAP.

Other interim analyses might occur at any time in order to support health authorityies' requests or submissions.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1.

2.2 COLLECTION OF BLEED AND MEDICATION DATA

Bleed and medication data are collected through a bleed and medication questionnaire (BMQ), which was developed by the Sponsor given that no standard questionnaire for collection of these data was available.

The BMQ was developed as a patient-reported outcome measure of bleeding episodes (including cause, type, and location of bleeds) and hemophilia-related medication use. The draft questions were developed following a review of the hemophilia A literature and discussions with medical professionals regarding what information related to bleeds was most important to capture.

The BMQ is completed by the caregiver, with use of an electronic handheld device. All bleeds, hemophilia related medications, and emicizumab administrations are entered at minimum weekly and as they occur. If a patient does not experience a bleed or does not receive any hemophilia related medications for a week, the caregiver will be prompted to log in to the device and confirm this. Of note, the caregiver is able to enter bleeds and medications for the past 8 days, including the day 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.

The caregiver is able to edit and delete bleeds and medications immediately after they are entered. However, if the data have been submitted to the vendor's database (i.e., after responses have been confirmed by the caregiver), the caregiver is no longer able to edit or delete the data. Furthermore, the investigator, the caregiver, and the patient are instructed to review the data together at every clinic visit. If the caregiver was unable to enter bleed, medication, or emicizumab data within the 8 days' timeframe, if the caregiver mistakenly entered data that require deletion, or if the caregiver mistakenly entered data that require modification (e.g., incorrect emicizumab dose), the investigator is able to submit a data clarification request (DCR) to the vendor on the caregiver's behalf at any time.

Furthermore, the Sponsor's data manager and Medical Monitor will review the data entered by the caregiver on the BMQ for 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 clarification requests are sent to the investigator, who reviews them together with the caregiver and the patient (if the patient is old enough) and may enter or change the data via a DCR, if necessary. In addition, HRQoL using the Haemo-QoL-Short Form (SF) (completed by patients aged 8 years and above), proxy-reported HRQoL and the Adapted InhibQoL including Aspects of Caregiver Burden questionnaire (completed by caregivers for all children), and the number of days of missed daycare/school (completed by caregivers for all children) will be assessed every 3 months as outlined in the schedule of assessments. The number

of days the child was hospitalized (if applicable) will be derived from data collected on eCRF.

The Haemo-QoL-SF, Adapted InhibQoL including Aspects of Caregiver Burden questionnaires, and number of days of missed daycare/school are completed with use of a tablet at the site during clinic visit. However, for this type of data, there is no possibility for retrospective data entry or data modification and these data will not be queried.

2.3 OBJECTIVES AND ENDPOINTS

2.3.1 Efficacy Period for All the Endpoints

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

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 period according to eCRF), whichever is earlier. For patients who withdraw from the study before reaching the Week 1 visit, the duration of efficacy period is set to 1 day and it starts and ends on the day of enrolment.

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 starts with the first day on this dose and ends on the day of the clinical cut-off, the date of withdrawal, or on the last day on this specific dose, whichever is earlier.

2.3.2 Bleed-Related Objectives and Endpoints

The bleed efficacy objectives for this study are as follows:

- To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time
- To evaluate the reduction in bleeding rate on-treatment with emicizumab compared with the patient's historical bleeding rate (intra-patient comparison, only patients in Cohort A who previously participated in the non-interventional study (NIS), as patients enrolled in Cohorts B and C will not have previously participated in the NIS)
- To characterize the efficacy of up-titration on an intra-patient level, based on the number of bleeds over time.

The endpoint is the bleed rate and is defined as the number of bleeds over the efficacy period. Different analyses will be conducted as outlined in the sections below.

2.3.2.1 Treated Bleeds

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.

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

72-Hour Rule:

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

2.3.2.2 All Bleeds

Given that some patients may report bleeds that they did not treat, 'all bleeds' will be analyzed as an additional endpoint definition to treated bleeds and comprise 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 'treated bleed' analysis.

The endpoint of all bleeds fulfills the adapted ISTH criteria, as described in the protocol and the 72-hour rule, in particular. For treated bleeds, it is implemented exactly as defined for the 'treated bleed' definition (see Section 2.3.2.1). 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.

2.3.2.3 Treated Spontaneous Bleeds

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

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

2.3.2.4 Treated Joint Bleeds

In the analysis of treated 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".

2.3.2.5 Treated Target Joint Bleeds

Target joints are major joints into which repeated bleeds occur (i.e., ≥3 bleeds into the same joint over the last 24 weeks prior to study entry).

The target joints prior to study entry are identified through the eCRF. The bleeds in target joints during the efficacy period are defined by first selecting the bleeds that fulfill the definition of a treated joint bleed (see Section 2.3.2.4) and then counting how many of these occurred in a target joint prior to study entry. The locations to be taken into account are: shoulder, elbow, wrist, fingers/thumb, hip, knee, ankle, sole/heel, and toes. Left and right side of the same joint type are considered to be separate joints.

2.3.2.6 Intra-Patient Comparison

In the intra-patient comparison (on All Bleeds and on Treated Bleeds), only patients who participated in the NIS BH29768 are included. This is because it is possible to apply the detailed definition only if the data are collected with the same granularity for both time periods. Of note, for some patients who participated in NIS BH29768, the total time in that study prior to enrolment in Study BH29992 may be short.

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 before the patient is enrolled in Study BH29992. Usually, the date of the first entry is the date the Training Module on the electronic, handheld device is completed.

2.3.2.7 Up-Titration

In the analysis of efficacy of the up-titration, only patients whose dose was up-titrated will be included. The analyses will be done with both treated bleeds and all bleeds definitions. Of note, for the interim CSR these analyses will not be performed.

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

The patient-reported outcome (PRO) objectives and endpoints for this study are as follows:

- Evaluate the HRQoL of children 8-17 years of age according to Haemo-QoL-SF (completed by patients)

  The Haemo-QoL-SF is a self-report questionnaire for children. Only patients 8 years of age and above will be assessed for HRQoL with use of this questionnaire, which will be completed by the patients as per the schedule of assessments. The Haemo-QoL-SF is derived from the Haemo-QoL questionnaire, which has been developed in a series of age-related questionnaires to measure HRQoL in children and adolescents with hemophilia.

  The Haemo-QoL-SF version contains 35 items, which cover nine dimensions considered relevant for the children's HRQoL (Physical Health, Feelings, View of

self, Family, Friends, Other people, Sports and school, Dealing with hemophilia, and Treatment). The Physical Health scale assesses hemophilia-related symptoms (painful swellings and presence of joint pain) and physical functioning (pain with movement) and is of particular interest given that it has been responsive to change with modifications in treatment regimen (Santagostino et al. 2014). Items are rated with five respective response options: never, seldom, sometimes, often, and always.

