

PROTOCOL

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

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MEDICAL MONITOR: [REDACTED] M.D., M.A.S.

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

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PROTOCOL AMENDMENT APPROVAL

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Title
[REDACTED]

Approver's Name
[REDACTED]

CONFIDENTIAL

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RO5534262—F. Hoffmann-La Roche Ltd
Protocol BH30071, Version 4

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol BH30071 has been amended primarily to extend study duration to enable collection of long-term safety and efficacy data; patients will be able to continue in the study until 5 years after the last patient is enrolled. Changes to the protocol, along with a rationale for each change, are summarized below:

- The duration of the study has been extended to enable the collection of additional safety and efficacy data, including data on adverse events and anti-drug antibody development. Thromboembolic events and thrombotic microangiopathy, both protocol-defined adverse events of special interest, have been reported when an average cumulative dose of > 100 units/kg/24 hours of activated prothrombin complex concentrate (aPCC) was co-administered with emicizumab. Continued collection of data related to concomitant hemophilia medications, emicizumab administration, and bleeds will contribute to a better understanding of these adverse events of special interest should they occur. The total length of the study, from screening of the first patient to the end of study, has been extended from 2 years to 6 years accordingly (Sections 3.1 and 3.2).
- The opportunity to switch to a preferred dosing regimen (1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/ kg every 4 weeks) during study prolongation has been added to provide the same flexibility in choosing preferred dosing regimen as with commercial drug (Sections 3.1 and 4.3.2).

Additional changes made to the protocol are as follows:

- The Background and Safety sections have been updated, including information regarding a fourth case of thromboembolic event observed in the Phase IIIb study MO39129 of prophylactic emicizumab in patients with congenital hemophilia A who have inhibitors; and a third case of thrombotic microangiopathy observed in the Phase III study BH29884 of prophylactic emicizumab in patients with hemophilia A who have inhibitors (Sections 1.2.2, 1.3, 5.1.2.3, and 5.1.2.4).
- Testing of factor IX antigen and factor X antigen after Week 24 will no longer be performed, as no emicizumab-induced changes in these biomarkers have been observed across the emicizumab program (Sections 3.1 and 3.3.6; Appendix 2). A footnote has been added to Appendix 2 to indicate that factor XIII (FXIII) activity testing was conducted only at Week 1 due to emicizumab interference with the FXIII assay.
- Language has been added to clarify that continued use of antiplatelet and anticoagulation treatment is allowed if deemed medically necessary (Section 4.4.2).
- Language has been added to clarify that, after withdrawal of consent for participation in the RCR, remaining RCR samples will be destroyed or will no longer be linked to the patient. However, if RCR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data (Section 4.5.10.6).

- To align with other studies in the emicizumab program and the current Emicizumab Investigator's Brochure, life-threatening bleeding due to unreliable standard coagulation tests and inhibitor assays has been added as an additional risk associated with emicizumab (Section 5.1.2.5).
- The reporting of the term "sudden death" has been updated to also require the presumed cause of death (Section 5.3.5.8).
- To align with other studies in the emicizumab program, additional clarification has been added on adverse event reporting for patients who experience a worsening of hemophilia (Section 5.3.5.10).
- Adverse event reporting for hospitalization has been clarified (Section 5.3.5.11).
- A global change has been made to update the Medical Monitor and emergency contact information (Section 5.4.1).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.6).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).
- Language has been revised to clarify that data posting will include clinical trial registries and to clarify that redacted Clinical Study Reports and other summary reports will be made available upon request (Section 9.6).
- Appendix 10 (Anaphylaxis Precautions) has been added for alignment with the Roche protocol template.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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

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TEST PRODUCT: Emicizumab (RO5534262)

MEDICAL MONITOR: [REDACTED] M.D., M.A.S.

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

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL SYNOPSIS

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

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EUDRACT NUMBER: 2016-000072-17

IND NUMBER: 122,954

NCT NUMBER: NCT02847637

TEST PRODUCT: Emicizumab (RO5534262)

PHASE: Phase III

INDICATION: Hemophilia A without inhibitors

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

Objectives and Endpoints

Primary Efficacy Objective

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

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

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

Secondary Efficacy Objectives

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of prophylactic emicizumab (in each individual emicizumab arm) on the basis of the following endpoint:
 - Change in the number of bleeds over time compared with the patient's historical bleed rate *
- To evaluate the efficacy of prophylactic emicizumab administered at 1.5 mg/kg/wk or 3 mg/kg/2wks subcutaneously compared with no prophylaxis for patients previously treated with episodic FVIII on the basis of the following endpoints:
 - All bleeds over time
 - Spontaneous bleeds over time (spontaneous bleed rate)
 - Joint bleeds over time
 - Target joint bleeds over time (target joints are defined as joints with ≥ 3 bleeds occurring in the same joint over the last 24 weeks prior to study entry)

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

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

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

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

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

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To assess satisfaction regarding treatment with emicizumab prophylaxis versus FVIII prophylaxis according to the Satisfaction Questionnaire–Intravenous Subcutaneous Hemophilia Injection (SQ-ISHI) in patients previously treated with prophylactic FVIII
- To assess treatment preference for emicizumab prophylaxis versus FVIII prophylaxis or episodic therapy according to the preference survey
- To assess changes in number of days away from school/work during treatment with prophylactic emicizumab compared with no prophylaxis
- To assess changes in number of hospitalization days during treatment with prophylactic emicizumab compared with no prophylaxis
- To assess potential pharmacodynamic (PD) biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and FVIII activity
- To assess potential serum and plasma biomarkers of bone and joint health
- To evaluate the effect of emicizumab prophylaxis treatment on activity compared with activity at baseline.
- To evaluate the effect of emicizumab prophylaxis treatment on activity compared with no prophylaxis

Safety Objective

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

- Incidence and severity of adverse events
- Incidence and severity of thromboembolic events
- Changes in physical examination findings and vital signs
- Incidence of laboratory abnormalities
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to drug discontinuation
- Incidence of severe hypersensitivity, anaphylaxis, or anaphylactoid reactions
- Incidence and severity of thrombotic microangiopathy
- Incidence and clinical significance of anti-emicizumab antibodies
- Incidence of de novo development of FVIII inhibitors in patients receiving emicizumab prophylaxis

Pharmacokinetic Objective

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

- Every week during Weeks 1–4 on emicizumab

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

Study Design

Description of Study

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

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

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

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

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

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

Emicizumab is intended for prophylactic use only (i.e., not to treat bleeds that have already occurred). The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic emicizumab versus no prophylaxis will be conducted at the earliest timepoint when all randomized patients (Arms A, B, or C) and a minimum of 40 patients from Arm D have either completed 24 weeks in the study or discontinued from the study. Therefore, there will be a range of observation periods from 6 to approximately 12 months, or longer. Study patients will be enrolled globally from the Americas, Europe, Africa, and Asia-Pacific region.

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

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

A 6 mg/kg every 4 weeks (4wks) maintenance dosing regimen is being evaluated in Phase III studies BH29992 and BO39182 in addition to the 1.5 mg/kg/wk and 3 mg/kg/2wks maintenance dosing regimens evaluated in this study. The observed exposures (i.e., average concentration at steady state) of multiple doses of these three dosing regimens are comparable and lead to similar efficacy and safety profiles. Hence, 6 mg/kg/4wks will be offered as a permitted dosing regimen for patients who continue in this study during study prolongation. Upon implementation of protocol Version 4, treatment duration will be extended until 5 years after the last patient is enrolled to enable the collection of additional safety and efficacy data. During this study prolongation, each patient may choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg/wk, 3 mg/kg/2wks, or 6 mg/kg/4wks) and continue on that dosing regimen until discontinuation from the study. Instructions for switching the dosing regimen are outlined in the protocol.

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

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

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for some of these tests are normalized by low plasma concentrations of emicizumab, a variety of assay formats (one stage, chromogenic) and modifications (predilution of patient plasma) will be investigated for assessment of PD response at higher emicizumab plasma concentrations. However, it is not expected that these biomarkers will be used to guide dosing or the selection of patients to be treated with emicizumab. Rather, these biomarkers may be used to identify a future assay for the monitoring of emicizumab activity.

Physical examinations, including Hemophilia Joint Health Score (HJHS; see protocol), vital signs assessments, ECGs, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients, with the exception that emicizumab PK and ADAs will not be measured in patients in Arm C prior to the switch to emicizumab treatment. Adverse events will be captured as they occur for the duration of the study.

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

An independent Data Monitoring Committee (iDMC) composed of at minimum hemostasis/thrombosis experts and a statistician will be in place for the duration of the study and will monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study (to be described in the iDMC charter).

Breakthrough bleeds for patients receiving emicizumab will be treated with FVIII at the lowest FVIII dose expected to achieve hemostasis and captured as they occur on the handheld device. Patients (or their caregiver) will report bleed information, including site of bleed, type of bleed, category of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed. During the study patients will enter bleed and medication data at least weekly. Of note, the clinical experience in the ongoing Phase I and I/II clinical studies includes the treatment of breakthrough bleeds with FVIII or bypassing agents in patients receiving emicizumab (over 60 bleeds treated) without any related safety concerns reported. However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), 3 events of TMA and 2 thromboembolic events were observed in patients on emicizumab who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds (see protocol). Although FVIII and aPCC are fundamentally different in their potential interaction with emicizumab, investigators should keep in mind that circulating emicizumab increases patients' coagulation potential. Therefore, it is recommended that:

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

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

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

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

Activity assessment will be conducted at all sites participating in this study, and all patients screened and enrolled will be expected to participate. Participation will not be mandatory and will not impact participation in Study BH30071. Patients will be asked to wear the study device for 2 weeks during Weeks 1–2, 23–24, and 47–48. Patients will return their study devices to the respective site at Weeks 3, 25, and 49 and each site will transfer the data from the device to the database. These data will be analyzed to generate the daily step count (DSC) values for each patient.

Number of Patients

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

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

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

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

Examples of highly effective contraceptive methods with a failure rate of $< 1\%$ per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices.

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

Exclusion Criteria

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

- Inherited or acquired bleeding disorder other than hemophilia A
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may increase risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known HIV infection with CD4 count < 200 cells/ μ L within 24 weeks prior to screening. Patients with HIV infection who has CD4 > 200 and meet all other criteria are eligible.
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment.
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of:
 - Emicizumab in a prior investigational study
 - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration
 - A non-hemophilia-related investigational drug concurrently, within last 30 days or 5 half-lives, whichever is shorter
- Inability to comply with the study protocol in the opinion of the investigator
- Pregnant or lactating, or intending to become pregnant during the study
- Women who are not postmenopausal (\geq 48 weeks of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

End of Study

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

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

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

OR

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

OR

- Consent has been withdrawn

OR

- Lost to follow-up

Length of Study

The approximate length of the entire study from the first patient enrolled to the last patient last visit (LPLV [last patient, last visit]; see below) is 6 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

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

Used and unused IMP vials will be returned by study patients to the site and appropriately accounted for. Used vials will then be disposed of at the study site according to the study site's institutional standard operating procedure. Instructions regarding how to handle unused vials should be obtained from the Sponsor. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

Non-Investigational Medicinal Products

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/discontinuation visit. In addition, use of long-acting medications taken infrequently (e.g., zoledronic acid, Denosumab) will be recorded as well. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

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

- To avoid bleeds before adequate emicizumab level is reached, patients in Arm D will continue their regular FVIII prophylaxis until the second emicizumab loading dose. Concomitant routine FVIII prophylaxis is not permissible otherwise during the study.
- Drugs intended to treat bleeds on an episodic basis, including FVIII. Specific dosages of FVIII will not be mandated in the study; however, investigators should consider that circulating emicizumab may increase patients' coagulation potential. Investigators should review with patients the dose to be used to treat breakthrough bleeds. Breakthrough bleeds should be treated with the lowest FVIII dose expected to achieve hemostasis, which may be lower than the patients' prior FVIII dose. For information on the formulation, packaging, and handling of agents, see the local prescribing information for the marketed drug in question.
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to result in systemic exposure

Statistical Methods

Efficacy Analysis

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

Safety Analysis

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

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

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

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

Data on the impact of immunogenicity (anti-emicizumab antibodies) on safety, efficacy, and/or clinical pharmacology and PK will be summarized adopting standard language/terminology.

Pharmacokinetic Analyses

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

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

Exploratory Analyses

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

For the activity assessment all enrolled subjects that contribute reliable activity data (i.e., at least 8 valid days) will be analyzed. There will be no imputation of missing data. Subjects will be grouped according to the treatment regimen to which they are assigned in the main study. Because of the exploratory nature of the study, there will be no type-1 error control for multiplicity. Enrollment, discontinuations, protocol violations/deviations, and duration of activity monitoring follow-up will be summarized. Demographic and baseline characteristics, such as age, sex, race/ethnicity, and weight will be summarized using descriptive statistics. Relative change is defined as $100 \times (DSC_{\text{Week } n} - DSC_{\text{baseline}}) / DSC_{\text{baseline}}$.

Relative change from baseline at Week 25 or 49 in mean DSC and activity counts (total, mean, and peak) will be calculated within each treatment group provided the patient has reported data on at least 8 days within the 14 day observation period. Subject-level averages at each timepoint will be presented via dot-plots and descriptive statistics by treatment group.

The main comparisons will be within-patient changes, calculated within each treatment group. Within the control arm, where patients are expected to switch to emicizumab prophylaxis treatment at 24 weeks, an additional comparison of the relative change from Week 25 to Week 49 will be performed.

Formal statistical modeling may be performed as appropriate. Such analysis will be based on between-treatment comparisons of the change in activity from baseline to Week 25 between patients receiving emicizumab prophylaxis (Arms A or B) versus no prophylaxis (Arm C).

Determination of Sample Size

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

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a negative binomial (NB)

distribution. With consideration of enrollment feasibility, a sample size of 75 patients, assuming an allocation ratio of 2:2:1 (30 patients in each randomized treatment group and 15 patients in control group), will achieve a power of more than 90% assuming a mean ABR of 4 and 14 bleeds (with variances = mean \times 10) for the emicizumab treatment and control arms respectively, representing an expected 71% reduction in the ABR compared to the control arm. Initial sample size calculations were performed with East[®], Version 6 (Cytel, Cambridge, MA), assuming the patients from each treatment group are followed up to 0.5 units of time (i.e., 24 weeks).

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

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

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

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

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

Regarding the effect of emicizumab on changes of DSC from baseline at Weeks 23–24 or 47–48 in patients with hemophilia A, there is currently no published information on the variability or clinical significance of longitudinal changes in this measure with the study device in patients with hemophilia A. No data are available to allow detailed sample size calculation of these exploratory objectives. Participation will be offered to all patients in the study, leading to a maximum sample size of 145 patients. Of note, 40 subjects (20 per treatment group) were deemed sufficient to evaluate the related objectives with an adequate level of precision in similar studies that enrolled patients with chronic obstructive pulmonary disease, such as WB29804 Activity Substudy.

Interim Analyses

No interim analysis for efficacy is planned.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2wks	every 2 weeks
ABR	annualized bleeding rate
ADA	anti-drug antibody
aHUS	atypical hemolytic uremic syndrome
aPCC	activated prothrombin complex concentrate
AUC	area under the curve
BA	bioavailability
BMI	body mass index
C _{max}	maximum plasma concentration
cts	counts
CVAD	central venous access device
DSC	daily steps count
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
FDA	U.S. Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
FIX	factor IX
FIXa	activated factor IX
FVIII	factor VIII
FX	factor X
FXIII	factor XIII
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
HJHS	Hemophilia Joint Health Score
HRQoL	health-related quality of life
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
ICH	International Council for Harmonisation
IFU	Instructions for Use
IgG4	immunoglobulin G4
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board

Abbreviation	Definition
ITI	immune tolerance induction
IV	intravenous
IxRS	interactive voice or Web Response System
LPLV	last patient, last visit
MAD	multiple ascending dose
NB	negative binomial
NOAEL	no observed adverse effect level
PAQ	physical activity questionnaire
PD	pharmacodynamics
PK	pharmacokinetic
PRO	patient-reported outcome
QTcF	QT interval corrected using Fridericia's formula
QoL	quality of life
RCR	Roche Clinical Repository
rFVIII	recombinant FVIII
rFVIIa	recombinant activated factor VII
SAD	single ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
SQ-ISHI	Satisfaction Questionnaire–Intravenous Subcutaneous Hemophilia Injection
$t_{1/2}$	half-life
TMA	thrombotic microangiopathy
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
VAS	visual analog scale
WHO	World Health Organization
wk	week

1. BACKGROUND

1.1 BACKGROUND ON HEMOPHILIA A

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

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

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of the disease roughly correlates with the residual endogenous level of FVIII activity. Approximately 68% of people with hemophilia A have moderate (25%) or severe (43%) forms, characterized by FVIII activity levels <5% or <1%, respectively, leading to frequent bleeding events with the sequelae of musculoskeletal complications (e.g., arthropathy), local functional deficits, hemorrhagic shock, neurocognitive defects, or even death (World Federation of Hemophilia 2013).

A further complication is reduced bone mineral density, which is seen in both adults and children with hemophilia A (Paschou et al. 2014). Potential underlying causes include reduced weight-bearing activity, vitamin D deficiency, hemarthropathy, and direct links between coagulation factors and function of osteoblasts and osteoclasts responsible for bone architecture (Kempton et al. 2015). The significant negative impact of reduced bone mineral density was recently demonstrated in a single-center study of 316 patients. The incidence of bone fractures of individuals with hemophilia A was 22.9 fractures per 1000 patient-years, compared with 9.6 for the general population, and was higher for those with severe versus mild or moderate hemophilia A but with no difference for those with or without inhibitors (Gay et al. 2015). These disease-related issues can have a

significant impact on the health-related quality of life (HRQoL) of both adult and adolescent patients (Brown et al. 2009).

1.1.1 Management

Prophylactic FVIII replacement therapy (i.e., administered on a scheduled basis with the intent to prevent bleeds) has been proven to minimize bleeding events and complications (Manco-Johnson et al. 2007). Since the 1990s, recombinant FVIII (rFVIII) concentrates have been standard-of-care treatment options for patients with hemophilia A (Kingdon and Lundblad 2002). Treatment regimens to achieve optimal prevention of bleeding events vary between individuals: some patients tolerate trough FVIII levels of 1%, whereas, others require higher nadir FVIII levels to achieve the desired therapeutic outcome (Ahnstrom et al. 2004; Collins et al. 2010). Current prophylactic regimens commonly use infusion therapy administered three times weekly; other regimens use every other day administration (Shapiro 2013).

Prophylactic FVIII replacement therapy has been recognized as superior to episodic treatment of symptomatic bleeds for several decades (Khawaji et al. 2012) and was adopted by national and international organizations as the desired treatment approach. However, the burden of treatment (Eton et al. 2013, Mair and May 2014) is extraordinarily onerous, as adequate prophylaxis requires a lifetime of self-administered intravenous (IV) infusion of FVIII 3–4 times each week. In addition to the obvious toll on the quality of patients' life (Teal et al. 2014), this burden results in suboptimal care for many who elect to avoid routine prophylaxis, despite its medical advantage (Geraghty et al. 2006; Lindvall et al. 2006; De Moerloose et al. 2008; Collins et al. 2014; Oldenburg 2015). Thus, episodic therapy is a standard-of-care for many patients with hemophilia in developed countries, where approximately one-third to one-half of the patients use FVIII on-demand and avoid continuous prophylaxis. For example, a recent analysis revealed that in North America and Europe only 44.3% of 1238 patients with severe hemophilia A are treated with routine FVIII prophylaxis (Oldenburg and Brackmann 2014). Similarly, prophylaxis was routinely offered to adults in only 18 of 35 European countries surveyed, and in 12 out of those 18 countries, 50% or fewer adults received FVIII prophylaxis (O'Mahony et al. 2013). In addition to treatment burden, other reasons including venous access and cost concerns underlie this problem (Gringeri et al. 2012), which contributes to hemophilia-associated long-term morbidity.