- Evaluate proxy-reported HRQoL and aspects of caregiver burden using the Adapted InhibQoL including Aspects of Caregiver Burden questionnaire for all children (completed by caregivers)

  This will be completed by caregivers as per the schedule of assessments for all children regardless of age. The Adapted InhibQol Including Aspects of Caregiver Burden is composed of 32 items that make up 7 domains (Physical Health, Treatment, Perceive condition, Dealing with Inhibitor, Perceive treatment, Family life, Others). In addition, if the child has siblings, there is an additional question that creates 1 domain (Siblings) for a total of 8 domains. All questions on the Ada[ted InhibQoL are responded to on 5-point scale from 'Never' (1) to 'All the time' (5).

  The Physical Health domain consists of five questions focused on the child's hemophilia-related symptoms (bruises, bleeds, painful swellings, presence of joint pain and joint stiffness) and two questions on physical functioning limitations (pain with movement, sleep through the night because of pain) because of hemophilia. Two other domains cover issues related to the burden on caregivers of dealing with a child with inhibitors. The Dealing with Inhibitor domain includes questions on the psychological impact (anxiety, fear and worry) associated with their son's hemophilia A. Additionally, the Perceive treatment domain includes questions focused on the impact that treatment has on the caregiver in terms of the interference with daily life, difficulty in preparing the injections, and satisfaction with the amount of time to administer treatment. These three domains are of particular interest given the consistency with the Haemo-QoL-SF (for Physical Health) and the potential reduction in burden as a result of emicizumab treatment.

- Assess the number of days missed from daycare/school (completed by caregivers) and days hospitalized

  Caregivers will be asked to report as per the schedule of assessments the number of days of daycare/school that were missed and this will be completed following the Adapted InhibQoL including Aspects of Caregiver Burden questionnaire. The number of days the child was hospitalized (if applicable) will be derived from data collected on eCRF.

Of note, the Haemo-QoL-SF, caregiver-reported HRQoL, and aspects of caregiver burden questionnaires are completed every 3 months from the Week 1 assessment and request inputs from the past 4 weeks.

2.3.4 Pharmacokinetic Endpoint

The pharmacokinetic (PK) endpoint for this study is the exposure (Ctrough) of emicizumab in patients receiving 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W, assessed prior to drug administration on Day 1 and at the following timepoints:

- Every week during Weeks 1-4 on emicizumab
- Every 2 weeks during Weeks 5-9 on emicizumab
- Every 4 weeks during Weeks 13-37 on emicizumab
- Every 8 weeks during Weeks 41-49 on emicizumab
- Every 12 weeks from Week 57 thereafter while continuing on emicizumab until the end of the study.

Additional PK samples will be taken in patients who require up-titration.

2.3.5 Safety Objectives and Endpoints

Safety parameters to be measured include exposure, adverse events (AEs; including serious AEs [SAEs]; AEs of special interest [AESI], AEs leading to drug discontinuation, and deaths), clinical laboratory values and abnormalities (including hematology, coagulation, chemistry, and anti-emicizumab antibodies), vital signs, ECG, and concomitant medication use.

2.3.6 Biomarker Objectives and Endpoints

Biomarker parameters to be measured include but are not limited to coagulation-related assays such as aPTT, PT/INR, D-dimer, and FVIII activity assays.

2.4 DETERMINATION OF SAMPLE SIZE

The sample size for this study is based on feasibility and clinical considerations rather than statistical considerations, taking into account the number of pediatric patients with hemophilia A with inhibitors available for participation in this trial. Hence, at least 40 children younger than 12 years of age and up to approximately 80 patients with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents will be enrolled in this study: approximately 60 patients in Cohort A with allowance of patients 12-17 years of age who weigh < 40 kg at the time of informed consent and with allowance for approximately 5 additional patients < 2 years of age in Cohort A - and approximately 10 patients each in Cohort B and Cohort C.

During the study, a re-assessment of the initially specified sample size based on enrolment consideration may be performed. This may result in an increase in sample size, if necessary, to expand the safety database.

2.5 ANALYSIS TIMING

The primary analysis will be performed 52 weeks after the last patient in the primary population of Cohort A has been enrolled or withdrawn prematurely, whichever occurs

first. The primary population of Cohort A consists of all patients who will receive emicizumab at 1.5 mg/kg QW enrolled prior to the close of enrollment for patients ≥ 2 years of age (up to approximately 60 patients) and is used to define the timing of the primary analysis. If no patients < 2 years of age are included in the primary population of Cohort A, the final analysis will still occur at the specified time; however, enrolment in the study may be left open exclusively for patients < 2 years of age in order to enroll up to 5 such patients.

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

Timing of interim analyses is detailed in Sections 3.1and 4.9.

3. STUDY CONDUCT

3.1 DATA MONITORING

A Joint Monitoring Committee (JMC) composed of selected internal Sponsor members (Pediatric Medical Specialist, Safety Scientist, Clinical Pharmacologist, and Statistician) constituting the Internal Monitoring Committee and external pediatric hemostasis/thrombosis experts (including an external Clinical Pharmacology expert) will be in place throughout the duration of the study. Internal Monitoring Committee members have been selected on the basis that they have no contact with the sites as part of their responsibilities. The external pediatric hemostasis/thrombosis experts function to enhance safety monitoring, leverage external experts' scientific expertise by providing advice on data interpretation, and serve as a consultative body to the Sponsor.

If a majority of the initial 3-5 patients, aged $\geq$2 to $<$12 years, treated for a minimum of 12 weeks require up-titration or if their plasma emicizumab trough concentrations do not meet a target of 45 µg/mL, the JMC may suggest adaptation of the starting maintenance dose. Thus, in a first interim data review, all cumulative data (e.g., safety, efficacy, and pharmacokinetics) will be evaluated by the JMC to provide recommendations of changing the starting maintenance dose for the subsequent patients to be enrolled.

Once at least 10 patients, aged $\geq$2 to $<$12 years, have been dosed for a minimum of 12 weeks, a second interim data review of all available data (e.g., safety, efficacy, and pharmacokinetics) will be conducted to draw study and/or dosing recommendations produced by the JMC and to allow children from $<$2 years of age to participate. As a result of this interim data review, further adjustments to the maintenance dose may also be made, if necessary. The JMC may, if needed, monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study.

If rapid study enrolment occurs and the fifth and tenth patient are enrolled within 2 weeks of each other, the two data review meetings may be combined and take place at the same time.

The evaluation of the interim data reviews will be performed on the efficacy endpoints – number of bleeds over time –as well as on the safety and PK results.

Specific operational details, such as committee composition, member roles and responsibilities, frequency, and timing of meetings and interim data review are detailed in a separate JMC Agreement.

Of note, because patient recruitment occurred faster than anticipated, the first and second interim data reviews were combined into one interim data review. Following the interim review on 7 December 2016, the JMC recommended that enrolment to Cohort A could continue with the selected maintenance dose of 1.5 mg/kg QW and that the Cohort A of the study should be opened for recruitment of children $<$ 2 years of age.

4. STATISTICAL METHODS

For continuous variables, means, medians, ranges, and standard deviations will be presented. For categorical variables, the number and percentage of patients within each category will be presented. For each variable (continuous or categorical), the number of available observations will be reported. No formal hypothesis testing will be performed as the study is entirely descriptive.

4.1 OUTPUT LAYOUTS

The key output layout is designed to address the study objectives in a flexible manner and provide an overall view of the efficacy and safety of emicizumab for all dosing regimens. The key output layout is as follows:

All patients: these outputs will provide an overall view of all the data collected under emicizumab prophylaxis. Patients will be grouped according to their original maintenance regimen at study entry (QW, Q2W and Q4W) with a total column provided as well.

Listings will include all the data for all the patients with a flag indicating the dose related to each event and the dosing regimen of the patients. As appropriate, outputs will be produced for each dosing regimen separately.

Patients may be allowed to up-titrate their emicizumab dose if they meet the pre-specified criteria as described in the protocol. Patients will be grouped according to their original maintenance dose at study entry.

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

For Cohort A, the primary set of outputs will include patients from 0 to $<$ 12 years of age. Three additional limited sets of outputs will be produced: one for patients $\geq$ 12 years of age, one for the combined sets (0 to $<$ 12 years of age and $\geq$ 12 years of age) and one for patients ≤2 years old at time of enrolment.

For Cohorts B and C, only one set of outputs will be produced for each cohort and will include all the patients enrolled in these cohorts.

4.2 ANALYSIS POPULATIONS

4.2.1 All Patients

All patients' population includes all patients enrolled in the study.

4.2.2 Treated Population

Treated population corresponds to all patients who received at least one dose of emicizumab. This population will be the primary population for efficacy and safety analyses.

4.2.3 Non-Interventional Population

This population includes patients who participated in Cohort B of the NIS BH29768 prior to enrolment to this study. All the NIS patients enrolled in BH29992 are enrolled to Cohort A.

4.2.4 Pharmacokinetic-Evaluable Population

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

4.2.5 Patients 12-17 Years of Age Who Weigh <40 kg

This population includes patients 12-17 years of age who weigh $<$ 40 kg at the time of informed consent.

4.2.6 Patients ≤ 2 Years of Age

This population includes patients $\leq$ 2 years of age at the time of informed consent.

4.2.7 Up-titrated Patients

This population includes patients who had at least one dose up-titration.

4.3 ANALYSIS OF STUDY CONDUCT

The flow of patients through the study will be displayed in a 'CONSORT' diagram. A clear account of all patients who entered the study, who were enrolled, who dose up-

titrated, and who completed each period of the study will be displayed. In addition, reasons for premature discontinuation 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 assessment schedule and compliance with data entry into the electronic handheld device, will also be evaluated.

4.4 EFFICACY ANALYSIS

The efficacy objectives of this study will be investigated without any formal hypothesis testing. All analyses will be of descriptive nature only.

4.4.1 Efficacy Endpoint

4.4.1.1 Bleed Rate

A bleed is defined in two ways. The first definition uses adapted ISTH definition of a bleed (Blanchette 2014; see Section 2.3.2.1; see Protocol Section 4.7.8). The second definition is counting all the bleeds regardless of the treatment (see Section 2.3.2.2).

The number of bleeds over time (bleed rate) will be calculated using a negative binomial (NB) regression model, which accounts for different follow-up times, with time that each patient stays in the study (efficacy period) included as an offset in the model. In addition, the number of bleeds will also be annualized for each patient using the following formula:

ABR = (Number of bleeds/number of days during the efficacy period) × 365.25.

For the interim CSRs, the population ABR may not be robust as it might be driven by only a few extreme observations because of the short follow up time. Therefore, the bleed rate will be characterized through individual patient data collected on the BMQ. In addition, with such short follow up, the NB model might not converge or the results might be unreliable. For all the patients, the number of bleeds will be described with use of descriptive statistics. The individual ABR will be calculated for patients who have been on the study for at least 12 weeks on the same dose (including the loading doses) with use of the given formula above.

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

4.4.1.2 Intra-Patient Comparison

The definition of treated bleeds and all bleeds is described in Section 2.3.2. The analysis methodology is the NB regression model.

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 the historical bleeding events (λ_c). The analysis will be performed overall and for each dose titration.

The treatment effect therein is based on a repeated statement in the model with use of the SAS GENMOD procedure. Bleed rates for prophylactic emicizumab and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The intra-patient comparison will be performed on patients who have been enrolled at least 12 weeks before the cut-off.

For the Interim CSR, individual patient's ABR will be provided in a descriptive manner including the reduction in ABR comparing before and after entering into Study BH29992. At this stage, the patients included in the analysis will have been on the study for at least 12 weeks.

4.4.1.3 Health-Related Quality of Life (HRQoL)

For Haemo-QoL-SF, descriptive analyses including summaries and 95% confidence intervals of change from baseline for each individual subscale and the overall score will be performed. Individual patient plots of the overall score at each timepoint will be generated. For the interim CSRs, individual patient plots will be performed, and if at least 8 patients have been on the study for at least 12 weeks, the descriptive analysis including summaries and 95% confidence intervals will be performed. Note that the number of patients contributing to the analysis is very limited because the questionnaire is completed only by a subset of patients (those 8 years of age and above).

For aspects of caregiver burden using Adapted InhibQoL including Aspects of Caregiver Burden questionnaire for all children (completed by caregivers), descriptive analyses and 95% confidence intervals of change from baseline for each individual subscale will be performed. Individual patient plots of the overall score at each timepoint will be generated. For the interim CSRs, individual patient plots will be performed, and if at least 8 patients have been on the study for at least 12 weeks, the descriptive analysis including summaries and 95% confidence intervals will be performed.

Number of days of missed day care/school and days hospitalized will be analyzed using descriptive statistics and 95% confidence intervals. For the interim CSR, if at least 8 patients have been on the study for at least 12 weeks, the descriptive analysis including summaries and 95% confidence intervals will be performed.

The Week 12 timepoint has been chosen because the patients/caregivers are completing the QoL questionnaires every 12 weeks. Therefore at least 1 questionnaire in addition to baseline should have been completed for these patients.

4.4.2 Subgroup Analyses

Comparative subgroup analyses describing the bleed rate (treated and all) will be conducted. In addition, estimated ABR including 95% confidence interval will be calculated in each subgroup. Note that 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.

The pre-specified subgroups are:

- Age: 0 to <2, 2 to <6, 6 to $<12, \geq 12$ years
- Race: Asian, Black or African American, White, Other
- Pre-study hemophilia treatment type: Episodic versus Prophylactic
- Number of target joints at baseline: no target joint, any target joint

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

These subgroup analyses will not be performed at the time of the interim analyses. For the Primary CSR, these analyses will be performed for the all patients population regardless of the dosing regimen as sample size will be too small per regimen.

4.5 PHARMACOKINETIC ANALYSES

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively at each timepoint by dose group, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of emicizumab following SC administration. Population PK parameters, such as clearance 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 curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies and Study BH29884. These analyses will be reported in a dedicated report.

In addition, region- and/or country-specific analyses will be performed to support regulatory submissions as needed (e.g., PK analysis in Japanese vs. non-Japanese patients or analyses based on ethnicity).

The PK will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg/QW), Cohort B (3 mg/kg/ Q2W), and Cohort C (6 mg/kg Q4W).

4.6 SAFETY ANALYSES

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

4.6.1 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 listings and summary tables.