Although patients on FVIII prophylaxis experience a low number of bleeds, MRI scans demonstrate progressive arthropathy in up to two-thirds of patients who receive an adequate primary prophylaxis regimen. These changes begin within the first decade of life and involve clinically "bleed-free" joints (Kraft et al 2012; Olivieri et al. 2012). Accordingly, 40% of men in the third decade of life reported presence of a target joint, reduced mobility, or chronic pain (Fischer et al. 2013; Noone et al. 2013). These findings indicate that FVIII prophylaxis delays, but does not completely prevent,

long-term skeletal morbidity (Oldenburg 2015). This is in part due to the challenges of adherence and in part due to micro-bleeds associated with low FVIII trough levels (Ljung and Gretenkort 2015). Due to the short half-life of FVIII, current prophylaxis regimens aim at maintaining FVIII levels at a trough of $\geq 1\%$, which restores hemostasis for only part of the time (Valentino et al. 2012). A study of patients with varying severities of hemophilia suggests that protection from joint bleeds occurs only at continuous levels over 12% (Den Uijl et al. 2011), and achieving higher FVIII activity, though difficult to accomplish with current regimens, has been recognized as a goal for optimal care in a position paper from the World Federation of Haemophilia (Skinner 2012).

Routine intravenous FVIII therapy relies on venous cannulation skills of patients and their care providers (Hacker et al. 2001). In particular, this issue plagues the care of children with hemophilia, in whom central venous access devices (CVADs [i.e., port-a-cath]) have been used regularly to overcome technical difficulties. Although CVADs make prophylaxis feasible in young children, they are associated with complications, including mechanical failure, dehiscence of the skin over the reservoir, infection, and thrombosis (Ewenstein et al. 2004). A recent prospective study reported that 183 lines were implanted in 99 patients and that 41% of patients had at least one infectious episode. The median time to line removal was 483 days (IQR [143–1071]) (Rodriguez et al. 2015). A Finnish retrospective study similarly reported that 47% of 106 catheters implanted in 58 patients had to be removed due to a complication (Vepsalainen et al. 2015). In addition, significant healthcare provider (HCP) efforts are required to manage optimal treatment solutions and to overcome identified issues (Schrijvers et al. 2013). Thus, both the disease and its treatment affect patients' HRQoL.

FVIII replacement therapy is the cornerstone of hemophilia A management, but unfortunately, it does not restore normal health and lifestyle to these patients. Given the incomplete efficacy and the significant management challenges in adults and children with hemophilia, there is a true need for therapeutics that have reliable efficacy, a long half-life, and low treatment burden to prevent bleeding and minimize long-term morbidity of individuals with hemophilia A.

1.2 BACKGROUND ON EMICIZUMAB

1.2.1 Molecule and Preclinical Data

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 pharmacokinetic (PK) properties of this antibody are expected to enable marked extension of 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 low burden prophylactic therapy.

Binding studies of emicizumab to cynomolgus monkey factor IX (FIX) and FX showed a similar affinity as to the human factors. Mechanistic in vitro studies were conducted in human and cynomolgus FVIII-neutralized plasma and in various coagulation factor-specific assay-testing systems, which revealed that emicizumab shortened aPTT and promoted thrombin generation. Emicizumab bound to human Fc γ receptor (hFc γ R), cynomolgus monkey Fc γ receptor (cyFc γ R), human neonatal Fc receptor (hFcRn), and cynomolgus monkey neonatal Fc receptor (cyFcRn) with similar affinities as a human IgG4 antibody, natalizumab.

In vivo pharmacology experiments in cynomolgus monkeys were conducted in a hemophilia A model where endogenous FVIII levels were neutralized by a FVIII-specific monoclonal antibody. This model mimics essential characteristics of patients with hemophilia A and was used to test in vivo pharmacodynamics and efficacy under spontaneous or local trauma-induced bleeding conditions. In summary, emicizumab demonstrated the ability to significantly reduce bleeding tendency under both sets of conditions.

Potential prothrombotic risks associated with emicizumab-induced FVIII mimetic activity were further explored in an in vivo cynomolgus monkey venous stasis model. In this model, thrombus formation in the presence of emicizumab was compared with that in the presence of FVIII or bypassing agents recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC). Thrombus formation with emicizumab did not markedly exceed thrombus formation observed with rFVIIa, aPCC, or FVIII.

The pharmacokinetics/toxicokinetics of emicizumab were assessed in cynomolgus monkeys after single and multiple doses were administered intravenously and via the intended clinical SC route. After a single IV dose of 6 mg/kg emicizumab in male cynomolgus monkeys, the plasma clearance was 3.62 mL/day/kg and the terminal plasma half-life ($t_{1/2}$) of emicizumab was 19.4 days. The single SC administration study (dose levels: 0.06, 0.6, and 6 mg/kg) indicated slow (time to maximum plasma concentration [t_{max}]: 3.00–5.33 days) and complete absorption (bioavailability [BA]: 102% at 6 mg/kg). The IV and SC multiple dosing studies (toxicokinetic monitoring) revealed a $t_{1/2}$ in the range of 14.9–30.8 days. Overall, exposures in terms of maximum plasma concentration (C_{max}) and area under the curve (AUC) increased in an approximately dose proportional manner.

A subfraction of the cynomolgus monkeys treated with repeated doses of emicizumab showed the formation of anti-emicizumab antibodies (which is expected with humanized monoclonal antibodies) with few animals also showing neutralizing antibodies.

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

See the RO5543262 (Emicizumab) Investigator's Brochure for additional details on nonclinical studies with emicizumab.

1.2.2 Clinical Experience

Currently available experience with emicizumab in humans includes data from one completed Phase I study (ACE001JP—Last Patient Last Visit on 17 April 2015) and its ongoing extension, a Phase I/II study (ACE002JP; see the RO5543262 [Emicizumab] Investigator's Brochure for additional details on clinical studies with emicizumab). ACE001JP was a single study conducted in 3 parts, including both healthy subjects (Part A and Part B) and patients with hemophilia A (Part C). The objective of Parts A and B in healthy subjects was to investigate the tolerability, safety, PK, and pharmacodynamic (PD) response of SC administered emicizumab in adult Japanese and Caucasian men and to evaluate for racial differences, if any, in their PK and PD response. Healthy men volunteers aged 20–44 were eligible for enrollment. A total of 64 healthy volunteers were enrolled in Parts A and B from August 2012 to April 2013. In Part C, the objective was to investigate the tolerability, safety, PK, and PD response of SC administered emicizumab in patients with hemophilia A. Patients were eligible for enrollment if they were 12–59 years of age, >40 kg in weight, had a diagnosis of severe congenital hemophilia A, and had documentation of bleeds and/or treatment with coagulation factor in the last 6 months. For those with inhibitors, patients must have had ≥ 6 bleeds in the 6 months prior to enrollment, and for those without inhibitors, patients were required to have received ≥ 150 lifetime doses of FVIII replacement, including in the last 6 months. A total of 18 patients with hemophilia A were enrolled from May 2013 to June 2014.

Parts A and B of Study ACE001JP (completed) consisted of a randomized, placebo-controlled, single ascending dose (SAD) study, which was conducted in Japanese (n=40; Part A) and Caucasian (n=24; Part B) healthy men; 48 subjects received a single SC injection of 0.001 mg/kg to 1 mg/kg of emicizumab and 16 subjects received a single SC injection of placebo. Part C of Study ACE001JP was an open-label, multiple ascending dose (MAD) study in 18 Japanese patients with hemophilia A, both with and without inhibitors. Of note, patients received concurrent coagulation factor products to control breakthrough bleeds. Of the 18 patients in Part C of Study ACE001JP, 6 patients were dosed with 0.3 mg/kg/week SC following a single loading dose of 1 mg/kg SC, 6 patients were dosed with 1 mg/kg/week SC following a

single loading dose of 3 mg/kg, and 6 patients received 3 mg/kg/week of emicizumab without a loading dose.

Study ACE002JP is an extension study that allows patients enrolled in Part C of Study ACE001JP to continue treatment with emicizumab. In order to be eligible for the extension study, patients must have completed 12 weeks of assigned treatment in Study ACE001JP and had bleeds prior to study entry. Seventeen of 18 patients in Part C of Study ACE001JP completed the 12-week treatment period. One patient moved to the post-discontinuation follow-up period. A total of 16 of the 17 patients who completed the 12-week treatment period subsequently enrolled into extension Study ACE002JP, and 1 of the 17 patients moved to the post-treatment observation period of Study ACE001JP. Thus, the ongoing extension study ACE002JP includes 6 patients from the 0.3 mg/kg/week group, 5 patients from the 1 mg/kg/week group, and 5 patients from the 3 mg/kg/week group of Study ACE001JP. The investigator discontinued emicizumab for 1 adolescent patient with mild local injection-site reactions and a pre-study history of allergic reactions. Another patient, who had a pre-enrollment annualized bleeding rate (ABR) 0 on FVIII prophylaxis, was not allowed to enroll in the extension study due to a health authority requirement for a history of bleeds pre-enrollment. As Study ACE002JP allows for dose escalation in patients with a suboptimal response but no significant toxicity on their current emicizumab dose, 2 of 6 patients eventually had their dose escalated from 0.3 mg/kg/week to 1 mg/kg/week and then to 3 mg/kg/week.

Data from the completed Parts A, B, and C of Study ACE001JP and interim data from Study ACE002JP (as of the cutoff date of 17 April 2015) are presented here (see the RO5543262 [Emicizumab] Investigator's Brochure for additional details on clinical studies with emicizumab). All continuing patients in Study ACE002JP have been observed for at least 96, 72, or 48 weeks in the 0.3, 1, and 3 mg/kg/week dosing groups, respectively, except for 1 patient in the 3 mg/kg/week group who has only been followed for 44 weeks.

The median age and body mass index (BMI) of the healthy volunteers across the dose groups in Part A ranged from 25.5–35.5 years and 20.28–21.44 kg/m², respectively. In Part B, the median age ranged from 28.5–30.5 years, and the median BMI ranged from 21.60–22.56 kg/m² across the dose groups. Among the 0.3, 1, and 3 mg/kg/week groups in Part C, the median age was 32, 30, and 33 years, respectively; the median BMI was 22.54, 22.87, and 22.31 kg/m², respectively. There were 5 adolescent patients (12–18 years): 1 patient (■■ years old) in the 0.3 mg/kg/week group; 2 patients (■■ years old and ■■ years old) in the 1 mg/kg/week group; and 2 patients (■■ years old and ■■ years old) in the 3 mg/kg/week group. There were 11 patients with inhibitors: 4 patients in the 0.3 mg/kg/week group; 4 patients in the 1 mg/kg/week group; and 3 patients in the 3 mg/kg/week group. All patients in Part C of Study ACE001JP have completed the treatment period and have either subsequently enrolled in the extension Study ACE002JP (16 of 18 patients) or moved to the follow-up or observation period (2 of 18 patients).

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In the 0.3 mg/kg/week cohort, 1 patient transitioned to the observation period of the ACE001JP study after 12 weeks of treatment and restarted the study treatment in the ACE002JP study at the increased dose of 1 mg/kg/week, approximately 35 weeks later. Another patient in the 0.3 mg/kg/week cohort had his dose increased in Study ACE002JP after completing 12 weeks of treatment in Study ACE001JP. Both of these patients eventually had their dose further increased to 3 mg/kg/week. A third patient in this group started to receive 1 mg/kg/week just prior to the data cutoff. At the data cutoff date of 17 April 2015, 6 patients in the 0.3 mg/kg/week group, 5 patients in the 1 mg/kg/week group, and 5 patients in 3 mg/kg/week group have continued emicizumab treatment in Study ACE002JP (see the RO5543262 [Emicizumab] Investigator's Brochure for additional details on clinical studies with emicizumab).

The efficacy parameter of ABR was calculated by annualizing the number of bleeds that required treatment with coagulation factor products during the 6 months prior to study enrollment and during the treatment period after first emicizumab administration. During the 6 months before study enrollment, the patients without inhibitors had received FVIII prophylactic replacement therapy, while the patients with inhibitors had received episodic therapy and/or prophylactic therapy with bypassing agents.

During the course of emicizumab administration, the ABR decreased in all patients compared with the ABR prior to study enrollment, regardless of whether or not they had inhibitors, with the exception of 1 patient without inhibitors in the 3 mg/kg/week group. This patient, who was previously on FVIII prophylaxis, had a baseline ABR of 0 and maintained an ABR of 0 during treatment with emicizumab. In the 0.3 mg/kg/week group, the ABR reduction ranged from 22.8%–100% in all patients and 22.8%–80.2% in patients without inhibitors. In the 1 mg/kg/week group, the ABR reduction ranged from 78.9%–100% in all patients and 78.9%–100% in patients without inhibitors (excluding the patients who were dose escalated from the 0.3 mg/kg/week group). In the 3 mg/kg/week group, the ABR reduction ranged from 86.4%–100% in all patients and 86.4%–100% in patients without inhibitors (excluding the patient with the baseline ABR of 0 and patients who were dose escalated from the 1 mg/kg/week group).

Emicizumab was safe and well tolerated in patients in the Phase I/II study (see Investigator's Brochure). The majority of adverse events were of mild intensity, except for 5 moderate adverse events (upper respiratory tract infection, bipolar I disorder, hemophilia [i.e., left hip joint bleeding due to hemophilia], headache, and asthma) and 2 severe adverse events (appendicitis and mesenteric hematoma). Both severe events were considered to be serious adverse events and not related to emicizumab administration. A total of 7 patients reported injection-site reactions (including erythema, hematoma, rash, pain, discomfort and pruritus). All injection-site reactions were of mild intensity. Besides injection-site reactions, the most frequently reported adverse events (≥ 4 patients) were nasopharyngitis, pharyngitis, dental caries, excoriation, and headache. There were no dose dependent increases in adverse events, and the majority of the adverse events were not considered related to emicizumab. Treatment

was discontinued for 1 patient with injection-site erythema in the 1 mg/kg/week group; the event was mild in intensity and resolved. This same patient also reported one non-related serious adverse event (hemophilia [i.e., left hip joint bleeding due to hemophilia]) approximately 24 weeks after the last dose of study drug. In the Phase I/II studies ACE001JP and ACE002JP no thromboembolic adverse events have been reported when emicizumab has been administered alone or concomitantly with FVIII products as episodic therapy or bypassing agents as episodic therapy.

In Study BH29884, as of *May 2019*, thrombotic microangiopathy (TMA) was observed in 3 patients receiving emicizumab and bypassing agents; and 2 cases of thromboembolic events were observed in 2 patients receiving emicizumab and bypassing agents. *In addition, 1 patient experienced a serious adverse event of acute myocardial infarction in Phase IIIb study MO39129, a single-arm study of prophylactic emicizumab in patients with congenital hemophilia A who have persistent inhibitors against FVIII. For more details refer to Sections 5.1.2.3 and 5.1.2.4 and the current RO5543262 (Emicizumab) Investigator's Brochure.*

Emicizumab exhibited linear PK after single SC administration. Following single SC injection, its mean elimination $t_{1/2}$ (4–5 weeks) was similar to that of other human IgG antibodies. Furthermore, comparison of PK profiles between Japanese and Caucasian healthy volunteers did not reveal racial differences. In patients with hemophilia A, emicizumab trough plasma concentrations increased in a dose-proportional manner with weekly dosing to achieve a plateau after approximately 12 weeks in the first two dosing groups, in which a loading dose was administered, and after approximately 24 weeks in the highest dose group, in which no initial loading dose was administered.

Until the April 2018 cutoff in four Phase III clinical trials of emicizumab (Studies BH29884, BH29992, BH30071, and BO39182), <5% of patients tested positive for anti-drug antibodies (ADAs) to emicizumab and <1% of patients developed ADAs with neutralizing potential (based on declining pharmacokinetics). A similar safety profile was observed in patients, irrespective of the presence of ADAs. One patient who developed ADAs with neutralizing potential experienced loss of efficacy after 5 weeks of treatment and discontinued emicizumab treatment. For further updated information, consult the current RO5534262 (Emicizumab) Investigator's Brochure.

Based on 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. See the Investigator's Brochure for additional details on clinical studies with emicizumab.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The ultimate goal of treatment for patients with hemophilia A is continuous restoration of near normal FVIII activity. Indeed, effective prophylaxis was adopted as the desired approach. Despite the availability of FVIII agents, patients and providers face significant

challenges. Due to the burden associated with therapy, a large proportion of patients decide against continuous prophylaxis, and there is an unmet need for an approach that will allow most patients to adopt effective prophylaxis. In part due to adherence and in part due to low FVIII trough levels, prophylaxis only reduces and postpones but does not eliminate long-term morbidity (Kraft et al. 2012, Noone et al. 2013, Oldenburg 2015). Thus, there is a need to ensure continuous FVIII activity higher than the approximately 1% trough activity achieved with current regimens to protect patients from long-term morbidity. FVIII replacement requires frequent IV dosing. This poses a challenge for all patients and in particular, to children, necessitating occasional placement of CVADs and exposing patients to the associated risks. In addition, frequent IV sticks is challenging for older patients plagued by significant arthropathy in hands, elbows, and shoulders and by vein scarring from repeated infusions. There is, therefore, a need for agents that are bioavailable in a non-IV route.

The nonclinical and clinical data related to emicizumab support a positive benefit-risk assessment. As described in Section 1.2, evaluation in vivo demonstrated the safety and efficacy of emicizumab in cynomolgus monkeys. This was corroborated in the Phase I/II studies, where significant and stable ABR reductions of 85%–100% were observed in patients receiving weekly emicizumab. In terms of safety, emicizumab did not induce thrombus formation in an in vivo cynomolgus monkey venous stasis model or in patients. No toxicologically relevant changes attributable to SC (at doses up to 30 mg/kg weekly) or IV (at doses up to 100 mg/kg weekly) administration of emicizumab were observed, and the NOAEL was the highest tested dose in each toxicity study. In the Phase I/II Studies ACE001JP and ACE002JP, no thromboembolic or systemic hypersensitivity adverse events were seen; however, in Study BH29884, 3 cases of TMA and 2 thromboembolic events were observed in patients on emicizumab who received bypassing agents for the treatment of breakthrough bleeds. Three out of these 5 patients have fully recovered and the fourth patient's condition has improved. *One event of thrombotic microangiopathy (Grade 4) occurred in a patient who was experiencing a serious adverse event of rectal hemorrhage (Grade 4), with the latter serious adverse event associated with a fatal outcome. In addition, 1 patient experienced a serious adverse event of acute myocardial infarction in Study MO39129 (see Sections 5.1.2.3 and 5.1.2.4 and the current RO5534262 [Emicizumab] Investigator's Brochure).*

Rationale for physical activity monitoring in patients with hemophilia A

Hemophilia A is associated with prolonged bleeding after trauma; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage leading to crippling musculoskeletal complications (e.g., arthropathy), local functional deficits, neurocognitive defects, or even death (World Federation of Hemophilia 2013). These disease-related issues can have a significant impact on patients' mobility and the HRQoL of both adult and adolescent patients (Brown et al. 2009).