4.6.2 Adverse Events

To evaluate the overall safety of prophylactic emicizumab, adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade (WHO Criteria). All AEs will be coded using the current version of MedDRA at the time of each database closure (interim and primary analysis). For the purpose of summarization, a patient is counted once in a system organ class or preferred term if the patient reported one or more events in that system organ class or preferred term. Percentages will be based on the number of patients overall.

The total number and percentage of patients with at least one AE and total number of AEs will be summarized. Separate AE summaries for SAEs, AESIs, severity, relatedness, and discontinuation/modification will be provided.

An overall summary of adverse events (including SAEs, AESIs, AEs leading to drug discontinuation, and deaths), which tabulates the number and percentage of patients who experienced any or serious adverse events and the number and percentage of patients who died, will be provided.

For adverse events with a missing intensity, seriousness, or relationship, the worst case will be assumed and the adverse events will be considered life-threatening (Grade 4) or serious.

4.6.3 Laboratory Data

For clinical laboratory data, which were collected from local laboratories, summary statistics in SI units will be presented. 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).

4.6.4 Vital Signs

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

4.6.5 ECG

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

4.7 BIOMARKER ANALYSIS

Pharmacodynamic (PD) parameters (e.g., aPTT, FVIII activity) and other exploratory markers (FIX and FX antigens, PT/INR, D dimer) will be presented using summary statistics, including means, median, range, standard deviations, and coefficients of variation. In addition, individual patient plots will be provided. At the time of the interim analysis, only listings and patient plots will be performed.

4.8 MISSING DATA

On the electronic handheld device, it is not possible to leave questions unanswered or to enter partial data in one BMQ.

In the site data entry system, it is possible to leave the time (but not the date) of a treatment or a bleed blank because the caregiver might not be able to remember these in a reliable way.

In order to implement the 72 hour rule, it is assumed that the bleeds and treatments with missing time occurred at 12:00 a.m. If at a given day only the treatment time or the bleed time is partial and the other one complete, the partial time is assumed to be the same as the complete time. In case of multiple events per day, the last complete time is used.

4.9 INTERIM ANALYSES

Interim data reviews by the JMC are described in Section 3.1. An additional interim analysis for Study BH29992 will occur at the same time as the primary analysis of Study BH29884. This interim analysis will be based on all available data from these pediatric patients and will be reported in an interim CSR. Other interim analyses might occur at any time in order to support health authority requests or submissions.

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Appendix 1 Protocol Synopsis

TITLE:	**A MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF SUBCUTANEOUS ADMINISTRATION OF EMICIZUMAB IN HEMOPHILIA A PEDIATRIC PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	BH29992
VERSION NUMBER:	4
EUDRACT NUMBER:	2016-000073-21
IND NUMBER:	122954
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase III
INDICATION:	Hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.

Objectives and Endpoints

The objectives of the study are to investigate (with no formal hypothesis testing) the efficacy, safety, and pharmacokinetics of SC emicizumab *administered at 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W* in pediatric patients with hemophilia A and factor VIII (FVIII) inhibitors who are currently receiving treatment with bypassing agents. *A total of approximately 80 patients are planned: approximately 60 patients in Cohort A (1.5 mg/kg QW) and approximately 10 patients each in Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W). P*atients younger than 12 years *of age* are planned for enrollment, with allowance of patients 12–17 years of age who weigh <40 kg at the time of informed consent to further evaluate dosing of emicizumab in patients <40 kg. *Of note, enrollment in Cohort A may be left open exclusively for patients <2 years of age until approximately 5 such patients have been enrolled.*

Efficacy Objective

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W), and overall as appropriate.

The efficacy objectives for this study are as follows:

- To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate) *
- To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate (intra-patient comparison*, Cohort A only, as patients enrolled in Cohorts B and C will not have previously participated in the non-interventional study*) *
- To characterize the efficacy of up-titration on an intra-patient level, *based* on the basis of the number of bleeds over time *
- To evaluate the health-related quality of life (HRQoL) of children 8–17 years of age according to Haemo-QoL-Short Form (SF) (completed by patients)

- To evaluate proxy-reported HRQoL and aspects of caregiver burden using the Adapted InhibQoL Including Aspects of Caregiver Burden questionnaire for all children (completed by caregivers)
- To assess the number of days missed from daycare/school and days hospitalized

* Analyses will be performed for: treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds.

Safety Objective

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W), and overall as appropriate.

The safety objective for this study is to evaluate the overall safety of emicizumab in pediatric patients with hemophilia A and 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, and anaphylactoid events
- Incidence and severity of thrombotic microangiopathy
- Incidence and clinical significance of anti-emicizumab antibodies

Pharmacokinetic Objective

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W).

The pharmacokinetic (PK) objective for this study is to characterize the exposure (C_{trough}) of emicizumab in patients *receiving 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W* prior to drug administration on Day 1 and at the following timepoints:

- Every week during Weeks 1–4 on emicizumab
- Every 2 weeks during Weeks 5–9 on emicizumab
- Every 4 weeks during Weeks 13–37 on emicizumab
- Every 8 weeks during Weeks 41–49 on emicizumab
- Every 12 weeks from Week 57 thereafter while continuing on emicizumab, until the end of the study
- Additional PK samples will be taken in patients who require up-titration (see schedule of assessments in the protocol)

Pharmacodynamic Biomarker Objective

The pharmacodynamic (PD) biomarker objective for this study is as follows:

- To assess potential PD biomarkers of emicizumab, including but not limited to aPTT and FVIII activity, at designated timepoints throughout the study.

Appendix 1 Protocol Synopsis (Cont)

Study Design

Description of Study

This *non-randomized*, multicenter, open-label, Phase III clinical study will enroll children with hemophilia A who have inhibitors against FVIII. Children with hemophilia A and documented historical FVIII inhibitor titer (≥ 5 BU) must currently be receiving treatment with bypassing agents. At least *40* patients younger than 12 years age and up to *approximately 80* patients are planned for enrollment, with allowance of patients 12–17 years of age who weigh < 40 kg at the time of informed consent. Patients will receive SC doses of emicizumab *at 1.5 mg/kg QW (Cohort A)*for a minimum of 52 weeks or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first. After 52 weeks of treatment, an individual patient who continues to derive clinical benefit may continue receiving prophylactic emicizumab as part of this study or a future separate emicizumab extension study.

Because of the uncertainty of the dosing regimen needed in patients < 12 years of age or < 40 kg to achieve similar exposure as in adults and adolescents, this study will *first* evaluate the appropriate dosing regimen in children by starting with the same *weekly* dosing regimen *(1.5 mg/kg QW)* being evaluated in the Phase III study (BH29884) in adult/adolescent patients with hemophilia A with inhibitors (see protocol for details). Emicizumab will be administered with a weekly dose of 3 mg/kg *QW* for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg *QW (Cohort A) for the remainder of the treatment period*. During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab (see protocol).