Compared with control populations, people with hemophilia have been shown to have moderate impairment of balance and mobility and reduced levels of physical activity (Fearn et al. 2010; O'Donnell and Gebke 2014). Improving mobility and safely increasing activity level in this population are important goals that will result in significant health and quality-of-life benefits (von Mackensen et al. 2010; Czepa et al. 2013). Ample scientific evidence and guidelines support the health promoting value of physical activity underlining the importance of assessing activity in adolescents and adults with hemophilia (WHO 2010). As expected, the degree of joint damage correlates with the level of activity. However, this parameter accounts for only a small fraction of the variability in the amount of activity performed by different people with hemophilia (Baumgardner et al. 2013), which is not surprising as level of activity reflects both ability and motivation. Motivation (or lack thereof) is particularly important in people with hemophilia who are at risk of bleed with physical activity (Broderick et al. 2012), even when receiving standard therapies. Therefore, we hypothesize that the superior bleed control provided by emicizumab prophylaxis will be associated with increased physical activity in people with hemophilia.

In conclusion, the management challenges of adults and children with hemophilia A highlight the unmet need for therapeutics that have reliable efficacy, long half-life, and reduced treatment burden to prevent bleeding for patients with hemophilia A. Given this significant unmet medical need and the positive benefit-risk assessment, initiation of a larger, confirmatory Phase III study is indicated.

2. OBJECTIVES AND ENDPOINTS

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

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

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

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

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are as follows:

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

Change in the number of bleeds over time compared with the patient's historical bleed rate *

- To evaluate the efficacy of prophylactic emicizumab administered at 1.5 mg/kg/wk or 3 mg/kg/2wks subcutaneously compared with no prophylaxis for patients previously treated with episodic FVIII on the basis of the following endpoints:
 - All bleeds over time
 - Spontaneous bleeds over time (spontaneous bleed rate)
 - Joint bleeds over time
 - Target joint bleeds over time (target joints are defined as joints with ≥ 3 bleeds occurring in the same joint over the last 24 weeks prior to study entry)
 - HRQoL of patients according to Haem-A-QoL (aged ≥ 18) or Haemo-QoL-Short Form (aged 12–17) scores after 24 weeks
 - Health status of patients according to European Quality of Life 5-Dimensions-5 Levels Questionnaire (EQ-5D-5L) scores after 24 weeks
- To evaluate the efficacy of prophylactic emicizumab administered at 1.5 mg/kg/wk subcutaneously for patients previously treated with prophylactic FVIII on the basis of the following endpoint:
 - Maintaining adequate control of bleeding by evaluation of the bleed rate *

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

2.1.3 Exploratory Objectives

The exploratory objectives for this study are as follows:

- To assess satisfaction regarding treatment with emicizumab prophylaxis versus FVIII prophylaxis according to the Satisfaction Questionnaire–Intravenous Subcutaneous Hemophilia Injection (SQ-ISHI) in patients previously treated with prophylactic FVIII
- To assess treatment preference for emicizumab prophylaxis versus FVIII prophylaxis or episodic therapy according to the preference survey
- To assess changes in number of days away from school/work during treatment with prophylactic emicizumab compared with no prophylaxis
- To assess changes in number of hospitalization days during treatment with prophylactic emicizumab compared with no prophylaxis
- To assess potential PD biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and FVIII activity
- To assess potential serum and plasma biomarkers of bone and joint health
- To evaluate the effect of emicizumab prophylaxis treatment on activity compared with activity at baseline.
- To evaluate the effect of emicizumab prophylaxis treatment on activity compared with no prophylaxis

2.2 SAFETY OBJECTIVE

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

- Incidence and severity of adverse events
- Incidence and severity of thromboembolic events
- Changes in physical examination findings and vital signs
- Incidence of laboratory abnormalities
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to drug discontinuation
- Incidence of severe hypersensitivity, anaphylaxis, or anaphylactoid reactions
- Incidence and severity of thrombotic microangiopathy
- Incidence and clinical significance of anti-emicizumab antibodies
- Incidence of de novo development of FVIII inhibitors in patients receiving emicizumab prophylaxis

2.3 PHARMACOKINETIC OBJECTIVE

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

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

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

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

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

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

In addition, 40–60 patients with severe hemophilia A who received FVIII prophylaxis prior to study entry will be enrolled and will receive emicizumab prophylaxis at 3 mg/kg/wk subcutaneously for 4 weeks, followed by 1.5 mg/kg/wk subcutaneously (Arm D; see [Figure 1](#)). A minimum of 40 patients in this group will complete at least 24 weeks of observation in an ongoing non-interventional study (BH29768) prior to enrollment in this study. Eligibility for all patients in Arm D will be based on investigator's attestation of adequate prophylaxis regimen in the 24 weeks prior to study entry.

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

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

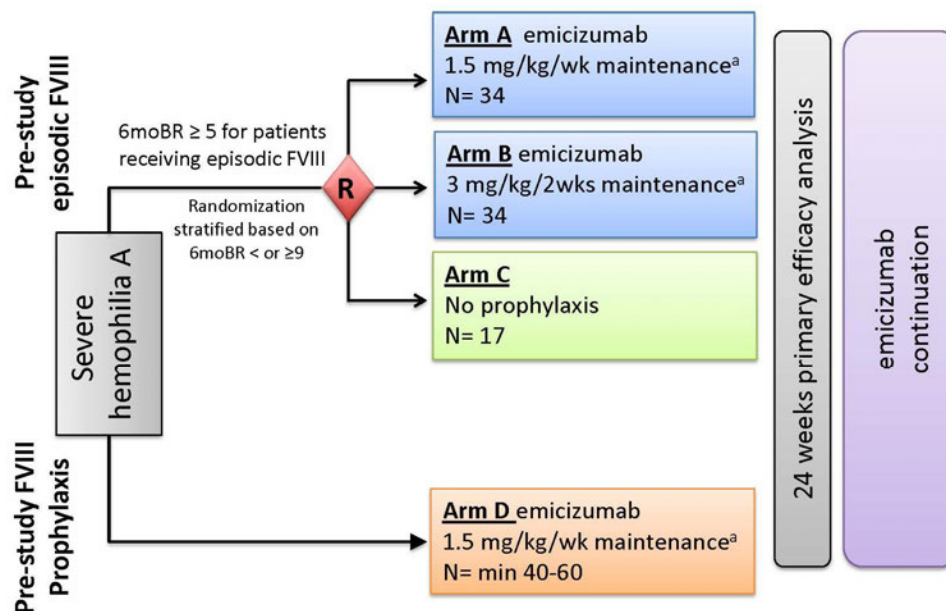
Emicizumab is intended for prophylactic use only (i.e., not to treat bleeds that have already occurred). The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic emicizumab versus no prophylaxis will be conducted at the earliest timepoint when all randomized patients (Arms A, B, or C) and a minimum of 40 patients from Arm D have either completed 24 weeks in the study or discontinued from the study. Therefore, there will be a range of observation periods from 6 to approximately 12 months, or longer. Study patients will be enrolled globally from the Americas, Europe, Africa, and Asia-Pacific region.

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

After completing at least 24 weeks of treatment with prophylactic emicizumab, patients who receive emicizumab prophylaxis (Arms A, B, D, or Arm C after treatment switch) and derive clinical benefit will be allowed to continue emicizumab until marketing authorization as part of this study or a separate extension study, as long as they continue to derive clinical benefit and emicizumab is still in clinical development (see Section 4.3.4). Those who are well controlled ($ABR < 4$) will continue treatment on their assigned emicizumab regimen; whereas, patients in Arms A, B, or C (after 24 weeks on emicizumab) who experience suboptimal control ($ABR \geq 4$) will be offered the option to escalate to 3 mg/kg/wk after approval from the Medical Monitor. Patients in Arm D who experience suboptimal control while on emicizumab prophylaxis at the maintenance dose, will have the opportunity to escalate to 3 mg/kg/wk immediately after the second qualifying bleed. Criteria and details of dose escalation are described in Section 4.3.2.

Figure 1 Study Schema

Phase III Non-Inhibitor - Design



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

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

A 6 mg/kg every 4 weeks (4wks) maintenance dosing regimen is being evaluated in Phase III studies BH29992 and BO39182 in addition to the 1.5 mg/kg/wk and 3 mg/kg/2wks maintenance dosing regimens evaluated in this study. The observed

exposures (i.e., average concentration at steady state) of multiple doses of these three dosing regimens are comparable and lead to similar efficacy and safety profiles (see Section 3.3.1). Hence, 6 mg/kg/4wks will be offered as a permitted dosing regimen for patients who continue in this study during study prolongation.

Upon implementation of protocol Version 4, treatment duration will be extended until 5 years after the last patient is enrolled to enable the collection of additional safety and efficacy data. During this study prolongation, each patient may choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg/wk, 3 mg/kg/2wks, or 6 mg/kg/4wks) and continue on that dosing regimen until discontinuation from the study. Instructions for switching the dosing regimen are outlined in Section 4.3.2.

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

Throughout the study, biomarkers related to thromboembolism (e.g., D-dimer, prothrombin 1.2 fragment) and emicizumab trough concentrations will be collected as per the schedule of assessments. Immunologic biomarkers (i.e., anti-emicizumab antibodies and anti-FVIII antibodies) will also be measured as per the schedule of assessments (see [Appendix 1](#)).

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for some of these tests are normalized by low plasma concentrations of emicizumab, a variety of assay formats (one stage, chromogenic) and modifications (predilution of patient plasma) will be investigated for assessment of PD response at higher emicizumab plasma concentrations. However, it is not expected that these biomarkers will be used to guide dosing or the selection of patients to be treated with emicizumab. Rather, these biomarkers may be used to identify a future assay for the monitoring of emicizumab activity.

Physical examinations, including Hemophilia Joint Health Score (HJHS; see [Appendix 8](#)), vital signs assessments, ECGs, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients, with the exception that emicizumab PK and ADAs will not be measured in patients in Arm C prior to the switch to emicizumab treatment. Adverse events will be captured as they occur for the duration of the study.

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

An independent Data Monitoring Committee (iDMC) composed of at minimum hemostasis/thrombosis experts and a statistician will be in place for the duration of the study and will monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study (to be described in the iDMC charter).

Breakthrough bleeds for patients receiving emicizumab will be treated with FVIII at the lowest FVIII dose expected to achieve hemostasis and captured as they occur on the handheld device. Patients (or their caregiver) will report bleed information, including site of bleed, type of bleed, category of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed. During the study patients will enter bleed and medication data at least weekly. Of note, the clinical experience in the ongoing Phase I and I/II clinical studies includes the treatment of breakthrough bleeds with FVIII or bypassing agents in patients receiving emicizumab (over 60 bleeds treated) without any related safety concerns reported. However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), 3 events of TMA and 2 thromboembolic events were observed in patients on emicizumab who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds (see Sections 1.2, 1.3, 5.1.2.4, and 5.1.3). Although FVIII and aPCC are fundamentally different in their potential interaction with emicizumab, investigators should keep in mind that circulating emicizumab increases patients' coagulation potential. Therefore, it is recommended that:

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

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

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

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

Activity assessment will be conducted at all sites participating in this study, and all patients screened and enrolled will be expected to participate. Participation will not be mandatory and will not impact participation in Study BH30071. Patients will be asked to wear the study device for 2 weeks during Weeks 1–2, 23–24, and 47–48. Patients will return their study devices to the respective site at Weeks 3, 25, and 49 and each site will transfer the data from the device to the database. These data will be analyzed to generate the daily step count (DSC) values for each patient.

3.2 END OF STUDY AND LENGTH OF STUDY

LENGTH OF STUDY

The approximate length of the entire study from the first patient enrolled to the last patient last visit (LPLV [last patient, last visit]; see below) is 6 years.

END OF STUDY

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

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

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

OR

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

OR

- Consent has been withdrawn

OR

- Lost to follow-up

3.3 RATIONALE FOR STUDY DESIGN

The Sponsor proposes a randomized, multicenter, open-label, Phase III clinical study that will enroll patients aged 12 years or older with severe hemophilia A (intrinsic FVIII level < 1%) without inhibitors against FVIII. In the randomized arms of the study, patients who received episodic treatment with FVIII prior to enrollment will be randomized to receive one of the following regimens:

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

This prospective, randomized design allows uniform collection of bleed data, medication use and patient-reported outcomes through the utilization of patient-validated measurement tools in all groups, enabling analysis of the effect of emicizumab versus episodic FVIII therapy on these important measures. Reporting of bleeds by patients to their providers (e.g., doctors, nurses) is not standardized and can be incomplete in routine clinical care. In addition, the recording of bleeds by providers in medical records may be inconsistent. Therefore, testing the primary endpoint using a prospective randomized design is superior to comparison to historical control in patients who were not on prophylaxis prior to enrollment.

Given the proven efficacy of FVIII prophylaxis, it can be expected that standard-of-care may evolve towards more widespread treatment of patients with prophylaxis regimens. However, for myriad of reasons currently only about half the patients in developed countries are managed with routine prophylaxis, making the episodic approach a commonly used standard care (Richards et al. 2007; Gringeri et al. 2012; Zappa et al. 2012; Jackson et al. 2014, 2015; Oldenburg and Brackmann 2014; Oldenburg 2015). Thus, for the primary efficacy endpoint, patients on episodic FVIII will be compared with patients treated with prophylactic emicizumab. Limiting the randomized portion of the study and primary efficacy analysis to patients who previously received episodic FVIII will reduce heterogeneity in the study population, which is appropriate since the bleed rates for patients receiving therapy on an episodic versus prophylactic basis are significantly different (Valentino et al. 2012; Manco-Johnson et al. 2013; Powell et al. 2013; Antunes et al. 2014;

Mahlangu et al. 2014; Windyga et al. 2014). To help balance measured and unmeasured covariates between the emicizumab and episodic FVIII groups, randomized patients will be stratified according to the number of bleeds they had over the 24 weeks prior to study entry (less than versus greater or equal to 9 bleeds).

The study will include a cohort of non-inhibitor patients treated with prophylactic FVIII agents prior to enrollment. Prophylaxis was endorsed in 1994 by the World Health Organization as the optimal approach for patients with hemophilia (Berntorp et al. 1995), and, therefore, it is important to demonstrate that these patients are adequately controlled with emicizumab. The design and conduct of a study comparing emicizumab to FVIII prophylaxis is challenging due to the low rate of bleeding events in this population. Rarity of events precludes definition of a meaningful non-inferiority margin and would require an unfeasibly large sample size. In determining a clinically meaningful bleed rate to define successful prophylaxis treatment in patients on previous FVIII prophylaxis, the Sponsor relies on findings from recent studies, which explored prophylaxis using novel rFVIII agents (Valentino et al. 2012; Mahlangu et al 2014; Kavakli et al. 2015; Konkle et al 2015). Examining interquartile ranges for bleed rate in patients receiving FVIII prophylaxis reveals that approximately a quarter of patients experienced ABR higher than 6.5. Therefore, clinically meaningful control of bleeding in this patient group can be characterized through an upper limit of a 95% CI for the mean bleed rate of ≤ 6 . The proposed threshold of upper limit of a 95% CI ABR ≤ 6 is lower than the previously reported outcome of patients on prophylactic treatment and is therefore clinically meaningful. A similar approach, utilizing a predefined threshold based on published experience was recently utilized in assessing the efficacy of a novel long-acting FIX product (Collins et al. 2014). In addition, to improve the validity of historical comparison in this group, a minimum of 40 patients will be observed on FVIII prophylaxis in the non-interventional study for a period of at least 24 weeks before enrolling in Arm D of this study.

The primary efficacy analysis to assess the effect of emicizumab on bleed rate reduction will be performed at the earliest timepoint when all randomized patients (Arms A, B, and C) and a minimum of 40 patients from Arm D have either completed 24 weeks of study treatment or discontinued from the study. Indeed, a similar follow up period was utilized in recent studies that investigated the safety and efficacy of novel FVIII formulations (Mahlangu et al. 2014; Kavakli et al. 2015; Konkle et al. 2015). Further, patients who experience frequent bleeds may not find it acceptable to be randomized to their usual episodic FVIII therapy for longer than 24 weeks prior to receive emicizumab. For this reason, individual patients in the control arm will be offered the opportunity to switch to emicizumab after 24 weeks in the study.

3.3.1 Rationale for Emicizumab Dose and Schedule

Emicizumab prophylaxis has been administered subcutaneously in 18 Japanese patients with hemophilia A (with and without FVIII inhibitors) in Study ACE001JP and in its ongoing extension Phase I/II Study ACE002JP. Three dose groups (of 6 patients each) received the following treatment (administration period: 12 weeks):

- A loading dose of 1 mg/kg followed by weekly doses of 0.3 mg/kg
- A loading dose of 3 mg/kg followed by weekly doses of 1 mg/kg
- Weekly doses of 3 mg/kg

Emicizumab was safe and well tolerated in these patients (see Section 1.2 and the RO5543262 [Emicizumab] Investigator's Brochure). The maximum clinical dose of 3 mg/kg/wk is associated with a 10.3-fold and 11.2-fold safety margin based on C_{max} and AUC_{τ} , respectively. No clear difference in the plasma concentrations of emicizumab was observed between adolescents (12–18 years) and adult (aged 19–58 years) patients.

A substantial reduction in bleeding events has been observed with prophylactic emicizumab treatment, especially at doses ≥ 1 mg/kg/wk (see Table 1, based on data cutoff 17 April 2015. See the RO5543262 (Emicizumab) Investigator's Brochure for additional details on clinical studies with emicizumab). ABR decreased in all patients, regardless of age or the presence of FVIII inhibitors.

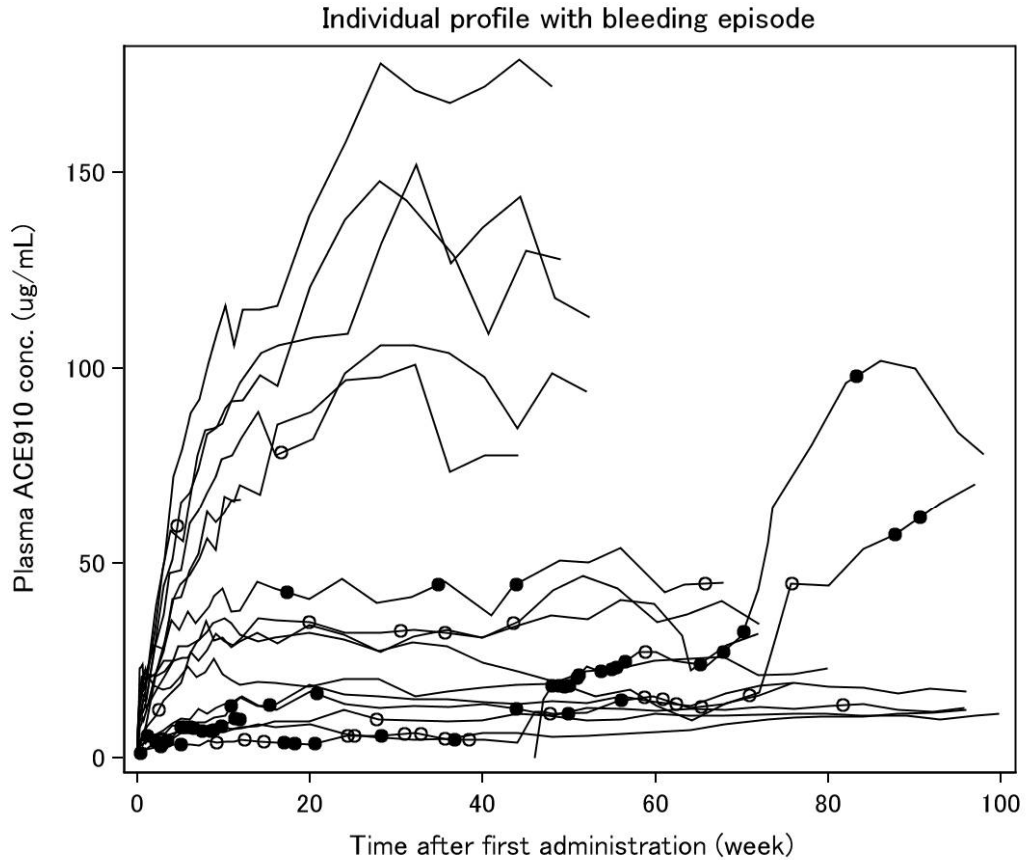
Table 1 Mean Reduction (%) of Annualized Bleeding Rates in Inhibitor and Non-Inhibitor Patients Enrolled in ACE001JP/ACE002JP

Emicizumab Dose	0.3 mg/kg/wk	1 mg/kg/wk	3 mg/kg/wk
ABR reduction	74.5%	95.3%	96.4%

ABR = annualized bleeding rate; wk = week.

A median ABR of 0 was achieved with weekly maintenance doses of 1 and 3 mg/kg. The number of bleeding events decreased with increased emicizumab plasma concentrations (see Figure 2).

Figure 2 Individual Pharmacokinetic Profile with Corresponding Bleeding Event



0.05 ug/mL was assigned if below the lower limit of quantification.
 Filled and open circles represent the predicted values of analyte at the beginning time of each bleeding episode required coagulation factor treatment including and not including joint bleeding, respectively.
 Predicted value was obtained based on linear interpolation between previous and next observed values around the beginning time of each bleeding episode, or last observation carried forward if bleeding episode occurred after the last observed time of analyte included in the analysis.
 Datetime: June 8, 2015 14:59:00

ACE910=emicizumab (also known as RO5534262)

- Joint bleed
- Non-joint bleed

The exposure-response relationship of emicizumab was quantitatively characterized and simulations suggested that a median ABR of 0 is achieved for emicizumab trough plasma $\geq 45 \mu\text{g/mL}$. On the basis of population PK modeling, a median trough plasma concentration of $45 \mu\text{g/mL}$ is predicted to be achieved after one month of treatment with 4 weekly doses of 3 mg/kg and maintained, thereafter, with either weekly doses of 1.5 mg/kg or biweekly doses of 3 mg/kg. The loading doses of 3 mg/kg/wk for 4 weeks were chosen in order to rapidly achieve the effective trough concentration of $45 \mu\text{g/mL}$ without exceeding the maximum dose of 3 mg/kg/wk investigated in the Phase I/II studies. The two maintenance dosing regimens, both predicted to maintain median plasma concentrations above $45 \mu\text{g/mL}$ over the entire dosing interval, will offer flexibility

of dosing frequency to patients. These prophylaxis regimens (i.e., 3 mg/kg/wk for 4 weeks followed by 1.5 mg/kg/wk or 3 mg/kg/2wks) will, therefore, be investigated in this study.

The dose of 6 mg/kg/4wks being evaluated in Phase III studies BH29992 and BO39182 is equivalent, in terms of cumulative dose, to dose levels of 1.5 mg/kg/wk or 3 mg/kg/2wks. Assuming linear PK up to 6 mg/kg, model-based simulations were used to explore whether a dosing regimen every 4 weeks could provide sufficient efficacy. Simulations showed that a once-weekly loading dose of 3 mg/kg for the first 4 weeks, followed by an every 4 week–maintenance dose of 6 mg/kg would provide a steady-state C_{max} and AUC_{τ} of $78.1 \pm 20.9 \mu\text{g/mL}$ and $1570 \pm 447 \text{ day} \cdot \mu\text{g/mL}$, respectively. While more than half of the patients would not be expected to have a trough level of $\geq 45 \mu\text{g/mL}$ at steady state, the simulated ABR distribution was similar to the other planned dosing regimens. This 6 mg/kg/4wks dosing regimen is therefore expected to maintain similar efficacy to the 1.5 mg/kg/wk and 3 mg/kg/2wks dosing regimens and it is being offered to patients as an optional maintenance dosing regimen after implementation of protocol Version 4.

3.3.2 Rationale for Patient Population

As described in Section 3.3, patients with hemophilia A who were treated with episodic FVIII prior to study entry will comprise the primary population for this Phase III study of prophylactic emicizumab compared with no prophylaxis in investigating the efficacy, safety, and PK of emicizumab.

Although the severity of a patient's hemophilia A is directly related to the endogenous FVIII activity, inter-patient variability may exist based on level of physical activity, bleeding history and other features. Therefore, patients previously treated with episodic FVIII will be required to have at least 5 bleeds in the last 24 weeks prior to study entry to be eligible for enrollment in the randomized portion of Study BH30071. This is to select a group of patients with hemophilia A without inhibitors who have a high, unmet medical need and to enable detection of a clinically and statistically significant difference in bleed rates in this population. Similar approaches were previously employed (Manco-Johnson et al. 2013; Mahlangu et al. 2014).

Patients who were treated with prophylactic FVIII prior to enrollment are included in a separate arm in Study BH30071, as combining them with those previously treated with episodic FVIII would introduce significant heterogeneity in baseline bleed rates and goals of care.

3.3.3 Rationale for Control Group

The control group for the primary efficacy endpoint will be a concurrent, no prophylaxis “usual care” arm, to which patients who were on episodic FVIII prior to study entry will be randomized (2:2:1 prophylactic emicizumab 1.5 mg/kg/wk:prophylactic emicizumab 3 mg/kg/2wks:no prophylaxis), which will enable an inter-patient comparison of the

treatment and control groups. All patients, whether assigned to receive prophylactic emicizumab or no prophylaxis, will continue to receive FVIII on an episodic basis for the treatment of breakthrough bleeds during the study. Specific doses of FVIII will not be mandated in the study, but investigators should review with patients the dose to be used to treat breakthrough bleeds. Breakthrough bleeds should be treated with the lowest FVIII dose expected to achieve hemostasis, which may be lower than the patients' prior FVIII dose.

A second comparison will be an individual patient's bleed rate calculated over the 24 weeks prior to study entry, from the medical record and/or Study BH29768. This will enable intra-patient analyses of bleed rates to be performed.

3.3.4 Rationale for the Primary Efficacy Analysis

The objective of the primary efficacy analysis is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis based on the number of bleeds over time (i.e., bleed rate). As mentioned in Section 3.1, the primary analysis will take place at the earliest timepoint when all randomized patients (Arms A, B, and C) and a minimum of 40 patients from Arm D have either completed 24 weeks of treatment or discontinued from the study. This will lead to a range of observation periods from 6–12 months or longer in the prophylactic emicizumab arm and is deemed to be sufficient to reliably assess the effect of prophylactic emicizumab on bleed rate reduction. In the MAD Phase I study involving Japanese patients with hemophilia A (Study ACE001JP), a statistically significant reduction in median ABR to 0 after 12 weeks of treatment (approximately 3 months) in the 1 and 3 mg/kg/wk emicizumab dose cohorts was demonstrated. In the Japanese Phase I/II extension study (Study ACE002JP), the median ABR of the 1 and 3 mg/kg/wk dose cohorts continued to remain zero in patients who continued to receive prophylactic emicizumab after a minimum of 24 weeks, which is consistent with evidence suggesting longer duration of prophylactic therapy is associated with maintenance of ABR reduction (Antunes et al. 2014). Patients in the 1 and 3 mg/kg/week cohorts in Study ACE001JP/Study ACE002JP have been observed for at least 72 and 48 weeks, respectively, except for 1 patient in the 3 mg/kg/week group who has only been followed for 44 weeks at the cutoff of 17 April 2015 (see the RO5543262 [Emicizumab] Investigator's Brochure for additional details on clinical studies with emicizumab).

A recent publication of hemophilia B patients with FIX activity levels $\leq 2\%$ who received episodic therapy showed no distinguishable trend in prospectively collected ABRs over approximately 59 weeks (Shafer et al. 2014), indicating that 24 weeks may be a sufficiently representative follow-up period. As the number of bleeds over time is not expected to differ between patients with hemophilia A or B, it is reasonable to extrapolate this study's findings to the hemophilia A population.

In addition, because this will be a global study with enrollment from different continents occurring approximately over a year, all seasons will be represented in the bleed rate data.

3.3.5 Rationale for Patient-Reported Outcome Assessments

The study design utilizes the electronic capture of HRQoL, health status, satisfaction, preference, and days of work/school missed using a tablet device in the clinic. HRQoL is an important outcome in the care of patients with hemophilia (Brown et al. 2009). HRQoL in hemophilic patients is multifaceted and impacted by disease symptoms (e.g., pain, bleeding), treatment (prophylactic, on demand, side effects), limitations on daily functioning, anxiety/depression, and time spent in hospital.

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

The inclusion of HRQoL measures in the current study will allow for the assessment of the impact of prophylactic treatment with emicizumab in adolescents and adults with hemophilia A and an evaluation of the changes in HRQoL in patients receiving prophylaxis with emicizumab compared with that of patients receiving only episodic treatment for breakthrough bleeds

The study will also include measures designed to capture patient satisfaction and preference with treatment. Patient satisfaction with treatment will be evaluated in order to understand whether satisfaction with hemophilia treatment is different between IV and SC administration of hemophilia treatment. Previous studies have noted that patients express preference for treatments that do not have negative effects (e.g., pain that results from infusions), are not time-consuming, are not associated with high treatment burden, and have a goal of achieving a “normal life” (Cimino et al. 2014). The inclusion of a fit-for-purpose satisfaction measure (SQ-ISHI) prior to and after 24 weeks of treatment with emicizumab in the group of patients previously treated with prophylactic IV FVIII will provide information on whether satisfaction levels differ by route of administration. Additionally, a preference survey after completion of 17 weeks of emicizumab in Arms A, B, or D will provide information on whether SC emicizumab is preferred to IV FVIII administration and explore potential underlying reasons. This assessment will be performed at Week 17 when patients gained sufficient experience with emicizumab and SC injection, while still reliably recall their experience with prior therapy.

3.3.6 Rationale for Biomarker Assessments

Biomarkers to measure the PD effect of emicizumab on hemostasis have not been fully validated to-date and require further testing to determine which assays and technical conditions are most suitable for use with emicizumab treatment. Refer to Section 5.1.4 for more information about effects of emicizumab on existing laboratory assays. Plasma samples will be collected for PD biomarker assessment in parallel with PK samples at all clinic visits to demonstrate evidence of biologic activity of emicizumab in patients. These PD biomarkers include but are not limited to coagulation assays such as aPTT, thrombin generation, and FVIII activity assays. All of these assays were previously shown in the Phase I/II study to exhibit a dose-response relationship to emicizumab concentration (for more information, see the RO5543262 [Emicizumab] Investigator's Brochure). The aPTT assay will be run both in standard form and with a modification to ensure that the assay range covers all levels of emicizumab exposure. In addition, clot waveform analysis may be run as an exploratory PD coagulation assay. Exploratory plasma biomarkers will include FVIII antigen and may include measurement of other coagulation or hemophilia-related factors as well. Serum and plasma will be collected periodically for the assessment of bone and joint health related markers such as procollagen type 1 amino-terminal propeptide (P1NP), C-terminal telopeptide of collagen 1 (CTX-1), osteoprotegerin (OPG), and soluble RANK-L. Finally, residual blood from collected samples may be stored for 5 years and used for additional emicizumab-related research.

3.3.7 Rationale for Activity Assessment

This study provides an opportunity to evaluate whether activity levels of patients treated with emicizumab change over the course of treatment or when compared with patients who continue without prophylaxis. There are two potential approaches to assess activity levels: physical activity questionnaires (PAQs) and actigraphy-based sensors (e.g., accelerometers). PAQs can either be interviewer- or self-administered, and rely on the individual to recall, usually over a 7-day period, the type and duration of moderate or vigorous activities that were performed. Use of these measures in patients with hemophilia, as well as in patients with other diseases, revealed several weaknesses that limit the utility of this approach in the current study. These issues include a tendency for patients to over report their activity level, averaging of activity over the course of the recall period (typically a week), and lack of sufficient resolution to capture modest changes in daily activity. In addition, methodological challenges such as multi-culture validation and test-retest fidelity make these instruments unsuitable to reliably, serially, quantify individuals' activity within the population of interest (Craig et al. 2003; Wolin et al. 2008; Bull et al. 2009; Chinapaw et al. 2009; Garriguet et al. 2015). In contrast, accelerometer-based instruments provide a subject-independent, objective movement count. However, these movement counts only modestly correlate with gold standard global activity assessment such as directly measured activity-related energy expenditure (Van Remoortel et al. 2012; Rabinovich et al. 2013). Weighing these considerations, we will employ an objective assessment using an accelerometer that is

worn on the waist and will focus on DSC as a reliably derived outcome measure with high clinical relevancy (Gironda et al. 2007; Garriguet et al. 2015).

Participants will be instructed to wear the device for 2 weeks at the beginning of the study and for 2 weeks approximately every 6 months subsequently. Intermittent sampling of approximately a week was commonly employed in similar studies that assessed physical activity in patients with chronic diseases (Lavie et al. 1992; Watz et al. 2014; Ahn et al. 2015; Chu et al 2015; Yu et al. 2015). The incremental added value of additional days of data collection (Briscoe et al. 2014) is likely offset by diminishing compliance with a longer observation period. Due to logistical considerations, baseline activity will be captured during the first 2 weeks after enrollment rather than prior to starting treatment. Although patients will have started emicizumab, its level will be below steady state, and the relatively short duration on emicizumab at this time is unlikely to inspire a change in activity habits. Therefore, activity during Weeks 1 and 2 is expected to be similar to pre-study activity, and a change, if any, from pre-enrollment will likely only underestimate the effect of emicizumab rather than overestimate it. The alternative approach of delaying initiation of therapy to allow measurement of baseline DSC may be unacceptable to many patients and investigators.

The purpose of this activity assessment in this study is to evaluate the effects of emicizumab treatment on patients' DSC as measured by a waist-worn ActiGraph (a medical device used to continuously monitor and measure activity through a triaxial accelerometer) in patients with hemophilia A. The data collected by the study device will be scored to identify active and rest periods for each patient within each 24-hour period. This device continuously captures frequency, duration, and intensity of acceleration and through a proprietary algorithm converts the pattern of motion into step counts and activity counts (a value used to quantify both intensity and duration of physical activity). Although steps are not counted directly, the number of steps for each individual can be reliably derived from data obtained by a waist-worn device (Gironda et al. 2007; Garriguet et al. 2015). In general, the available technology is well suited to accurately capture DSC (Case et al. 2015), supporting its use in this study.

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population will be patients with hemophilia A without FVIII inhibitors who have been treated with FVIII agents to control or prevent bleeds.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by the patient or a legal guardian
- Able to comply with the study protocol, in the investigator's judgment

- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of patient-reported outcome questionnaires and bleed and medication diary through the use of an electronic device
- Aged 12 years or older at the time of informed consent
- Body weight ≥ 40 kg at the time of screening
- Diagnosis of severe congenital hemophilia A (intrinsic FVIII level $< 1\%$)
- A negative test for inhibitor (i.e., < 0.6 BU) within 8 weeks of enrollment
- No documented inhibitor (i.e., < 0.6 BU), FVIII half-life < 6 hours, or FVIII recovery $< 66\%$ in the last 5 years
- Patients who completed successful immune tolerance induction (ITI) at least 5 years before screening are eligible, provided they have had no evidence of inhibitor recurrence (permanent or temporary) as may be indicated by detection of an inhibitor, FVIII half-life < 6 hours, or FVIII recovery $< 66\%$ since completing ITI (Antun et al. 2015).
- Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks
- For patients on no prophylaxis (episodic treatment) pre-study, ≥ 5 bleeds in the last 24 weeks prior to study entry
- Patients who were on FVIII prophylaxis for at least the last 24 weeks, can be enrolled regardless of the number of bleeds during this period. Eligibility will be based on investigator's attestation of adequate prophylaxis regimen.
- At least 40 patients who were on FVIII prophylaxis pre-enrollment will have been enrolled for a minimum of 24 weeks in Study BH29768 (non-interventional)
- Adequate hematologic function, defined as platelet count $\geq 100,000/\mu\text{L}$ and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN) (excluding Gilbert's syndrome) and both AST and ALT $\leq 3 \times$ ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine $\leq 2.5 \times$ ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year and are approved by local health authorities and ethics committees during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug.

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

Examples of highly effective contraceptive methods with a failure rate of < 1% per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices.

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

4.1.2 Exclusion Criteria

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

- Inherited or acquired bleeding disorder other than hemophilia A
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may increase risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known HIV infection with CD4 count < 200 cells/ μ L within 24 weeks prior to screening. Patients with HIV infection who has CD4 > 200 and meet all other criteria are eligible.
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment.
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of:
 - Emicizumab in a prior investigational study
 - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration
 - A non-hemophilia-related investigational drug concurrently, within last 30 days or 5 half-lives, whichever is shorter

- Inability to comply with the study protocol in the opinion of the investigator
- Pregnant or lactating, or intending to become pregnant during the study
- Women who are not postmenopausal (≥ 48 weeks of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

4.2 METHOD OF TREATMENT ASSIGNMENT

Patients who received episodic treatment with FVIII prior to study entry will be randomized in a 2:2:1 ratio to receive either prophylactic emicizumab at 3 mg/kg/wk subcutaneously for 4 weeks, followed by 1.5 mg/kg/wk (Arm A) or 3 mg/kg/2wks (Arm B) subcutaneously, or to the control arm (no prophylaxis; Arm C). The time between screening and enrollment of eligible patients should be ≤ 6 weeks; otherwise, patients must be re-screened to determine if they continue to meet the inclusion and exclusion criteria. A central randomization procedure will be used for all patients who fulfill the entry criteria at screening. A block-based randomization method will be used, stratified by the number of bleeds in the last 24 weeks (< 9 or ≥ 9). The proposed randomization method is designed to balance treatment group assignment within the prognostic stratification factor.