In a first interim data review, the appropriateness of the initial dosing regimen will be evaluated (maintenance dose of 1.5 mg/kg *QW*) after the first 3–5 patients (≥2 to < 12 years of age) have been dosed for a minimum of 12 weeks. A Joint Monitoring Committee (JMC; see protocol) will review all cumulative data (e.g., safety, efficacy, and pharmacokinetics) to provide recommendations on increasing the starting maintenance dose (if necessary) to target a similar plasma emicizumab trough concentration as the one being targeted in adolescents and adults (i.e., 45 µg/mL). All patients enrolled following the first interim data review will receive the starting maintenance dose selected by the JMC. Those patients enrolled prior to the first interim data review who had not had their dose up-titrated will remain on their current maintenance dose, unless they meet eligibility for up-titration based on protocol-defined criteria (see protocol).

In order to include and safely treat the youngest patients (birth to < 2 years of age), this study will include a staggered approach to enrollment by age. Patients ≥ 2 to < 12 years of age and patients 12–17 years of age who weigh < 40 kg will enroll first. A second interim data review will occur once at least 10 patients between ≥ 2 and < 12 years of age have been dosed for a minimum of 12 weeks, at which time all cumulative data (e.g., safety, efficacy, and pharmacokinetics) will be evaluated to provide recommendations for enrollment of children < 2 years of age, as well as on any additional adaptations of the maintenance dose if necessary.

Furthermore, should patient recruitment be faster than anticipated, enrollment will be placed on a temporary hold following the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose *(Cohort A)*. After the JMC recommendations are released following both interim data reviews, the study will continue to enroll *in Cohort A* up to approximately 60 patients.

Once 1) the exposure at 1.5 mg/kg QW has been characterized in this pediatric population; 2) Cohort A is fully enrolled; and 3) review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifies no safety concerns, this study will open two additional non-randomized cohorts to investigate Q2W and Q4W regimens in pediatric patients. Recruitment to Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W) will occur in parallel with alternate cohort allocation via IxRS, for a total of approximately 10 patients per cohort.

Appendix 1 Protocol Synopsis (Cont)

Of note, enrollment to Cohorts B and C will be limited to patients 2–11 years of age. Emicizumab will be administered with a loading dose of 3 mg/kg QW for the first 4 weeks followed by a maintenance dose of 3 mg/kg Q2W (Cohort B) and 6mg/kg Q4W (Cohort C) for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first (see protocol). During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab.

The entire study will enroll up to approximately 80 patients with allowance for additional patients < 2 years of age in Cohort A.

A patient who fulfills the inclusion and exclusion criteria should be enrolled at the Week 1 visit. Prophylactic use of bypassing agents should be discontinued *the day before* the first dose of emicizumab is given.

The primary analysis *for all cohorts* will be performed 52 weeks after *all* patient*s* in the primary *population of Cohort A have* been enrolled or withdrawn prematurely, whichever occurs first. The primary *population of C*ohort *A* consists of all patients enrolled prior to the close of enrollment for patients ≥2 years of age (up to approximately 60 patients) and is used to define the timing of the primary analysis *of Cohorts A, B, and C*. If no patients <2 years of age are included in the primary *population of C*ohort *A*, the primary analysis will still occur at the specified time; however, enrollment *to Cohort A* may be left open exclusively for patients <2 years of age in order to enroll *approximately* 5 such patients. Note that these patients will be included in the primary *analysis of C*ohort *A* regardless of their follow-up time. *Additionally, all available data from patients enrolled in Cohorts B and C (efficacy period approximately 6 months) will be included in the primary analysis of Cohort A.*

During the study, caregivers will be asked to enter any individual bleeds, hemophilia-related medications, and emicizumab treatments that occur on an electronic, handheld device. Entries should be made at least weekly, *and also* at any time a bleed occurs or a hemophilia medication*, including emicizumab,* is administered. Detailed information about bleeds (type, location, date/time) will be captured. Detailed information about hemophilia medications (agent, dose, reason for administration, date/time) and emicizumab dosing (total volume, date/time) will also be captured. In addition, HRQoL using the Haemo-QoL-SF (completed by children 8 years of age and older), proxy-reported HRQoL and aspects of caregiver burden using Adapted InhibQoL (completed by caregivers of all children) and missed daycare/school will be collected on a separate electronic, handheld device during a patient's visit prior to emicizumab injection at Week 1 and every 12 weeks thereafter, as outlined in the schedule of assessments (see protocol). The number of days the child was hospitalized, if applicable, will be derived from data collected on eCRF.

Emicizumab is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred). Therefore, in this study all patients will continue to receive episodic treatment for breakthrough bleeds as needed. Breakthrough bleeds should preferably be treated with rFVIIa at the lowest expected dose to achieve hemostasis and captured as they occur on the electronic, handheld device. There is clinical experience in the ongoing Phase I/II clinical studies with the treatment of over 80 breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents. FVIII, aPCC, and rFVIIa do not interfere with emicizumab PK assessments, and no safety signals have been observed when breakthrough bleeds were treated with standard-of-care regimens during Phase I/II studies. However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), *3* events of TMA and *3 serious* thromboembolic events were observed in patients who concomitantly used *> 100 U/kg/day of aPCC on average for ≥ 24 hours* for the treatment of breakthrough bleeds (see protocol). Therefore, it is recommended that breakthrough bleeds are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided or limited (see protocol). Also, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments (see protocol). Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of emicizumab in order to discuss potential laboratory

evaluations (e.g., anti-emicizumab antibodies, coagulation tests) to be performed as well as to re-evaluate the patient's benefit-risk of continued treatment.

Physical examinations, vital sign assessments, ECG, and safety laboratory assessments will be collected as per the schedule of assessments (see protocol). Adverse events will be captured on an ongoing basis as they occur during the study. All patients in this study will undergo PK assessments. Blood samples will also be collected to assess the PD properties of emicizumab (i.e., aPTT, FVIII activity), as well as to assess immunogenicity (i.e., anti-emicizumab antibodies and anti-FVIII antibodies). A detailed list is provided in the schedule of assessments (see protocol).

Of note, a non-interventional study (Study BH29768) has been initiated to document the number and types of bleeds and current treatment with episodic or prophylactic bypassing agents, as well as collect information on HRQoL, health status, and safety in patients with hemophilia A (including children < 12 years of age). The assessments in the non-interventional study will mitigate the risk of inaccurate reporting of bleeds that may occur with historical data collection and may provide data collected prospectively for over 24 weeks. Pediatric patients who are enrolled in the non-interventional Study BH29768 are eligible to 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. *All patients who participated in the non-interventional study will be enrolled in Cohort A.*

Number of Patients

At least *40* children younger than 12 years of age and up to *80* patients with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents will be enrolled in this study*: approximately 60 patients in Cohort A* with allowance of patients 12–17 years of age who weigh < 40 kg at the time of informed consent *and approximately 10 patients each in Cohort B and Cohort C.*