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

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Emicizumab

Emicizumab Drug Product will be supplied by the Sponsor as a sterile liquid for SC injection, contains no preservatives, and requires storage at 2–8° C (do not freeze and protect from light). Each single-use vial contains 150 mg (nominal) of emicizumab at pH 6.0. The Drug Product is formulated as 150 mg/mL emicizumab in 150 mmol/L arginine, 0.5 mg/mL poloxamer 188, 20 mmol/L histidine–aspartic acid buffer (pH 6.0). For information on the formulation and handling of emicizumab, see the Investigator's Brochure. In order to minimize the number of injections for patients in certain weight categories, the administration per single injection of up to 2 mL drug product solution will be permitted. This will require pooling of emicizumab drug product solution from up to two 1-mL vials into a single syringe, using a new transfer needle for each vial. The detailed procedure for vial pooling is described in the Instructions for Use (IFU).

4.3.2 Dosage, Dose Adjustment, and Administration

As discussed in Section 3.3.1, when each patient starts on prophylactic emicizumab, he or she will receive 3 mg/kg/wk for 4 weeks as loading doses, followed by 1.5 mg/kg/wk or 3 mg/kg/2wks, for a total of at least 24 weeks and as long as they continue to derive sufficient clinical benefit.

Patients in Arms A or B with ≥ 2 qualifying bleeds within 24 weeks, may have the opportunity to increase their emicizumab maintenance dose to 3 mg/kg/wk starting on Week 25, if they receive approval from the Medical Monitor. Qualifying bleeds are defined as spontaneous, verified by investigator (e.g., by imaging or physical examination) and occurring while on prophylactic emicizumab at steady-state on the maintenance dose (after the Week 5 visit). Similarly, patients in Arm C who switch to emicizumab at Week 25 and experience ≥ 2 qualifying bleeds may have the opportunity to increase their emicizumab maintenance dose to 3 mg/kg/wk starting on Week 49, if they receive approval from the Medical Monitor.

Patients in Arm D who experience suboptimal control (two qualifying bleeds or more) on prophylactic emicizumab at the maintenance dose may have the opportunity to escalate to 3 mg/kg/wk immediately after the second qualifying bleed, with approval from the Medical Monitor.

If the investigator believes that a specific patient warrants dose escalation based on a different reason, they may discuss the case with the Medical Monitor for consideration and potential approval.

During study prolongation, each patient may choose a preferred emicizumab dosing regimen among those permitted (i.e., emicizumab 1.5 mg/kg/wk, 3 mg/kg/2wks, or 6 mg/kg/4wks) and continue on that dosing regimen until discontinuation from the study. A change from 1.5 mg/kg/wk to 3 mg/kg/2wks or 6 mg/kg/4wks can be initiated at the next scheduled treatment of the QW dosing regimen. A change from 3 mg/kg/2wks to 1.5 mg/kg/wk or 6 mg/kg/4wks can be initiated at the next scheduled treatment of the Q2W dosing regimen. A patient may switch dosing regimens only once. However, if the investigator believes that a patient warrants an additional change in dosing regimen, he or she may discuss the case with the Medical Monitor for consideration and potential approval.

If a patient has a systemic hypersensitivity reaction or severe adverse reaction that may be attributable to emicizumab, subsequent doses should be held until the situation is discussed with the Medical Monitor and approval to resume dosing is given. Should certain, unanticipated events occur during the study that require treatment with multiple daily administrations of FVIII concentrates, such as non-elective surgery or severe/life-threatening bleeds, the investigator should contact the Medical Monitor immediately to discuss such cases and the management of future emicizumab doses. Due to emicizumab's unique mechanism of action and the characteristics of its binding to FIX and FX, co-administration of FVIII and emicizumab is believed to be safe and in general should be continued on schedule. However, an individualized decision should be made in consultation with the Medical Monitor. Any other emicizumab dose adjustment request will require discussion of the clinical case with and approval from the Medical Monitor.

Study site HCPs will be trained on how to properly prepare the study medication and administer the correct calculated dose subcutaneously as described in the IFU document. Patients will in turn be trained on study medication preparation and self-administration by an HCP using the IFU as support. In the event that a caregiver will ultimately administer study drug to the patient in the home setting, the caregiver is to be trained. The HCP is to inform the patient/caregiver of the volumetric dose to be administered and dosing frequency.

Details on the devices to be used for study medication withdrawal from vial and SC injection are provided in the Pharmacy Manual.

Elicizumab will be administered as a SC injection in the home setting, with one dose every week or every 2 weeks, 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 as described in Section 5.1.2.2 should be considered. The fourth and fifth scheduled study drug administrations must also be performed in the monitored setting. At that time, the patient/caregiver will also have the opportunity to ask any questions to the HCP before the scheduled start of home administration. The patient/caregiver will observe at least one SC injection performed by the HCP and successfully administer at least one SC injection while being observed by a 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, arrangements may be made to identify an alternative trained caregiver or HCP to administer the SC injections. At the investigator's discretion, study drug may be administered by a trained home nursing professional at the patient's home or another suitable location.

Patients/caregivers will be provided with the clinic contact information, to use in case they have questions related to self-administration between visits.

Medication administration errors during training will be recorded and competence of the patient or caregiver to administer at home will be documented in the electronic Case Report Form (eCRF). If necessary, patients or their HCP may choose to continue administration of study drug in the clinic. Compliance in the home setting is to be monitored by recording emicizumab administration on the handheld device and recording collected used and unused vials at each site visit.

Patients shall administer study medication on the schedule dosing days. On days when trough plasma samples are to be collected, patients will be dosed after samples are drawn, potentially at the clinic (self-administration). On the other days, for patients on once weekly dosing, if the patient forgets or cannot administer study medication on the

scheduled dosing day, study medication should be administered as soon as possible within a window of 3 days from the scheduled dosing date. If more than 3 days has passed, the missed dose should be skipped and the patient should take his or her next dose at the next scheduled time with the study medication dosing resumed in accordance to the original dosing schedule. For patients on once every 2 weeks dosing, if the patient forgets or cannot administer study medication on the scheduled dosing day, study medication should be administered as soon as possible within a window of 7 days from the scheduled dosing date. If more than 7 days has passed, the patient should take his or her next dose at the next scheduled time with the study medication dosing resumed in accordance with the original dosing schedule. All emicizumab dosing should be clearly documented on the handheld device, both during patient's visits in clinic and when the patient is out of the clinic.

Any overdose or incorrect administration of study drug will be determined from emicizumab data entered into the handheld device. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Patients and/or the caregiver will be provided with alert cards, which they will be requested to carry at all times. These will include guidance on recognizing signs/symptoms of thromboembolic events or allergic/anaphylactic/anaphylactoid reactions and how to obtain emergency care. In addition, alert cards are designed to notify non-study HCPs that emicizumab will interfere with certain coagulation laboratory tests (see the RO5543262 [Emicizumab] Investigator's Brochure for more information) and the investigator should be contacted for assistance in interpreting the test results.

Guidelines for dosage modification are discussed in Section 3.1, and those for treatment interruption or discontinuation are provided in Section 4.6.

4.3.3 Investigational Medicinal Product Accountability

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

Used and unused IMP vials will be returned by study patients to the study site and appropriately accounted for. Used vials will then be disposed of at the study site according to the study site's institutional standard operating procedure. Instructions regarding how to handle unused vials should be obtained from the Sponsor. If the investigator prefers to destroy the IMP at his or her site, the site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Post-Study Access to Emicizumab

The Sponsor will offer post-study access to the study drug (emicizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and the treating physician comply with and satisfy any legal or regulatory requirements that apply to them

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

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

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

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

4.4 CONCOMITANT AND RESCUE THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/discontinuation visit. In addition, use of long-acting medications taken infrequently (e.g., zoledronic acid, Denosumab) will be recorded as well. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

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

- To avoid bleeds before adequate emicizumab level is reached, patients in Arm D will continue their regular FVIII prophylaxis until the second emicizumab loading dose. Concomitant routine FVIII prophylaxis is not permissible otherwise during the study.
- Drugs intended to treat bleeds on an episodic basis, including FVIII. Specific dosages of FVIII will not be mandated in the study; however, investigators should consider that circulating emicizumab may increase patients' coagulation potential. Investigators should review with patients the dose to be used to treat breakthrough bleeds. Breakthrough bleeds should be treated with the lowest FVIII dose expected to achieve hemostasis, which may be lower than the patients' prior FVIII dose. For information on the formulation, packaging, and handling of agents, see the local prescribing information for the marketed drug in question.
- The use of bypassing agents is unexpected in hemophilia A patients without inhibitors. In the interest of completeness, [Appendix 9](#) includes dosing and monitoring guidance for the use of bypassing agents for patients in Study BH30071, in case such unforeseen circumstances occur.
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to result in systemic exposure

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 4 weeks prior to initiation of study treatment:

- Drugs that would affect hemostasis (e.g., aspirin, non-steroidal anti-inflammatory drugs that are not selective or preferential COX-2 inhibitors, or anticoagulants [other than to flush, dwell, or de-clot a venous access device])

Drugs intended to control bleeding episodes or used in the context of minor surgery (e.g., tooth extraction) or injuries (e.g., concussion) to prevent deterioration or given if deemed medically necessary for management of certain conditions (e.g., post cardiac surgery) are permitted.

- Use of systemic immunomodulators (e.g., interferon) other than anti-retroviral therapy
- Elective surgery (excluding minor procedures such as tooth extraction, CVAD removal, or incision and drainage as well as emergency surgeries)
- Use of other investigational drugs

Use of concomitant prophylactic regimen is prohibited during the study, except for patients on Arm D who will continue FVIII prophylaxis until the Week 2 dose. (Short-term prophylaxis [e.g., around the time of surgery], however, is permitted.)

If prohibited therapy is administered for any reason, it should be recorded on the eCRF (except any hemophilia-related medication, which will be recorded on the Bleed/Medication Questionnaire). If prohibited treatment is prescribed or considered

medically necessary, the medical monitor should be consulted to discuss any changes in the benefit/risk and determine whether the patient should continue on the study.

4.5 STUDY ASSESSMENTS

See [Appendix 1](#) for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Patients who elect not to sign the optional activity monitoring portion of the Informed Consent Form will continue to undertake the screening tests or evaluations for Study BH30071. Informed Consent Forms for enrolled patients and for patients who are not enrolled will be maintained at the study site. Parents or legally authorized representative of adolescents will complete an Informed Consent Form and adolescents will complete an Informed Assent Form.

All screening evaluations must be completed within 6 weeks prior to the first dose and reviewed to confirm that patients meet all eligibility criteria before enrollment and randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, procedures, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of FVIII inhibitor, anaphylaxis or known thrombophilia. It should also include all medication taken in the 4 weeks prior to screening (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies) or in the 24 weeks prior to screening for medications intended to treat osteopenia or osteoporosis. If imaging tests of bone health (e.g., densitometry, dual energy X-ray absorptiometry [DEXA]) were performed in the year prior to screening, the results should be recorded. Finally, number of bleeds during the 24 weeks prior to study enrollment should be documented, as well as the number of school/work days missed and number of days hospitalized during the 24 weeks prior to study entry.

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

4.5.3 Physical Examinations

A complete physical examination should include but not necessarily be limited to the evaluation of head, eye, ear, nose, and throat and include cardiovascular, dermatological, musculoskeletal (including HJHS; see [Appendix 8](#)), respiratory, gastrointestinal, and neurological systems, height, and weight. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF. Subsequently, a targeted (i.e., musculoskeletal,

dermatological) and/or symptom-driven examination should be conducted as noted in the schedule of assessments or as clinically indicated. New or worsened abnormalities from screening should be recorded as adverse events. A complete physical examination will be performed at screening and at least targeted physical examinations will be performed at subsequent visits.

4.5.4 Vital Signs

Vital signs will include measurement of heart and respiratory rate, temperature, systolic and diastolic blood pressure, and weight and should be recorded before study drug administration. Frequency of vital sign assessments should follow the schedule of assessments but may also be taken anytime as unscheduled assessments as judged by the investigator.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Local laboratory assessments will be performed as indicated on the schedule of assessments. When study drug administration is scheduled on days of clinic visit, laboratory samples should be drawn before the administration of study drug. Laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width)
- Serum chemistries, (sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid).
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and within 7 days prior to initiation of study medication, if applicable.

Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

The following samples will be sent to the Sponsor or a designee for centralized analysis:

- Plasma samples for PK analysis
- Plasma samples for immunogenicity assessment (ADA)
- Serum and plasma for PD and exploratory PD biomarker assessments (aPTT, PT, FVIII activity, and others as listed in [Appendix 2](#))
- Plasma samples for anti-FVIII antibody measurement (inhibitor titer) will be sent to the Sponsor throughout the study, with the exception of the test needed at screening for patients who do not have a documented negative inhibitor test (<0.6 BU) within 8 weeks prior to enrollment.

4.5.6 Electrocardiograms

ECG recordings will be obtained at study sites at specified timepoints, as outlined in the schedule of assessments (see [Appendix 1](#)).

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The following parameters will be obtained: QT, RR, HR, QTcB, QTcF, PR and QRS and T- and U-wave morphology. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and ideally should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

Any ECG changes that are deemed clinically significant by the investigator (e.g., associated with symptoms or lead to a change in study treatment or concomitant treatment, or discontinuation from study treatment), must be reported as an adverse event on the adverse event eCRF. The investigator or designee must review, sign, and date all ECG tracings. The ECG may be repeated if investigator deems it appropriate. Paper copies will be kept as part of the patient's permanent study file at the site.

4.5.7 Electronic Patient-Reported Outcomes

Patient reported data will be collected electronically using two devices: a personal handheld mobile device for the Bleed/Medication Questionnaire and a tablet at study sites for HRQoL questionnaires. To capture bleed data, emicizumab use, and other hemophilia medication use during study treatment, patients will complete the Bleed/Medication Questionnaire on a handheld device that will be provided to them during the Week 1 visit at the study site. This device will remain with the patient for the duration of the study to enter bleed and medication data weekly at a minimum. Patients who withdraw from emicizumab treatment will continue to record bleeds and hemophilia medication administration until they complete the safety follow-up visit. In addition, at specified visits, patients will complete HRQoL, health status, and satisfaction/preference questionnaires on a tablet device that will remain at study sites. The instructions for completing the patient-reported outcome (PRO) questionnaires electronically will be provided by the investigator staff during the Week 1 visit at the site. The data will be transmitted automatically after entry to a centralized secure database at the vendor. Of note, if the electronic data collection system becomes unavailable, the Sponsor may instruct sites to collect PRO data (bleed data, emicizumab use, hemophilia medication use, and HRQoL) on paper.

HRQoL:

The Haem-A-QoL and the Haemo-QoL-SF will be used to measure HRQoL in adults and adolescents, respectively (see [Appendix 3](#) and [Appendix 4](#)). The Haem-A-QoL was designed for adult patients with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, feelings, view, sport and leisure time, work and school, dealing, treatment, future, family planning, and relationships/partners) and a scale representing total score. Items are rated along 5 response options, although for some items there is also a 'not applicable' option (von Mackensen and Gringeri 2005; 2010).

The Haemo-QoL has been developed in a series of age-related questionnaires to measure HRQoL in children and adolescents with hemophilia (Bullinger et al. 2002; von Mackensen and Bullinger 2004; Pollak et al. 2006). These versions include a 77-item long form, a 35-item as well as a 16-item short form, and an 8-item index form. The short version for older children containing 35 items was selected for this study. This version covers nine dimensions considered relevant for the children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia and treatment). Items are rated with five respective response options: never, seldom, sometimes, often, and always. Higher scores for both HRQoL measures are indicative of poorer HRQoL.

Health Status:

The EQ-5D-5L (see [Appendix 5](#)) is a generic, preference-based health utility measure that assesses health status and is used to inform pharmacoeconomic evaluations. The EQ-5D-5L consists of two parts. The first part, health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al. 2011; Janssen et al. 2013). Published weights are available that allow for the creation of a single summary score. Overall scores typically range from 0 to 1, although a score below 0 is theoretically possible representing a state worse than death, with low scores representing a higher level of dysfunction. The second part is a 0 to 100-point visual analog scale (VAS) that assesses current health status; higher scores are reflective of better health.

Patient Preference and Satisfaction:

Patient preference and satisfaction will be assessed through two measures. Preference for emicizumab treatment will be assessed through the Preference Survey, which asks patients to report which treatment they would prefer to continue to receive after having been treated with IV FVIII (episodic or prophylaxis) and SC emicizumab. Patients who express a preference are then asked to identify which reasons may have influenced their decision and indicate the top three reasons for their choice. Patients in Arms A, B, or D will complete the Patient Preference Survey at Week 17 on emicizumab. In addition, understanding the preference and satisfaction of patients who were previously on FVIII prophylaxis is of particular interest. Patients in Arm D will complete the Patient Satisfaction questionnaire, SQ-ISHI, at baseline and at the Week 21 or 25 visit. This 13-item measure was designed to assess satisfaction with SC emicizumab or with IV

FVIII prophylaxis by probing the general concepts of discomfort, worry, and difficulty with injections; confidence with treatment; duration, and frequency of treatment; ease of treatment; impact on daily activities; adherence; and overall satisfaction.

Missed Days of School or Work

Patients will also be asked to document the number of days of school or work missed in the previous 4 weeks at the timepoints outlined in the schedule of assessments (see [Appendix 1](#)).

4.5.8 Definitions

DEFINITION OF A BLEED

For the purposes of the efficacy analyses, a standardized definition of bleed, adapted from criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Hemostasis, and similar to that used in a recent clinical study, will also be utilized in this study (Blanchette et al. 2014; Mahlangu et al. 2014).

An event is considered a treated bleed if coagulation factors are administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.).

- Bleeds starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections are ≤ 72 hours apart, are considered the same bleed.
- Any injection to treat the bleed, taken > 72 hours after the preceding injection, is considered the first injection to treat a new bleed at the same location.
- Any bleed at a different location is considered a separate bleed regardless of time from last injection.

An additional definition of all bleeds (i.e., both treated and not treated with coagulation factors) will be applied for certain secondary efficacy analyses.

DEFINITIONS OF BLEED SITES

- Target joints: defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of ≥ 3 bleeds into the same joint over the last 24 weeks prior to study entry)
- Joint bleeds (sites per the Bleed/Medication Questionnaire)
- Muscle bleeds (sites as per the Bleed/Medication Questionnaire)
- Other bleeds (sites as per the Bleed/Medication Questionnaire)

DEFINITIONS OF BLEED TYPES

In addition, the assessment of a bleed will be separated into spontaneous bleeds, traumatic bleeds, and bleeds related to procedure/surgery. Both spontaneous bleeds (i.e., the occurrence of hemorrhage where neither the patient nor a caregiver can identify a reason) and traumatic bleeds (i.e., hemorrhage occurring secondary to an event such as trauma, “strenuous” activity, or “overuse”) will be collected.

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

Patients (or patient’s legally authorized representative) will complete an electronic Bleed/Medication Questionnaire whenever a bleed occurs, or at least weekly to confirm all bleeds have been recorded. For each bleeding episode, they will provide information on the above topics as well as on the medication used to treat the bleed. Hemophilia medications that were taken will also be collected through the Bleed/Medication Questionnaire.

4.5.9 Activity Assessments

Patients who chose to participate in this part of the study should wear the study device while awake every day during three 2-week periods in the study: Weeks 1–2, Weeks 23–24, and Weeks 47–48. Patients will be instructed to wear the accelerometer on an elastic belt (supplied with the device) at the natural waistline on the right hip in line with the right axilla upon arising in the morning and continuously until retiring at night for 14 consecutive days. Patients will be instructed to charge the device weekly. A valid day of monitoring is defined as 10 or more wear hours per day. Wear time will be determined by subtracting non-wear time from 24 hours. Non-wear is defined by an

interval of at least 60 consecutive minutes of zero activity intensity counts, with allowance for 1–2 minutes of counts between 0 and 100. To provide reliable estimates, analyses will be restricted to participants with at least 8 valid days of accelerometer monitoring during each observation period (Troiano et al. 2008; Ahn et al. 2015).

The data will be collected using the study device to provide daily measures of DSC: DSC, mean activity (counts [cts]/min), peak activity (the largest activity value [cts/min]), and total activity counts (total cts/min over a 24-hour period) recorded each day. Mean daily activity is the average of the activity counts among all epochs (e.g., 1-minute period) that falls within the active periods during a 24-hour period.

An activity count is a measure of the acceleration that is measured by the device. The device measures acceleration as the sum of the maximum acceleration values each second during the epoch (acceleration is sampled 30 times/second). While DSC will be referenced as the primary physical activity measurement, it should be noted that activity counts (total, mean, and peak) do provide a secondary alternative for measuring physical activity relevant to the magnitude of energy expended by the subject. While DSC might provide more reliable correlation data, activity counts can help identify the possibility of increased activity intensity in the event that DSC remains relatively unchanged over time.

The number of hours the device was worn each day will also be derived from the activity counts data.

Patients will return their devices to the respective site at Weeks 3, 25, and 49 in order for the site to transfer the data from the device to the database.

4.5.10 Samples for Roche Clinical Repository

4.5.10.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (see Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers related to emicizumab, hemophilia A, or other coagulation disorders:

- Blood for DNA extraction (at Week 2, 3, 4, or 5)

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the central laboratory services manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.10.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, the blood sample is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other

reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.10.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient or patient guardian the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.10.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. *After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RCR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data.* If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if

the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. A patient's withdrawal from Study BH30071 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study BH30071.

4.5.10.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

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

Patients may elect to withdraw from the activity monitoring but continue participation in the remainder of the study. If a patient decides to withdraw only from the activity monitoring prematurely, the patient will continue treatment and follow-up as per the study protocol. The primary reason for withdrawal from activity monitoring should be documented on the appropriate eCRF. Patients who withdraw from this part of the study will not be replaced.

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

4.6.2 Study Treatment Discontinuation

Patients must stop study treatment if they experience the following:

- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced. Patients who become pregnant should immediately stop treatment and be managed as per local guidelines.

If the patient discontinues study treatment, bleed and bleed medication data should be provided by the patient via the electronic, handheld device until the safety follow-up visit (24 weeks after last study drug administration).

4.6.3 Study and Site Discontinuation

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

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

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Emicizumab is not approved and is currently in clinical development. Thus, the complete safety profile is not known at this time. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

5.1.1 Patient Selection

The inclusion and exclusion criteria in this study are designed to select patients who are not at increased risk based on the current understanding of the investigational medication. See Section 4.1.1 and Section 4.1.2 for full inclusion and exclusion criteria, respectively.

5.1.2 Risks Associated with Emicizumab

5.1.2.1 Injection-Site Reactions

In the completed and ongoing Japanese studies, injection-site reactions have been observed in some patients with hemophilia A. These local injection-site reactions included injection-site erythema, injection-site hematoma, injection-site rash, injection-site discomfort, injection-site pain, and injection-site pruritus. All local injection-site reactions were of mild intensity. Further details of the observed injection-site reactions are available in the RO5543262 (Emicizumab) Investigator's Brochure.

Directions for emicizumab administration should be followed, as outlined in Section 3.3.1, Section 4.3.2, and in the IFU.

5.1.2.2 Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction

Since emicizumab is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions, may occur. In completed and ongoing clinical studies of emicizumab, no severe hypersensitivity reactions have been reported. These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3.

HCPs administering the study medication in the clinic must be trained in the appropriate administration procedures, be able to recognize the signs and symptoms associated with potential hypersensitivity, anaphylactic, and anaphylactoid reactions, and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; see [Appendix 7](#) and [Appendix 10](#)). HCPs should also instruct patients how to recognize the signs and symptoms of hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an HCP or seek emergency care in case of any such occurrence. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should any of these reactions occur.

For patients with a previous history of a clinically significant hypersensitivity reaction, after each of the first three doses, the site will call the patient 24 hours after each dose to assess the status of the patient. Additional precautions following each of these doses may also be considered including having an extended observation period or IV access prior to dosing, etc. The investigator may include these or other precautions, as deemed appropriate.

5.1.2.3 Hypercoagulation and Thromboembolic Events

As of May 2019, four thromboembolic events have been observed in 4 patients receiving emicizumab, as follows. One event of Grade 1 device occlusion (non-serious) was reported in 1 patient (Study BH29884). The event resolved and was assessed by the investigator as not related to emicizumab. Also in Study BH29884, 2 patients experienced a total of two serious thromboembolic adverse events (thrombophlebitis superficial and cavernous sinus thrombosis). In Study MO391291, 1 patient experienced a serious adverse event of acute myocardial infarction. Details of the serious adverse events are described below.

The first patient from Study BH29884 experienced a right knee hemarthrosis and self-administered >200 units/kg/day of aPCC for 2 consecutive days. The patient was hospitalized after a diagnosis (by MRI) of Grade 3 cavernous sinus thrombosis. No anticoagulation was administered; treatment with emicizumab was withheld. The patient was discharged after symptoms improved with supportive care. A follow-up MRI was normal with no evidence of thrombus, and the event was considered resolved. Treatment with emicizumab was restarted. The investigator assessed the event as being related to emicizumab and aPCC.

The second patient from Study BH29884 experienced a spontaneous right knee hemarthrosis and self-administered 100 units/kg/day aPCC for 2 consecutive days. The patient [REDACTED] his right shin for several hours to treat pain. Extensive skin necrosis of the right shin and locally limited skin necrosis of the left shin subsequently developed. The patient was hospitalized and an ultrasound indicated superficial thrombosis of the right saphenous vein (no evidence of deep vein or arterial thrombosis). The patient was treated with supportive care and his condition improved. Emicizumab was permanently discontinued. The investigator assessed the skin necrosis as due to the thromboembolic event and related it to emicizumab and aPCC. Both skin necrosis (Grade 3) and thrombophlebitis superficial (Grade 2) were reported as recovering.

The third patient, enrolled in Study MO39129, presented with chest pain, sweating, and pallor and was diagnosed with ST-elevation myocardial infarction on Day 235 of the study. ECG showed ST elevation, right bundle branch block, and inferior Q waves. Troponin was 0.46 ng/ml (reference range: <0.04 ng/ml). Coronarography demonstrated stenosis of the right coronary artery due to thrombotic subocclusion. Treatment included stent, unfractionated heparin, clopidogrel, and aspirin. The event resolved after 5 days and treatment with emicizumab was maintained.

Hypercoagulation and thromboembolic events should be reported as serious adverse events or adverse events of special interest as described in Sections 5.2.2 and 5.2.3. HCPs should educate patients/caregivers to recognize signs and symptoms of potential thromboembolism (i.e., dyspnea, chest pain, leg pain or swelling; or if in the head, headache, numbness in the face, eye pain or swelling, or vision impairment) and ensure that they understand the importance of seeking appropriate medical attention.

Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should thromboembolism be suspected.

5.1.2.4 Thrombotic Microangiopathy

Thrombotic microangiopathy is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, or central nervous system, etc. As of *May 2019*, 3 cases of TMA were observed in a Phase III clinical study involving patients with hemophilia A with inhibitors while receiving emicizumab. The first patient self-administered 2 doses of aPCC 94 units/kg in 2 days to treat his left knee hemarthrosis. The next day, he started experiencing icterus and severe back pain and the patient self-administered 2 doses of rFVIIa 85 µg/kg and 2 doses of aPCC 94 units/kg. Then, the patient presented with thrombocytopenia, hyperbilirubinemia, and acute renal failure with schistocytes on peripheral blood smears. The patient was diagnosed with aHUS and treated with plasmapheresis, hemodialysis, and supportive care and his condition improved and resolved after 15 days. The patient discontinued treatment with emicizumab. The second patient self-administered 5 doses of aPCC 74 units/kg over 3 consecutive days before the serious adverse event onset. The patient had abdominal pain and emesis, acute renal failure, thrombocytopenia, elevated LDH, and a low haptoglobin with schistocytes on peripheral blood smears. The patient was diagnosed with aHUS and recovered without plasmapheresis or hemodialysis after 9 days. The patient restarted treatment with emicizumab approximately 10 days after resolution of the serious adverse event.

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

TMA events should be reported as serious adverse events or adverse events of special interest (see Sections 5.2.2 and 5.2.3).

5.1.2.5 ***Life-Threatening Bleeding Due to Unreliable Standard Coagulation Tests and Inhibitor Assays Associated with Emicizumab***

Coagulation laboratory tests (including, but not limited to, aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by Bethesda assay) are not reliable and do not accurately reflect the patient's underlying hemostatic status while receiving emicizumab prophylaxis (see Section 5.1.4). Due to the long $t_{1/2}$ of emicizumab, these effects on coagulation assays may persist for up to 6 months after the last dose.

Practitioners, especially emergency care practitioners, should note that life-threatening bleeding caused by unreliable standard coagulation tests and inhibitor assays poses a risk for patients receiving emicizumab treatment.

Emicizumab's mechanism of action and resulting interference was clearly demonstrated in a wide variety of coagulation laboratory tests approved for in vitro diagnostic use. Clinical trials also demonstrated the effects of emicizumab on laboratory tests. However, as of May 2019, no instances of under-treatment of bleeding events due to unreliable standard coagulation tests and inhibitor assays during and after emicizumab treatment were observed.

5.1.3 Management of Specific Adverse Events

Table 2 Guidelines for Monitoring and Management of Specific Adverse Events

Event	Actions to Be Taken
Injection-Site Reaction	<ul style="list-style-type: none"> • Injection-site reactions should be treated as clinically indicated. • Emicizumab should not be injected into areas where the skin is red, bruised, tender, or hard or into areas where there are moles or scars. • In the clinic setting, patients will be monitored for signs of injection-site reactions in the period immediately following injections. Patients will be given guidance on reporting injection-site reactions when administering drug at home or after they leave the clinic.
Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction	<ul style="list-style-type: none"> • Suspected cases should be fully evaluated and treated as clinically indicated. • Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) and resuscitation equipment must be available for immediate use during the initial administrations in the infusion center, clinic, or hospital. • If a patient has symptoms of anaphylaxis or severe hypersensitivity, administration of study drug must be immediately stopped and treatment of the reaction be initiated. • The investigator should contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk to determine if and when the patient should resume taking emicizumab and discuss the patient's continued study participation. If patient continues in the study, the next two scheduled doses must be in a monitored setting with at least a 60-minute observation period and resuscitation treatment immediately available. After each of these two doses in the clinic, the site will call the patient 24 hours after each dose to assess status of the patient. • Investigators may order any pertinent laboratory tests, including an unscheduled anti-drug antibody, in the event any of these reactions occur.
Hypercoagulation and Thromboembolic Events	<ul style="list-style-type: none"> • Please see Sections 3.1 and 3.3.3 for guidance on management of breakthrough bleeds. • HCPs should be vigilant for patients who exhibit signs/symptoms consistent with thromboembolic events and immediately begin work-up and treatment, as per local guidelines. • If a patient has a thromboembolic event, further administration of study drug should be interrupted. Decision to resume emicizumab after a thromboembolic event must be discussed with and approved by the Medical Monitor.

HCP = healthcare provider; TMA = thrombotic microangiopathy.

Table 2 Guidelines for Monitoring and Management of Specific Adverse Events (cont.)

Event	Actions to Be Taken
Thrombotic microangiopathy	<ul style="list-style-type: none"> • Please see Sections 3.1 and 3.3.3 for guidance on management of breakthrough bleeds. • HCPs should be vigilant for patients who exhibit signs/symptoms consistent with TMA and immediately begin work-up and treatment, as per local guidelines. • If a patient has a TMA event, further administration of study drug should be interrupted. Decision to resume emicizumab after an event of TMA must be discussed with and approved by the Medical Monitor.
Coagulation Disorder and Risk of Bleeding	<ul style="list-style-type: none"> • HCPs should be vigilant for abnormal or unusual bleeding tendencies. Coagulation tests or other work-up may be indicated if judged to be appropriate by the investigator. If bleeding is observed, appropriate action as per local guidelines must be taken immediately.

HCP = healthcare provider; TMA = thrombotic microangiopathy.

5.1.4 Interpretation of Coagulation Assays for Patients Receiving Emicizumab

Emicizumab interacts with standard laboratory assays used in the management of patients with hemophilia A. In one-stage assays, emicizumab is associated with a supra-physiologically short time to clot formation and thus normalization of aPTT at subtherapeutic levels and an overestimation of true FVIII activity. Emicizumab is not recognized or neutralized by FVIII inhibitors, and therefore FVIII inhibitors cannot be detected in patients receiving emicizumab by a functional test such as Bethesda or Nijmegen-Bethesda assays, which use a one-stage clotting based readout. Emicizumab activity cannot be detected by chromogenic assays using purified bovine coagulation proteins and can only be detected using an assay composed of human proteins. See the RO5543262 [Emicizumab] Investigator's Brochure for additional details on which tests can be used and how the test results can be interpreted.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

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

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

Bleeds considered as serious adverse events should be reported on the appropriate adverse event eCRF page regardless of whether the bleeds are consistent with patients' pre-study disease state (the bleed will remain recorded as well on the Bleed/Medication Questionnaire). New, non-serious bleeds consistent with patients' pre-study disease state will not be considered adverse events and will not be recorded on the eCRF but will be captured on the Bleed/Medication Questionnaire.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section [5.3.5.11](#))
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)

- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as grade 1–4, according to the World Health Organization [WHO] Toxicity Grading Scale for Determining The Severity of Adverse Events criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions (see Sampson's Criteria in Appendix 7)
- Thromboembolic events
- Microangiopathic hemolytic anemia or thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura, hemolytic uremic syndrome)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

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

After randomization (randomized arms) or initiation of study drug (non-randomized arm), all adverse events will be reported until the patient completes his or her last study visit (i.e., 24 weeks after the last dose of study drug). After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The WHO toxicity grading scale (see Appendix 6) will be used for assessing adverse event severity (WHO 2003). Table 3 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

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

Notes: Developed by the Division of Microbiology and Infectious Diseases.

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Injection-Site Reactions

Local adverse events that occur within 24 hours after study drug administration and, in the investigator's opinion, are judged to be related to study drug injection, should be captured as an "injection-site reaction" on the Adverse Event eCRF. An injection-related reaction that is localized should be marked as a "local injection-site reaction."

Associated signs and symptoms (e.g., injection-site erythema or injection-site rash) should be recorded on the dedicated Injection-Site Reaction eCRF. Systemic reactions should be recorded separately on the Adverse Event eCRF. The dedicated Injection-Site Reaction eCRF should only be used to capture the individual signs/symptoms for local injection-site reactions.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events, other than injection-site reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

For concerns about laboratory findings on coagulation-related tests in patients receiving emicizumab, please see Section 5.1.4 or contact the Medical Monitor.

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ baseline value) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event of special interest the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia

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

5.3.5.8 Deaths

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

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

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

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

5.3.5.10 Lack of Efficacy or Worsening of Hemophilic Bleeds

Medical occurrences or symptoms of deterioration that are anticipated as part of hemophilia should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in terms of severity (e.g., increased number of doses of bypassing agents to stop bleeds with emicizumab, in the absence of neutralizing anti-emicizumab antibodies, compared with before study entry), frequency of bleeds, or nature of hemophilia at any time during the study. Should any of these occur (according to the investigator's clinical assessment), they 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").

Events that are clearly consistent with the anticipated pattern of the underlying disease and do not indicate an unexpected worsening in severity or frequency should not be recorded as adverse events. These data will be reflected in efficacy assessment data only.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

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

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

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

No safety data related to overdosing or drug administration error of emicizumab are available, as no such instances have been observed to-date. To minimize the risk of

errors associated with future home administration of emicizumab, data related to medication errors with observed patient/caregiver administration of emicizumab during the first 5 weeks at the site by the investigator and/or clinical staff will be recorded and corrected at the time of occurrence. In addition, the recording of medication and handling errors associated with home administration, as well as drug compliance, will be collected at each clinic visit.

5.3.5.13 Patient-Reported Outcome Data

The PRO measurements are described in Section 4.5.7. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Although sites are not expected to review the PRO data pertaining to the health-related quality of life, health status, preference or satisfaction measures, they are expected to review the BMQ. Given that, it is possible that an investigator could become aware of PRO data that may be indicative of an adverse event. Under these circumstances, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF. The PRO data will be presented in separate tables, figures, and data listings from the adverse event data, and will be included in the appropriate section of the final study report.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor [REDACTED], M.D., M.A.S. (primary)

Telephone No.: [REDACTED]

Medical Monitor: [REDACTED] M.D. (secondary)

Telephone No.: [REDACTED]

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

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

5.4.2.1 Events That Occur prior to Randomization or Study Drug Initiation

After informed consent has been obtained but prior to randomization (randomized arms) or initiation of study drug (non-randomized arm), only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators.

5.4.2.2 Events That Occur after Randomization or Study Drug Initiation

After randomization (randomized arms) or initiation of study drug (non-randomized arm), serious adverse events and adverse events of special interest will be reported until the last scheduled study visit (see Section 5.6). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting post-study adverse events are provided in Section [5.6](#).

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

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

5.4.3.2 Pregnancies in Female Partners of Male Patients

Although embryo-fetal development studies are not available, condom use will not be required in male patients enrolled in the study because the margin between the minimal anticipated biological effect level (MABEL) plasma concentration (7 ng/mL) and the estimated maternal C_{max} (at both 1.5 and 3 mg/kg/wk dosing regimens) is greater than 10-fold (Banholzer et al. 2012). At this time, very little emicizumab is thought to transfer into semen, and there are no known reproductive risks to female partners of male patients treated with emicizumab. Therefore, contraception use by male patients is not required for participation in the study, and to be consistent with this, no proactive collection of pregnancy information for female partners of male patients treated with emicizumab will be required.

5.4.3.3 Abortions

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome. At the time of pregnancy outcome, reporting instructions provided in Section [5.4.3.1](#) should be followed.

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as LPLV), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or e-mail address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest (see Section 5.2.3) against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

- RO5543262 (Emicizumab) Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

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

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

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

previously described, the sample size is projected to have greater than 90% power at the 2-sided 0.05 level of significance.

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

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

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

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

Regarding the effect of emicizumab on changes of DSC from baseline at Weeks 23–24 or 47–48 in patients with hemophilia A, there is currently no published information on the variability or clinical significance of longitudinal changes in this measure with the study device in patients with hemophilia A. No data are available to allow detailed sample size calculation of these exploratory objectives. Participation will be offered to all patients in the study, leading to a maximum sample size of 145 patients. Of note, 40 subjects (20 per treatment group) were deemed sufficient to evaluate the related objectives with an adequate level of precision in similar studies that enrolled patients with chronic obstructive pulmonary disease, such as WB29804 Activity Substudy.