Target Population

Approximately 80 children < 12 years of age with hemophilia A and with FVIII inhibitors *previously* treated with bypassing agents *will be enrolled in the study (approximately 60 patients in Cohort A, 10 patients in Cohort B, and 10 patients in Cohort C).* In addition to this primary population of children < 12 years of age, patients 12–17 years of age who weigh < 40 kg at the time of informed consent will also be eligible to enroll. *These patients, as well as those < 2 years of age at the time of informed consent, will only be eligible to enroll in Cohort A. Of note, enrollment in Cohort A may be left open exclusively for patients < 2 years of age until approximately 5–10 such patients have been enrolled prior to the closure of Cohorts B and C, whichever occurs first.*

Inclusion Criteria

Children must meet the following criteria for study entry:

- Written informed consent must be obtained from parent/legally acceptable representative and an assent from the child when applicable (latest approved version by the Independent Ethics Committee [IEC]/Institutional Review Board [IRB]) prior to any of the study-specific assessments and procedures being performed.
- Children < 12 years of age at time of informed consent with allowance for the following:

  Patients 12–17 years of age and who weigh < 40 kg at the time of informed consent *(Cohort A only)*

  Patients < 2 years of age will be allowed to participate only after the protocol-defined interim data review criteria are met *(Cohort A only)*
- Body weight > 3 kg at time of informed consent
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures including the completion of applicable patient-reported outcome (PRO) questionnaires

- Caregivers of all children must have the willingness and ability to comply with all study procedures including the completion of the bleed/medication questionnaire and applicable HRQoL questionnaires
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥ 5 BU)
- Requires treatment with bypassing agents
- For patients ≥ 2 years of age:

  If on an episodic bypassing agent regimen: ABR of ≥ 6 (3 bleeds in the last 24 weeks)

  OR

  If on a prophylactic bypassing agent regimen: inadequately controlled (e.g., 2 bleeds since starting prophylaxis or 1 life-threatening bleed) or central venous access device (CVAD) placement medically not feasible or deemed unsafe by investigator
- For patients < 2 years of age *(Cohort A only)*: determined by investigator to be in high unmet medical need
- Adequate hematologic function, defined as platelet count of $\geq 100 \times 10^9$ cells/L and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin $\leq 1.5 \times$ age adapted upper limit of normal (ULN) (excluding Gilbert's syndrome) and both AST and ALT $\leq 3 \times$ age adapted ULN at the time of screening
- Adequate renal function: serum creatinine must be $\leq 1.5 \times$ ULN for age. When the serum creatinine is $\geq 1.5 \times$ ULN, creatinine clearance by Bedside Schwartz formula must be > 70 mL/min/1.73m^2
- At screening, in the rare cases of hemophilia in female patients who are of childbearing potential, patients will be required to have a negative serum pregnancy test result (with urine pregnancy tests performed at subsequent specified visits) and will have to agree to remain abstinent or use single or combined highly effective 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.

Exclusion Criteria

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

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or plan to receive during the study) immune tolerance induction (ITI) therapy or prophylaxis treatment with FVIII

  Patients awaiting initiation of ITI will be eligible

  Patients in whom ITI has failed will be eligible with a 72-hour washout period prior to the first emicizumab administration.
- 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 diseases (i.e., certain autoimmune disease [e.g., systemic lupus erythematosus], cardiovascular disease) 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 infection with HIV, hepatitis B virus (HBV), hepatitis C virus (HCV)
- Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment

- Use of systemic immunomodulators (e.g., interferon or corticosteroids) at enrollment or planned use during the study period
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- *Inability (or unwillingness by caregiver) to receive (allow receipt of) blood or blood products (or any standard-of-care treatment for a life-threatening condition)*
- Receipt of:

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

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

  An investigational drug concurrently
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results

End of Study

The primary analysis will take place at the same time for Cohorts A, B, and C. It will occur after all patients in the primary population of Cohort A have completed 52 weeks of treatment, or have withdrawn prematurely, whichever occurs first. All data from patients enrolled in Cohorts B and C will be included regardless of follow-up time.

After 52 weeks of treatment, an individual patient who continues to derive clinical benefit may continue receiving prophylactic emicizumab as part of this study or a future separate emicizumab extension study. Patients who discontinue emicizumab will have a safety follow-up visit at 24 weeks after the last emicizumab dose.

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 52 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 length of the entire study from screening of the first patient to the last patient completing 52 weeks in the study and/or the end-of-study follow-up visit (24 weeks after discontinuing emicizumab) will be approximately *152* weeks.

Investigational Medicinal Product

Test Product (Investigational Drug)

Emicizumab *treatment will begin with a* loading dose of 3 mg/kg *QW* for the first 4 weeks (Day 1 of each week) followed *on Week 5* by a maintenance dose of *either* 1.5 mg/kg *QW (Cohort A), 3 mg/kg Q2W (Cohort B), or 6 mg/kg Q4W (Cohort C). Note that the cumulative dose studied in all three cohorts is identical, but the dose administration schedule differs between cohorts.* Patients will receive *prophylactic* emicizumab for a minimum of 52 weeks or

until unacceptable toxicity or discontinuation from the study due to any cause. *See protocol for treatment details.*

Emicizumab will be administered as a SC injection in the home setting after a period of in-clinic administration and training. The first five drug administrations must be performed in a monitored setting such as an infusion center, clinic, or hospital, with a 60-minute observation period following each of the first three doses. For patients with a previous history of a clinically significant hypersensitivity reaction, additional precautions should be considered (see protocol). The fourth and fifth scheduled study drug administrations must also be performed in the monitored setting, and the patient/caregiver will be trained and have the opportunity to ask any questions to the HCP before the scheduled start of home administration. The patient (≥ 7 years of age)/caregiver will observe at least one SC injection performed by the HCP and successfully administer at least one SC injection while being observed by the HCP prior to starting home administration. Each site will have the discretion to provide additional training if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject emicizumab correctly, then arrangements may be made to identify a trained caregiver or HCP to administer the SC injections.

Non-Investigational Medicinal Products

None.

Statistical Methods

Efficacy Analyses

The efficacy analyses are to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate), and to characterize the efficacy of up-titration on an intra-patient level. These analyses will be conducted using different bleed definitions such as treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds.

The primary analysis will be performed 52 weeks after the last patient in the primary *population of C*ohort *A* has been enrolled or withdrawn prematurely, whichever occurs first. The primary *population* consists of all patients enrolled *in Cohort A* prior to the close of enrollment for patients ≥ 2 years of age (up to approximately 60 patients) and is used to define the timing of the primary analysis. *The primary analysis will also include all available data from patients enrolled in Cohorts B and C, regardless of their follow-up time.* Enrollment in *Cohort A* may be left open exclusively for patients < 2 years of age in order to enroll *approximately* 5–*10* such patients. Note that these patients will be included in the primary *population analysis* regardless of their follow-up time. Further analyses *may* be conducted while the study is ongoing (see protocol).

Safety Analyses

Safety analyses will be performed for each cohort separately and overall as appropriate.

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

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

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

Data on the impact of immunogenicity (anti-emicizumab antibodies and anti-FVIII antibodies) on safety, efficacy, and/or pharmacodynamics and pharmacokinetics will be summarized using standard language/terminology.

Appendix 1 Protocol Synopsis (Cont)

Pharmacokinetic Analyses

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively by dose groups *(1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W, 3 mg/kg QW in case of up-titration)*, 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, sex, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies and Phase III Studies. These analyses will be reported in a dedicated report.