6.2 GENERAL

This section provides a general overview of the methods. If any of the items require a unique approach that differs from the general overview, then it will be noted in the appropriate section.

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

All summary tables will be structured with a column for each treatment arm and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

Analyses will follow the principle of intention-to-treat (i.e., based on randomized population).

6.3 SUMMARIES OF CONDUCT OF STUDY

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

Variables from the eCRF used to establish how many patients reached the various stages of the study, how many dropped out and for what reasons will be described in the Statistical Analysis Plan (SAP).

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Comparisons between the treatment arms of demographic data and baseline characteristics will be conducted to establish if any observed differences between the treatment arms are not due to imbalances in patient characteristics at baseline. Only descriptive analyses are planned, and no formal statistical tests will be applied.

6.5 EFFICACY ANALYSES

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

6.5.1 Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in Section 4.5.8. The primary endpoint is based on treated bleeds.

The primary efficacy analysis will be conducted after all randomized patients (and a minimum of 40 patients previously treated with prophylactic FVIII) have completed

24 weeks in the study or the last randomized patient yet to complete 24 weeks in the study discontinues study participation, whichever occurs first, and using an intent-to-treat principle. The comparison of the number of bleeds over time between the randomized treatment arms will be performed using an NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (< 9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t/λ_c , which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level. Of note, hierarchical testing is used to account for multiple testing and the first test to be included in the hierarchy is the emicizumab 1.5 mg/kg/wk maintenance dose versus control. The second test will be 3 mg/kg/2wks maintenance dose versus control. The description below covers both hypotheses to be tested:

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

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the prespecified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic emicizumab and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

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

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

6.5.2 Secondary Efficacy Endpoints

For all patients, the number of bleeds over time will be compared with the patient's historical bleed rate, recorded in the medical record, and/or for the duration of their participation in the non-interventional study using an NB regression model similar to the one described for the primary efficacy endpoint.

In addition, the number of all bleeds (treated and not treated), spontaneous, joint and target joint bleeds over 24 weeks' time between the emicizumab prophylaxis and no prophylaxis arms will be evaluated by an NB regression model, as specified for the primary efficacy endpoint.

The efficacy of prophylactic emicizumab treatment in the cohort of non-inhibitor patients previously treated with prophylactic FVIII will be evaluated to demonstrate that these patients remain adequately controlled on emicizumab. The mean ABR will be estimated for each patient using the NB model and the one-sided 97.5% CI constructed around the estimated overall mean ABR. If the upper limit of the CI is less than or equal to 6, the treatment regimen will be considered to provide adequate control. This endpoint will be included as the third test in the hierarchical testing strategy.

Adherence with the HRQoL and health status measures will be summarized at the end of the study.

HRQoL (using the Haem-A-QoL or the Haemo-QoL-SF) and health status (using the EQ-5D-5L) will be assessed on a regular basis, as per the schedule of assessments (scheduled).

Because different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) are being used for the adult and adolescent patients, all calculations and analyses will be conducted separately for adults and adolescents. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively for all time points in the study. The HRQoL scale scores for all patients will be evaluated after 24 weeks in the study, a timepoint that is consistent with other recent registrational studies in hemophilia (Lentz et al. 2013; Powell et al. 2013; Mahlangu et al. 2014) and analyses of such data (Santagostino et al. 2014; Wyrwich et al. 2015). For each treatment arm, ANCOVA model will be used to compare the 24-week and final assessments with the baseline scale scores for each HRQoL measure. Within-subject and between-group changes from baseline on the different HRQoL scale scores will also be calculated at 24 weeks and the final HRQoL assessment. Statistical analysis of the Haemo-QoL-SF endpoints will be subject to sufficient adolescent patients being enrolled in the study to make meaningful statistical comparisons. Further details will be provided in the SAP after the completion of enrollment into the study if deemed necessary.

For the assessments of the EQ-5D-5L, the number and percentage of patients in each of the five categories for each question for each group will be assessed. Changes in the EQ-5D-5L index utility score from baseline will also be compared between groups. In addition, summary statistics including mean, standard deviation, median, minimum and maximum will be displayed for the patients' health state using the EQ-VAS both within and between groups. The proportion of patients who report changes in each group exceeding the clinically meaningful threshold on the EQ-5D-5L index and EQ-VAS scores in each group will be reported at 24 weeks and the final, scheduled EQ-5D-5L assessment.

Secondary endpoints used for labeling and those that are solely for scientific interest will be specified in the SAP.

6.6 SAFETY ANALYSES

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

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

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

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

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

6.7 PHARMACOKINETIC ANALYSES

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

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

6.8 EXPLORATORY ANALYSES

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

For the activity assessment all enrolled subjects that contribute reliable activity data (i.e., at least 8 valid days) will be analyzed. There will be no imputation of missing data. Subjects will be grouped according to the treatment regimen to which they are assigned in the main study. Because of the exploratory nature of the study, there will be no type-1 error control for multiplicity. Enrollment, discontinuations, protocol violations/deviations, and duration of activity monitoring follow-up will be summarized. Demographic and baseline characteristics, such as age, sex, race/ethnicity, and weight will be summarized using descriptive statistics. Relative change is defined as

$$100 \times (DSC_{\text{Week } n} - DSC_{\text{baseline}}) / DSC_{\text{baseline}}$$

Relative change from baseline at Week 25 or 49 in mean DSC and activity counts (total, mean, and peak) will be calculated within each treatment group provided the patient has reported data on at least 8 days within the 14 day observation period. Subject-level averages at each timepoint will be presented via dot-plots and descriptive statistics by treatment group.

The main comparisons will be within-patient changes, calculated within each treatment group. Within the control arm, where patients are expected to switch to emicizumab prophylaxis treatment at 24 weeks, an additional comparison of the relative change from Week 25 to Week 49 will be performed.

Formal statistical modeling may be performed as appropriate. Such analysis will be based on between-treatment comparisons of the change in activity from baseline to Week 25 between patients receiving emicizumab prophylaxis (Arms A or B) versus no prophylaxis (Arm C).

6.9 INTERIM ANALYSIS

No interim analysis for efficacy is planned.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

ActiGraph will be responsible for data management of the activity monitoring, including quality checking of the data. Sites will be responsible for setting up (initializing) activity monitors and downloading data from the monitors using ActiGraph's CentrePoint software, a web-based physical activity monitoring logistics platform. The CentrePoint solution consists of two components: a client-side software application (ActiSync), which directly interacts with the monitors on each site's computer and remotely distributed storage and processing servers hosted by Amazon® Web Services and Microsoft® Azure cloud computing platforms located in the United States. ActiGraph is in the process of completing the implementation of full server-side audit logging. Once complete, the CentrePoint solution will be fully CFR Part 11 compliant.

Actigraph will produce a Data Quality Plan that describes the quality checking to be performed on the data. Data will be transmitted to the Sponsor using the Sponsor's standard procedures to handle and process the electronic transfer of these data

7.2 ELECTRONIC CASE REPORT FORMS

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

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

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

PRO data will be collected electronically with use of electronic devices provided by a vendor. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted electronically in real-time to a centralized secure database at the vendor. The data from the devices are available for view access only via secure access to a Web portal provided by the vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor. The Sponsor will receive all data entered by patients on the devices and all relevant study documentation.

Once the study is complete, the data, audit trail, and study and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

The entire activity data collection, transmission, and analysis process is 21 CFR Part 11 compliant and includes a complete audit trail. The “source data” from ActiGraph will consist of the raw data, the epoch data (counts), and steps. Derived endpoints (such as calories or any other measure that is derived from raw, epoch, or steps data is not considered source data. ActiGraph will maintain all of the data in multiple redundant data centers hosted on the Amazon Web Services platform. ActiGraph will provide this information as needed for audits by Roche and/or appropriate regulatory agencies.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws.*

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Adolescent's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be

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provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

Patients who are declared legally incompetent or who are physically or mentally incapable of providing informed consent but otherwise meet the qualifications for participation in Study BH30071 will be included, as emicizumab prophylaxis may directly benefit this population with high unmet medical need. In such cases, investigators will obtain informed consent from a guardian or legally authorized representative of the patient in accordance with applicable law. In addition, the investigator must also obtain the assent of the patient when they are able to give assent to decisions made on their behalf. Any indication on the part of the patient that they are not willing to participate in the study will be honored.

In cases where there is reason to question the competence of a patient who has not been declared incompetent (e.g., a patient in the early stages of Alzheimer's disease), a patient advocate will be involved in the consent process and throughout the duration of the patient's participation in the study.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This global study will enroll approximately 125–145 patients.

Randomization and drug assignment will be performed by an IxRS, which will also manage emicizumab inventory for all sites globally.

PROs will be captured on electronic devices provided by a third-party vendor for all patients globally.

Central laboratories will be used for a subset of laboratory assessments specified in Section [4.5.5](#).

9.4.1 Independent Data Monitoring Committee and Independent Data Coordinating Center

An iDMC will be assembled to review the safety data collected during the study. The iDMC members will consist of, at minimum, independent hemostasis/thrombosis experts and a statistician, none of whom will be otherwise involved in the conduct of study. All analyses for review by the iDMC will be prepared by an independent Data Coordinating Committee (iDCC) that is independent of the Sponsor. At the beginning of the study, intensive monitoring and analysis of all significant safety events will be performed. Safety analyses of significant safety events will be conducted as prespecified intervals, the timing of which will be defined in the iDMC Charter. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor according to the emerging safety profile.

An iDCC will perform unblinded analyses and provide tables and listings to support the iDMC reviews of safety data. The safety data will include demographic data, adverse events, serious adverse events, and laboratory abnormalities (coagulation, hematology, and chemistry). Further information will be given on request.

Following each meeting, the iDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the iDMC may recommend stopping the study or closing a treatment arm for safety reasons. The iDMC will monitor the incidence of the anticipated adverse events, as well as the overall safety of patients, during the study.

The meeting schedule and all other iDMC-related activities will be specified in a separate iDMC charter. All results will be confidential and will not be divulged to non-members of the iDMC, including the Sponsor. All closed meetings will be summarized in written minutes available only to iDMC members and the iDCC statistician and kept by the iDCC statistician until the end of the study. The recommendations can be communicated to the Sponsor verbally but have to be confirmed in writing according to a predefined timeframe. Strict confidentiality rules will be applied to avoid any dissemination of either safety or efficacy interim results outside the iDMC.

The final decision of acting upon the iDMC's recommendations will rest with the Sponsor. The policies and procedures will be detailed in a separate iDMC Charter document.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on both the interim and final analyses of the study to healthcare professionals and to the public, at scientific congresses, *in clinical trial registries*, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request.* For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Website: http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf.

The results of this study may be published or presented at scientific congresses. For all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Assessments

Schedule of Assessments—Arms A, B, and D																			
	Screen- ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Every 8 Wks from Wk 33	Wk 49	Every 12 Wks from Wk 61	Every 24 Wks from Wk 73	Daily/ weekly ^a	Study Com- pletion/ ET	Safety F/U Visit ^b
Informed consent ^c	x																		
Inclusion/exclusion criteria	x																		
Medical history and demographics ^d	x																		
Physical examination (including weight) ^e	x	x				x						x		x	x	x		x	x
Height	x											x		x					
Vital signs (including weight) ^f	x	x ^f	x	x	x	x	x	x	x	x	x	x ^f	x	x ^f	x	x		x ^f	x
HJHS ^g	x													x					
Serum pregnancy test ^h	x	x																	
Concomitant medications ⁱ	x	x				x		x	x	x	x	x	x	x	x	x		x	x
ECG ^j	x	x ^j				x						x						x	
Safety laboratory assessments ^h	x ^h	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Anti-FVIII antibodies ^k	x ^k	x		x					x			x	x	x	x	x		x	x
Anti-emicizumab antibodies ^l		x ^l				x		x ^l	x	x ^l	x	x ^l	x ^l	x ^l	x ^l	x ^l		x	x ^l
Bleed/medication questionnaire ^m																	x		
Bleed/medication data review ⁿ		x				x		x	x	x	x	x	x	x	x	x		x	x

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Appendix 1 Schedule of Assessments (cont.)

Schedule of Assessments—Arms A, B, and D																			
	Screen- ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Every 8 Wks from Wk 33	Wk 49	Every 12 Wks from Wk 61	Every 24 Wks from Wk 73	Daily/ weekly ^a	Study Com- pletion/ ET	Safety F/U Visit ^b
Adverse events ^o		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
IMP management ^p		x	x	x	x	x	X	x	x	x	x	x	x	x	x	x		x	
HRQoL and health status (EQ-5D-5L) ^q		x							x			x		x		x ^q		x	
PK assessment ^r		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers ^s		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Bone biomarkers (fasted) ^t		x							x			x		x		x		x	
Activity measure (optional) ^u		x										x		x					
Patient preference survey										x									
Patient satisfaction (SQ-ISHI) ^v		x									x	x							
RCR blood DNA sample (optional) ^w			x ^w	x ^w	x ^w	x ^w													

Appendix 1 Schedule of Assessments (cont.)

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

Appendix 1 Schedule of Assessments (cont.)

Schedule of Assessments—Arm C (Continued, at Time of Switch to Emicizumab)																		
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Every 8 Wks from Wk 57	Wk 73	Every 12 Wks from Wk 85	Every 24 Wks from Wk 97	Daily/ weekly ^a	Study Compl- etion/ ET	Safety F/U Visit ^b
Physical examination (including weight) ^e	x				x						x		x	x	x		x	x
Vital signs (including weight) ^f	x ^f	x	x	x	x	x	x	x	x	x	x ^f	x	x ^f	x	x		x ^f	x
Height	x										x		x					
Serum pregnancy test ^h	x																	
HJHS ^g	x										x		x					
Concomitant medications ⁱ	x				x		x	x	x	x	x	x	x	x	x		x	x
ECG ^j	x				x ^j						x						x	
Safety laboratory assessments ^h	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Anti-FVIII antibodies ^k	x		x					x			x	x	x	x	x		x	x
Anti-emicizumab antibodies ^l	x ^l				x		x ^l	x	x ^l	x	x ^l	x	x ^l	x	x		x	x ^l
Bleed/medication questionnaire ^m																x	x	x
Bleed/medication data review ⁿ	x				x		x	x	x	x	x	x	x	x	x		x	x

Appendix 1 Schedule of Assessments (cont.)

Schedule of Assessments—Arm C (Continued, at Time of Switch to Emicizumab)																		
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Every 8 Wks from Wk 57	Wk 73	Every 12 Wks from Wk 85	Every 24 Wks from Wk 97	Daily/ weekly ^a	Study Compl- etion/ ET	Safety F/U Visit ^b
Adverse events ^o	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
IMP management ^p	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
HRQoL and health status ^q	x							x			x		x		x ^q		x	
PK assessment ^r	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers ^s	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Bone biomarkers (fasted) ^t	x							x			x		x		x		x	
Activity measure (optional) ^u	x										x							

BMQ=bleed and medication questionnaire; eCRF=electronic Case Report Form; EQ-5D-5L=EuroQoL Five-Dimension-Five Levels Questionnaire; ET=early termination; F/U=follow-up; FVIII=factor VIII; HRQoL=health-related quality of life; HJHS=Hemophilia Joint Health Score; IMP=investigational medicinal product, PD=pharmacodynamic; PK=pharmacokinetic; RCR=Roche Clinical Repository; SQ-ISHI=Satisfaction Questionnaire–Intravenous Subcutaneous Hemophilia Injection; wk=Week.

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

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

Appendix 1 Schedule of Assessments (cont.)

Schedule of Assessments—Arm C (Continued, at Time of Switch to Emicizumab)																			
																Every 24 Wks from Wk 97	Daily/ weekly ^a	Study Compl- etion/ ET	Safety F/U Visit ^b
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Every 8 Wks from Wk 57	Wk 73	Every 12 Wks from Wk 85					

- ^b A safety follow-up visit will occur 24 weeks after discontinuing emicizumab, *except for patients who have transferred to commercially available emicizumab.*
- ^c Obtain written informed consent (or patient's assent and legal representative written informed consent if patient is an adolescent) before distribution of BMQ handheld device and collection of any data. Patients will be enrolled and randomized after giving informed consent and assent when appropriate. A patient who fulfills the inclusion and exclusion criteria should be enrolled and assigned to a treatment arm on the same day when the first dose of emicizumab is due (Week 1 visit).
- ^d Collected from patient medical records and documented in the eCRF, including information on target joint(s).
- ^e Calculation of dose based on weight is required. A complete physical examination will be performed at screening and at least a targeted physical examination will be performed at subsequent visits. Targeted physical examination of joints (for bleeds, evidence of arthropathy) and skin (for bruises, hematomas, and injection-site reactions) as clinically indicated and/or with report of new or worsening adverse event. HJHS will be done as part of physical examination between screening to Week 2, at Week 49, and annually.
- ^f Body temperature, blood pressure, pulse rate, and respiratory rate only to be used to monitor during and after injection for hypersensitivity reactions and not to be entered into eCRF, except at Weeks 1, 25, 49, at study completion/early termination, and at the safety follow-up visit (i.e., 24 weeks after discontinuing emicizumab for patients in Arms A, B, and D and at Week 73 for patients in Arm C). If Screening and Week 1 occur on the same date, the vital signs should be measured only once. If Screening and Week 1 occur on different dates, vital signs entry should be repeated for both assessments. Height will be measured at screening and annually.
- ^g See [Appendix 8](#). HJHS will be done as part of physical examination between screening to Week 2, at Week 49, and annually.
- ^h Laboratory data (performed locally) include: complete blood count with differential (i.e., neutrophils, hemoglobin, platelet count), serum chemistries (including sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid). Laboratory assessments completed at the screening visit do not have to be repeated at Week 1, if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator. Female patients with childbearing potential will be required to have a negative serum pregnancy test result at Screening (and within 7 days of study drug initiation, if applicable) and urine pregnancy tests performed at every clinic visit, with the exception of Weeks 2–4 and 7. Patients in Arm C will have serum pregnancy test performed at Screening and before starting emicizumab (Week 25).

Appendix 1 Schedule of Assessments (cont.)