Patient-Reported Outcome Analyses

Scale scores for the Haemo-QoL-SF and the Adapted InhibQoL Including Aspects of Caregiver Burden will be calculated for each assessment, with change scores being examined for the assessments over the course of the study. These will be summarized descriptively *by cohort*. A descriptive summary of the number of daycare/school days missed and days hospitalized will also be presented *by cohort*.

Pharmacodynamic Biomarker Analyses

PD parameters (e.g., aPTT, FVIII activity) will be presented using summary statistics by dose groups, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. *These analyses will be presented by cohort.*

Interim Data Review

In a first interim data review, the appropriateness of the initial dosing regimen will be evaluated (maintenance dose of 1.5 mg/kg/week). This dosing regimen may be adapted following analysis of all available data (e.g., safety, efficacy, pharmacokinetics) by the JMC (see protocol) if a majority of the first 3–5 patients (aged ≥2 to < 12 years of age) fail to achieve optimal control of bleeds after the first 12 weeks of treatment; or if their plasma emicizumab concentration trough level is lower than the one being targeted in adolescents and adults (i.e., 45 µg/mL). Should patients ≥ 12 years of age and < 40 kg be enrolled at the time of this first interim data review, available data from these patients will also be included.

A second interim data review will occur once at least 10 patients between 2 and 12 years of age have been dosed for a minimum of 12 weeks. All available cumulative data (e.g., safety, efficacy, pharmacokinetics) will be evaluated by the JMC to provide recommendations for the enrollment of children < 2 years of age, as well as on any further adaptations of the maintenance dose if necessary. Again, should patients ≥ 12 years of age and < 40 kg be enrolled at the time of this second interim data review, available data from these patients will also be included.

Should patient recruitment be faster than anticipated, enrollment will be placed on a temporary hold following the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose.

JMC Recommendations and Enrollment of Q2W/Q4W in Pediatric Patients

On 7 December 2016, based on a combined interim analysis of the first 20 patients enrolled, the JMC recommended to continue enrolling patients to Cohort A at the maintenance dose of 1.5 mg/kg QW, and to begin enrollment of patients < 2 years of age. See protocol for details.

After the JMC recommendations *were* released following *this interim analysis*, the study continue*d* to enroll *up to approximately 60 patients in Cohort A. Upon completion of recruitment to Cohort A, and following review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifying no safety concerns, recruitment with alternating allocation of patients to Cohorts B and C via IxRS could begin up to a maximum of approximately 10 patients in each cohort. See protocol for details.*

Appendix 1 Protocol Synopsis (Cont)

Additional interim data reviews will be prespecified in the Statistical Analysis Plan; other analyses may be conducted at various timepoints to support regulatory submissions.

Determination of Sample Size

The sample size for this study is based on favorable recruitment feasibility and clinical considerations rather than statistical considerations, taking into account the limited number of pediatric patients with hemophilia A with inhibitors available for participation in this study. Hence, at least 40 children younger than 12 years of age and up to 80 patients with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents will be enrolled in this study: $approximately\ 60\ patients\ in\ Cohort\ A$ with allowance of patients 12–17 years of age who weigh $<$40 kg at the time of informed consent $and\ approximately\ 10\ patients\ each\ in\ Cohort\ B\ and\ Cohort\ C$.

During the study, a re-assessment of the initially specified sample size based on enrollment consideration may be performed. This may result in an increase in sample size, if necessary, to expand the safety database.

Appendix 2 Schedule of Assessments

Schedule of Assessments – Cohorts A, B, C																			
	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 29	Wk 33	Wk 37	Wk 41	Wk 49	*Study Drug Discontinuation Visit* [a]	Safety F/U Visit [a]
Informed consent/assent [b]	x																		
Inclusion/exclusion criteria	x																		
Medical history and demographics [c]	x																		
Physical examination [d]	x					x			x			x [d]			x		x	x [d]	x
Vital signs [e]	x	x [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [f]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG [g, h]	x	x				x												x	
Safety laboratory assessments [h, i, j]	x [i]		x		x			x	x	x	x	x	x	x	x	x	x	x	x
Anti-FVIII antibodies [j, k]	x [k]		x						x			x			x		x		x
Anti-emicizumab antibodies [h, j, l]		x				x				x				x			x	x	x
Bleed/medication questionnaire [m, n]		<----------weekly [o] ---------->															x	x	x

Appendix 2 Schedule of Assessments (cont.)

	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 29	Wk 33	Wk 37	Wk 41	Wk 49	*Study Drug Discontinuation Visit* [a]	Safety F/U Visit [a]
Bleed/medication data review [o]		x				x		x	x	x	x	x	x	x	x	x	x	x	x
Following treatment with bypassing agents		Monitoring for thromboembolic events and thrombotic microangiopathy [p]																	
Adverse events [q]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
IMP management [r]		x	x	x	x	x	x [r]	x	x	x	x	x	x	x	x	x	x	x	
Haemo-QoL-Short Form [s]		x							x			x			x		x	x	
Adapted InhibQoL [t]		x							x			x			x		x	x	
PK assessment [h, j, u]		x	x	x	x	x	x [r]	x	x	x	x	x	x	x	x	x	x	x	x	x
PD biomarkers assessment [h, j, v]		x		x		x		x	x	x	x	x	x	x	x	x	x	x	x

Appendix 2 Schedule of Assessments (cont.)

Schedule of Assessments – Cohorts A, B, and C				
	Every 12 Weeks from Wk 57	Every 24 Weeks from Wk 57	Study Completion/ET [a]	Safety F/U Visit [a]
Physical examination [d]	x		x	x
Vital signs [e]	x		x	x
Concomitant medications [f]	x		x	x
ECG [g, h]			x	
Safety laboratory assessments [h, i, j]	x		x	x
Anti-FVIII antibodies [j, k]	x			x
Anti-emicizumab antibodies [h, j , l]	x		x	x
Bleed/medication questionnaire [m, n]	x		x	x
Bleed/medication data review [o]	x		x	x
Adverse events [q]	x		x	x
IMP management [r]	x		x	
Haemo-QoL-Short Form [s]		x	x	
Adapted InhibQoL [t]		x	x	
PK assessment [h, j, u]	x		x	x
PD biomarkers assessment [h, j, v]	x		x	x

Appendix 2 Schedule of Assessments (cont.)

eCRF = electronic Case Report Form; ePRO = electronic patient-reported outcome; ET = early termination; F/U = follow-up; FVIII = factor VIII; HRQoL = Health-Related Quality of Life; IMP = investigational medicinal product, PD = pharmacodynamic; PK = pharmacokinetic; Wk = Week.

Notes: The maximum allowable time between screening and enrollment is 28 days; if the elapsed time between screening and enrollment is more than 28 days, screening must be repeated. All assessments should be performed within ±2 days of the scheduled visit for the first 12 weeks (including the Week 13 visit), then ±7 days thereafter. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. Except for the bleed/medication questionnaire, all other patient data will be collected during office visits. On treatment days, pre-injection blood collection should be made 0–120 minutes before the injection. Emicizumab will be administered subcutaneously at a loading dose of 3 mg/kg *QW* for the first 4 weeks (Day 1 of each week) followed by a starting maintenance dose of 1.5 mg/kg *QW (Cohort A), 3 mg/kg Q2W (Cohort B), and 6 mg/kg Q4W (Cohort C)*. During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab (see Protocol Section 3.3.5). In case of up-titration to a new maintenance dose, the next five weekly *visits must occur* at the site.

[a] *The study treatment discontinuation visit refers to the visit that occurs when a patient discontinues study drug.* A safety follow-up visit will occur 24 weeks after discontinuing emicizumab for any reason.

[b] Written informed consent must be obtained from parents/legally acceptable representative and an assent from the child (when applicable) before distribution of the electronic, handheld device and collection of any data. Enrollment form will be completed after informed consent form and assent form (when applicable) are obtained. If patient fulfills the inclusion/exclusion criteria, the patient should be enrolled in the study on the same day when the first dose of emicizumab is administered (Day 1).

[c] Collected from patient medical records and documented in the eCRF.

[d] A complete physical examination will be performed at screening and 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), in addition to other organ systems as clinically indicated and/or report of new or worsening adverse event.

[e] Body temperature (oral, rectal, axillary, or tympanic), blood pressure, pulse rate, respiratory rate, height/length, and weight to be entered into eCRF. 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 should be repeated for both assessments.

[f] Concomitant medications (e.g., extra pain medication with bleed) will be asked about at each clinic visit and documented in the eCRF, excluding treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), which will be collected on the bleed/medication questionnaire. Hemostatic medications to treat or prevent bleeds in the 4 weeks prior to starting emicizumab will be collected on eCRF.

[g] If screening ECG abnormal, repeat at Week 1 (or Week 2 if Screening and Week 1 occur on the same date). ECGs will also be performed 4 weeks after starting emicizumab or after each dose up-titration, as well as at study completion/early termination.

[h] In case of up-titration, additional assessments including PK, PD biomarkers, anti-emicizumab antibodies, safety laboratory samples, and ECG will be required, with the schedule of assessments resetting back to Week 1, including an ECG.

[i] Laboratory data (performed locally) includes complete blood count with differential and serum chemistries (i.e., sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, creatine phosphokinase, total protein, albumin, creatinine, total and direct bilirubin, alkaline phosphatase, ALT, and AST). Female patients of childbearing potential will be required to have a negative serum pregnancy test result at screening and urine pregnancy tests performed at Weeks 13, 25, 37, and 49; every 12 weeks starting from Week 57; and study completion/early termination.

[j] When blood is drawn via catheter or CVAD, a discard tube must be used prior to collection of samples for any laboratory assessment, due to the possibility of contamination by saline or anticoagulants used to flush the device. Please consult the study Laboratory Manual for details on sample collection and processing.

[k] Anti-FVIII antibodies will be measured at a central laboratory using citrate plasma. Anti-FVIII antibodies is the only biomarker sample taken at screening. In case a patient screen fails or does not enroll in the study for any reason, the sample should be destroyed and not sent to the central laboratory. Throughout the study, additional blood samples may also be drawn on an unscheduled basis (at the clinical judgment of the investigator) for analysis at a central laboratory.

[l] Samples to detect anti-emicizumab antibodies will be collected prior to emicizumab injection at Weeks 1, 5, 17, 33, 49, every 12 weeks starting from week 57, study completion/early termination and at the 24-week safety follow-up visit. If patients continue on emicizumab past 52 weeks of treatment, anti-emicizumab antibodies will be collected every 12 weeks. If any of these samples are positive and/or if there is suboptimal clinical response or low pharmacokinetic exposure, additional samples may be collected and analyzed for anti-emicizumab antibodies. Anti-emicizumab antibodies should also be drawn at the time of systemic hypersensitivity events. For each additional anti-emicizumab sample, a PK sample should be concomitantly drawn.

[m] At the Week 1 visit, caregivers will be trained on how to use their handheld device to record the bleeds and the hemophilia medication use. The bleeding/medication questionnaire will be completed by the caregiver and includes start date and time, reason, type, location of each bleed, as well as start date and time, reason, type, and dose of each injection.

[n] Caregivers will be instructed to complete on weekly basis to complete the bleed/medication questionnaire when the patient has a bleed or hemophilia medication use.

[o] At subsequent visits as marked, investigator review of patient-reported bleed/medication questionnaire information will be conducted for completeness and accuracy.

[p] Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be send to the local reference laboratory, if available, and if the results from the local reference laboratory can be obtained within a reasonable timeframe to allow for decision making. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed. If applicable, laboratory results should be recorded in the eCRF *page titled "Local Lab Following Treatment with Bypassing Agents."*

Appendix 2 Schedule of Assessments (cont.)

[q] Patients are advised to inform the investigator about adverse events at every visit. Adverse events will be reported on the eCRF by the investigator. 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 bypassing agents 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").

[r] Drug accountability will not be performed at the first visit of emicizumab receipt. Drug dispensation will not occur at the study completion/early termination visit. *Note: for Cohort C, there are visits where emicizumab is not administered per schedule.*

[s] Haemo-QoL-Short Form (children 8 years of age and older) assessed on an electronic, handheld device by patients during patient's visit in clinic prior to emicizumab injection at Weeks 1, 13, 25, 37, 49, every 24 weeks from Week 57, and study completion/early termination.

[t] Proxy assessment of HRQoL and aspects of caregiver burden using the Adapted InhibQoL Including Aspects of Caregiver Burden questionnaire for all children assessed on electronic, handheld device by caregivers during patient's visit in clinic prior to emicizumab injection at Weeks 1, 13, 25, 37, 49, every 24 weeks from Week 57 and study completion/early termination.

[u] Emicizumab concentration. Plasma samples for this assessment should be taken prior to emicizumab injection.

[v] PD biomarkers will be measured at a central laboratory. See Appendix 3, for detailed explanation of PD biomarker assessments. 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.

Appendix 3 Schedule of PD Assessments

Sample	Visit [a]	Biomarker assays [b]
PD Set 1	Weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, every 8 weeks from Week 41, every 12 weeks from Week 57 Study Completion/Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator) while on emicizumab [c]	PT/INR D-dimer aPTT
PD Set 2 [d]	Weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, every 8 weeks from Week 41, every 12 weeks from Week 57 Study Completion/Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator) while on emicizumab [c]	FVIII activity FIX antigen FX antigen

FIX = factor IX; FVIII = factor VIII; FX = factor X; PD = pharmacodynamic.

[a] All samples are to be collected on Day 1 of the indicated week, prior to emicizumab injection (if applicable). All PD samples will be citrate plasma.

[b] Biomarker assays will include but are not limited to those listed. Where blood volumes allow, additional plasma may be frozen and banked for future exploratory research related to emicizumab. Blood volumes and processing procedures will be specified in the Laboratory Manual.

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

[d] These plasma samples will only be collected if the permitted blood volumes allow (based on patient body weight as described in Protocol Section 3.3.5). Please refer to the Laboratory Manual for details.