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- ⁱ Concomitant medications (e.g., extra pain medication with bleed) will be asked about at the time of the monthly assessment, excluding treatments for bleeds (i.e., FVIII and other medications to treat bleeds), which will be collected on the bleeding questionnaire. Hemostatic medications to treat or prevent bleeds in the week prior to starting emicizumab will also be collected and during Week 1 for patients in Arm D who continue their prior FVIII prophylaxis for the first week of the study.
- ^j Performed locally. If screening ECG is abnormal, repeat at Week 1 (or Week 2 [or Week 5 for Arm C] if Screening and Week 1 occur on the same day), otherwise do not repeat. ECGs will also be performed 4–8 and 24 weeks after starting emicizumab or dose escalation (up-titration), as well as at study completion/early termination.
- ^k Patient must have a documented local inhibitor test with negative result (<0.6 BU) at screening or within the 8 weeks prior to enrollment. Starting at Week 1, all subsequent anti-FVIII antibodies will be measured at a central laboratory using an aliquot of the citrate plasma collected for PD biomarker assessments, so a separate blood draw is not necessary. Please consult the central laboratory services manual for details.
- ^l Samples to detect anti-emicizumab antibodies will be collected prior to emicizumab administration at every clinic visit. However, only samples from the following visits will be analyzed initially: (Arms A, B, and D) immediately prior to the first injection at Week 1, every 8 weeks from Weeks 9–49, every 12 weeks starting from Week 61, and at the 24-week post-emicizumab safety follow-up visit following initiation of emicizumab; Arm C immediately prior to the first injection at Week 25, every 8 weeks from Weeks 33–73, every 12 weeks starting from Week 85, and at the 24-week post-emicizumab safety follow-up visit following initiation of emicizumab. If any of these samples are positive and/or if there is suboptimal clinical response or low pharmacokinetic exposure, the remaining collected samples may be analyzed for anti-emicizumab antibodies. Anti-emicizumab antibodies may also be drawn at the time of systemic hypersensitivity events.
- ^m Reported by the patient, or the patient's legally authorized representative, and includes: start date and time, reason, type, location, and associated symptoms of each bleed, as well as start date and time, reason, type, number of injections, and dose of each hemophilia medication injection, including emicizumab. Patients who stop taking emicizumab should continue reporting bleeds and hemophilia medication administration on the handheld device until the safety follow-up visit.
- ⁿ At the Week 1 visit, patients will be trained on how to use and be provided their own handheld device. At subsequent visits as marked, investigator review of patient-reported bleed/injection questionnaire information will be conducted for completeness and accuracy.
- ^o Injection-site reaction adverse events will be collected on a separate form from the adverse event form. If there is unexpected worsening of the patient's hemophilia in terms of severity (e.g., increased number of doses of FVIII to stop bleeds compared with before study entry), frequency of bleeds, or nature at any time during the study, this should be documented as an adverse event on the Adverse Event eCRF, conveying that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia").
- ^p Drug accountability will not be performed at the first visit that includes emicizumab receipt. Drug dispensation will not occur at the study completion/early termination visit.
- ^q Haem-A-QoL questionnaire (age ≥ 18) and Haemo-QoL-Short Form (ages 12–17), health status questionnaire EQ-5D-5L. Patient-reported outcomes will be captured on-site by a device and transmitted to the database. After Week 49, HRQoLs will be captured every 24 weeks.
- ^r Emicizumab concentration. Plasma samples for this assessment should be taken prior to injection. Patients will be dosed at the clinics (self-administration) on days where trough plasma samples are to be collected

Appendix 1 Schedule of Assessments (cont.)

- ^s See [Appendix 2](#) for detailed explanation of PD biomarker assessments (Sets 1 and 2). Blood samples will be banked for 5 years for future exploratory PD biomarker analyses. Blood samples may also be drawn to conduct biomarker assays at the central laboratory on an unscheduled basis (at the clinical judgment of the investigator) at any time.
- ^t Serum and plasma for bone markers must be collected after fasting (no food or drink other than water for at least 8 hours prior to the blood draw). Ideally these samples should be collected in the morning (before noon), to control for diurnal variation as well.
- ^u Patients who consent to participate should receive ActiGraph device at Screening or Week 1 and on the visit prior to each assessment period. Assessment periods occur during Weeks 1–2, 23–24, and 47–48. During activity assessment periods, patients wear the study device while awake for 2 consecutive weeks within the period between the distribution and collection of the device.
- ^v Only Arm D patients at baseline and on Week 21 or 25.
- ^w Sample for the RCR is optional and requires an additional consent. This single sample may be drawn at Week 2, 3, 4, or 5 but is not drawn at Week 1 in order to avoid excessive blood draw.

Appendix 2 Schedule of Pharmacodynamic Assessments

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

FVIII = factor VIII; FXIII = factor XIII; PD = pharmacodynamic; RANK-L = Receptor activator of nuclear factor kappa-B ligand; VWF = von Willebrand factor.

Appendix 2 Schedule of Pharmacodynamic Assessments (cont.)

Sample	Visit ^a	Biomarker assays ^b
PD Set 3 ^d (Bone Biomarkers)	Starting on emicizumab (Arms A, B and D): Week 1 Week 13 Week 25 Week 49 <i>Every 24 weeks thereafter, while on emicizumab (Week 73 and beyond)</i> Study Completion/Early Termination	CTX-1 OPG P1NP soluble RANK-L
	Starting on no prophylaxis, switch to emicizumab after 24 weeks (Arm C): Week 1 Week 25 Week 37 Week 49 <i>Every 24 weeks thereafter, while on emicizumab (Week 73 and beyond)</i> Study Completion/Early Termination	

CTX-1=C-terminal telopeptide of collagen 1; CWA=clot waveform analysis; P1NP=procollagen type 1 amino-terminal propeptide; OPG=osteoprotegerin; PD=pharmacodynamic; RANK-L=Receptor activator of nuclear factor kappa-B ligand.

- ^a All samples are to be collected on Day 1 of the indicated week, prior to emicizumab injection (if applicable). PD samples will be citrate plasma, EDTA plasma, or serum. Refer to [Appendix 1](#) for exact study visits.
- ^b Biomarker assays will include, but are not limited to, those listed. Additional samples will be frozen and banked for future exploratory research related to emicizumab, which may include coagulation tests such as CWA and others. Blood volumes and processing procedures will be specified in the Central Laboratory Services Manual.
- ^c Reasons for unscheduled visits may include evaluation or treatment for bleeds or hypersensitivity reactions.
- ^d Serum and plasma for bone markers must be collected after fasting (no food or drink other than water for at least 8 hours prior to the blood draw). Ideally these samples should be collected in the morning (before noon), to control for diurnal variation as well. Please consult the Central Laboratory Services Manual for details.
- ^e *FXIII activity was tested only at Week 1 due to emicizumab interference with the FXIII assay.*

Appendix 3 Haemo-QoL-SF (United States/English)

In the past 4 weeks...		never	rarely	some- times	often	all the time
1.	...my swellings hurt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	...I had pain in my joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	...it was painful for me to move	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	...I was afraid of bleeds	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.	...I was sad because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	...my hemophilia was a burden (real problem) for me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.	...my hemophilia made me angry	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.	...I felt lonely because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.	...I was jealous of healthy boys my age	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10.	...I felt physically weaker than other boys	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11.	...I felt as well as other boys my age	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12.	...I felt comfortable with my body	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13.	...my mother protected me too much	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14.	...my parents criticized me when I hurt myself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15.	...my parents didn't allow me to do certain things because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16.	...I felt I was causing my family trouble because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17.	...my best friend cared about how I was feeling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18.	... there was a best friend that I felt very close to	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2

[II + III, kids, short]

Appendix 3 Haemo-QoL-SF (United States/English) (cont.)

In the past 4 weeks...		never	rarely	some- times	often	all the time
19.	...my friends took care of me when I felt bad	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20.	...I felt different from others because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21.	...other kids teased me because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22.	...people behaved differently towards me because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23.	...I felt left out when others did things together	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24.	...I had to avoid sports that I like because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25.	...I had to do indoor activities more than other kids because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26.	...I had to avoid sports like football or skateboarding	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27.	...I played sports just as much as any other kid	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28.	...I felt that my hemophilia problems were under control	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29.	...hemophilia was a normal part of my life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30.	...I felt healthy even with my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31.	...I accepted having hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32.	...the treatment I got was okay	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
33.	...I disliked visiting the hemophilia center	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34.	...the injections bothered me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
35.	...I was annoyed about the amount of time spent having the injections	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

[II + III, kids, short]

3

Appendix 4 Haem-A-QoL (United States/English)

Trial ID:		Page 1/7
	VISIT X	
Centre ID/No.:		_ _
Subject No.:		_ _ _ _ _ _ _
Visit Date:		_ _ _ _ _ _ _ D D M M Y Y Y Y

HAEM-A-QOL

Questionnaire for Adults

Dear Patient,

We would like to find out how you have been feeling during the past weeks. Please be so kind as to answer the following questions in this questionnaire, designed specifically for people with hemophilia.

Please follow the instructions below when answering the questions:

- ⇒ Please read each question carefully.
- ⇒ Think about how things have been for you over the past weeks.
- ⇒ Put an "X" in the box corresponding to the answer that fits you best.
- ⇒ Only mark one box for each question.
- ⇒ There are no right or wrong answers.
- ⇒ It's what you think that matters.
- ⇒ There are some aspects that might not concern you (Sports & Leisure, Family Planning, Work & School, e.g., if you don't work or don't go to school). In such a case, please mark the answer category "not applicable."

All your answers will be treated with the strictest confidence!

Date of completion: ___ / ___ / ___ (month/ day/ year)

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	Page 2/7								
VISIT X									
Subject No.:	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table>								

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

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

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

<i>In the past month...</i>	never	rarely	sometimes	often	all the time
1. ... my hemophilia was a burden for me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. ... my hemophilia made me angry	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. ... I was worried because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. ... I felt excluded	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	Page 3/7							
VISIT X								
Subject No.:	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table>							

3. How does hemophilia affect your VIEW OF YOURSELF?

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

4. These questions are about SPORTS AND LEISURE

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

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	Page 4/7								
VISIT X									
Subject No.:	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table>								

5. These questions are about WORK AND SCHOOL

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

6. The next questions are about DEALING WITH HEMOPHILIA

<i>In the past month...</i>	never	rarely	sometimes	often	all the time
1. ... I tried to recognize early on when a bleed developed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. ... I was able to tell whether or not I was bleeding	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. ... I was able to control my bleeds	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID:	VISIT X	Page 5/7								
	Subject No.:	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table>								

7. and what about your TREATMENT?

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

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Appendix 4 Haem-A-QoL (United States/English) (cont.)

Trial ID: <div style="text-align: center; font-weight: bold; font-size: 1.2em;">VISIT X</div> Subject No.: 	Page 6/7
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8. What do you think about the FUTURE?

<i>Recently...</i>	never	rarely	sometimes	often	all the time
1. ... I have been thinking that it will be difficult for me to lead a normal life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. ... I have been expecting that things will get better in the future	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. ... I have been worrying that my condition is worsening	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. ... my life plans have been influenced by my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. ... I have been afraid that I will need a wheelchair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

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

Appendix 4
Haem-A-QoL (United States/English) (cont.)

Trial ID:	VISIT X	Page 7/7							
	Subject No.:	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> <td style="width: 20px; height: 20px;"> </td> </tr> </table>							

10. What about PARTNERSHIP AND SEXUALITY?

<i>Recently...</i>	never	rarely	sometimes	often	all the time
1. ... I have been finding it difficult to date because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. ... I have been insecure in my relationships with women because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. ... I haven't been able to have a normal relationship because of my hemophilia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

THANK YOU FOR YOUR ASSISTANCE!

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

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

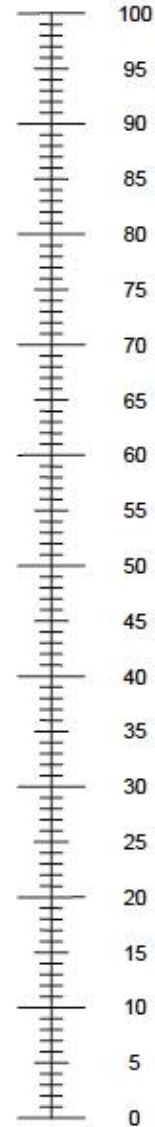
2
UK (English) v.2 © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

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

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	<6.5 g/dL
Absolute neutrophil count	1000–1500/mm ³	750–999/mm ³	500–749/mm ³	<500/mm ³
Platelets	75000–99999/mm ³	50000–74999/mm ³	20000–49999/mm ³	<20000/mm ³
Prothrombin time (PT)	1.01–1.25 × ULN	1.26–1.5 × ULN	1.51–3.0 × ULN	>3 × ULN
Activated partial thromboplastin (APTT)	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3 × ULN	>3 × ULN
Fibrinogen	0.75–0.99 × LLN	0.50–0.74 × LLN	0.25 - 0.49 × LLN	<0.25 x LLN
Fibrin split product	20–40 mcg/mL	41–50 mcg/mL	51–60 mcg/mL	>60 mcg/mL
Methemoglobin	5–9.9%	10.0–14.9%	15.0–19.9%	>20 %
LIVER ENZYMES				
AST (SGOT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	>10 × ULN
ALT (SGPT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	>10 × ULN
GGT	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	>10 × ULN
Alkaline phosphatase	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	>10 × ULN
Amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	>5.0 × ULN

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CHEMISTRIES				
Hypонатremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required.	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	> 7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	< 30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116–160 mg/dL	161–250 mg/dL	251–500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	< 6.1 mg/dL or life-threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CHEMISTRIES continued				
Hypomagnesemia	1.4–1.2 mEq/L	1.1–0.9 mEq/L	0.8–0.6 mEq/L	<0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0–2.4 mg/dL	1.5–1.9 mg/dL or replacement Rx required	1.0–1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1–1.5 × ULN	1.6–2.5 × ULN	2.6–5 × ULN	> 5 × ULN
BUN	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Creatinine	1.1–1.5 × ULN	1.6–3.0 × ULN	3.1–6 × ULN	> 6 × ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or <0.3% or <3g/L or 200 mg–1 g loss/day	2–3+ or 0.3–1.0% or 3–10 g/L or 1–2 g loss/day	4+ or > 1.0% or > 10 g/L or 2–3.5 g loss/day	nephrotic syndrome or > 3.5 g loss/day
Hematuria	microscopic only	gross, no clots	gross + clots	obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires treatment
Hypertension	transient inc. > 20 mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; no hospitalization	requires hospitalization

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CARDIAC DYSFUNCTION continued				
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1–2 units transfused	massive blood loss; > 3 units transfused
RESPIRATORY				
Cough	transient; no Rx	treatment-associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx < 70%–79% FEV ₁ (or peak flow)	requires Rx normalizes with bronchodilator; FEV ₁ 50%–69% (or peak Flow)	no normalization with bronchodilator; FEV ₁ 25%–49% (or peak flow retractions)	cyanosis: FEV ₁ < 25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
GASTROINTESTINAL continued				
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3–4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or > 7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
NEURO AND NEUROMUSCULAR				
Neuro-cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
NEURO AND NEUROMUSCULAR continued				
Neuro control (ADL=activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle strength	subjective weakness no objective symptoms/signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
OTHER PARAMETERS				
Fever: oral, > 12 hours	37.7–38.5 C or 99.9–101.3 F	38.6–39.5 C or 101.4–103.1 F	39.6–40.5 C or 103.2–104.9 F	>40.5 C or > 104.9 F
Headache	mild, no Rx therapy	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25–50%	normal activity decreased > 50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	Induration ≥ 10 cm or ulceration	necrosis

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
OTHER PARAMETERS continued				
Mucocutaneous	erythema; pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

NOTE: For coding purposes, the following toxicity grades may be used interchangeably: 1 =mild; 2 =moderate; 3 =severe; 4 =life threatening.

Appendix 7

Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network. Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue/uvula)
AND AT LEAST ONE OF THE FOLLOWING:
 - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
 - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
 - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure²
 - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

¹ Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–7.

² Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

Appendix 8 Hemophilia Joint Health Score (HJHS)

Subject ID #: _____

Name of physiotherapist: _____

Assessment #: _____

Date: _____

Time: _____

yyyy / mm / dd

Hemophilia Joint Health Score 2.1 – Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE
Duration (swelling)	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE
Muscle Atrophy	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE
Crepitus on motion	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE
Flexion loss	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE
Extension loss	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE
Joint pain	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE
Strength	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE	<input type="checkbox"/>	NE
Joint Total												

Sum of Joint Totals



NE = Non-Evaluable

Global Gait Score

(NE included in Gait items)

HJHS Total Score



Swelling

0 = None
1 = Mild
2 = Moderate
3 = Severe

Crepitus on Motion

0 = None
1 = Mild
2 = Severe

Strength (Using the Daniels & Worthingham's scale)

Within available ROM
0 = Holds test position against gravity within maximum resistance (gr. 5)
1 = Holds test position against gravity within moderate resistance (but breaks with maximal resistance) (gr. 4)
2 = Holds test position with minimal resistance (gr. 3+) or holds test position against gravity (gr. 3)
3 = Able to partially complete ROM against gravity (gr.3-/2+) Or able to move through ROM gravity eliminated (gr. 2) Or through partial ROM gravity eliminated (gr. 2-)
4 = Trace (gr.1) or no muscle contraction (gr. 0)
NE = Non-Evaluable

Duration

0 = No swelling
Or < 6 months
1 = ≥ 6 months

Flexion Loss

0 = < 5°
1 = 5° - 10°
2 = 11° - 20°
3 = > 20°

Muscle Atrophy

0 = None
1 = Mild
2 = Severe

Extension Loss

(from hyperextension)
0 = < 5°
1 = 5° - 10°
2 = 11° - 20°
3 = > 20°

Global Gait

0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-Evaluable

Joint Pain

0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

NOTE: there is an accompanying instruction manual and worksheets that are required when administering the HJHS

Appendix 8 Hemophilia Joint Health Score (HJHS) (cont.)

General comments:

The HJHS is designed for use by physiotherapists. In order to maintain the precision and validity of the tool (score), the developers of the tool strongly recommend that the tool be used by a physiotherapist/healthcare professionals who have hemophilia-related expertise/experience and have been trained in the use of clinical measures, musculoskeletal assessment and specifically administration of the HJHS.

It is essential for the physiotherapist to possess the requires expertise and skills necessary to use anthropometric measures such as muscle testing and range of motion /goniometry, as well as posture & gait assessment prior to performing the evaluation (HJHS).

Appendix 9

Guidelines for Dosing and Monitoring Bypassing Agents for Patients on Emicizumab

The use of bypassing agents is not expected in hemophilia A patients without inhibitors. For completeness, this appendix includes guidelines provided for treatment of breakthrough bleeds in patients with inhibitors. Careful consideration of the risks and potential benefits is advised when combining emicizumab, factor VIII (FVIII), and bypassing agent.

Drugs intended to control bleeds, including bypassing agents, should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase patients' coagulation potential, the doses required to achieve hemostasis may be lower than the FVIII or bypassing agent doses used prior to starting the study.

Caution should be taken for patients who are using recombinant activated factor VII (rFVIIa [e.g., consideration of using no more than 90 µg/kg of rFVIIa as an initial dose]).

Use of activated prothrombin complex concentrate (aPCC) in combination with emicizumab should be avoided completely in patients who have the option of using other bypassing agents to treat bleeds. In the event that aPCC is the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than 50 units/kg of aPCC to be administered as an initial dose.

Other bypassing agents (e.g., Byclot[®]) should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (e.g., no more than 60 µg/kg of Byclot[®]).

Exact dose and schedule of bypassing agents should be discussed with patients at the beginning and throughout the study. Repeated dosing of rFVIIa, aPCC, or other bypassing agents should be performed only under medical supervision, which includes laboratory monitoring by additional local and central laboratory assessments, and consideration should be given to verifying bleeds prior to repeated dosing.

Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab. The use of anti-fibrinolytics in conjunction with aPCC or Byclot[®] is prohibited.

MONITORING:

In the event of a bleed treated with bypassing agents, the following local laboratory tests will be performed within 24–48 hours of initial bypassing agent use so the investigator may monitor for potential thromboembolic events and thrombotic microangiopathy: platelet count, serum creatinine, LDH, and peripheral blood smear analysis to evaluate for schistocytes. A plasma sample should also be provided for local (first aliquot) and

Appendix 9

Guidelines for Dosing and Monitoring Bypassing Agents for Patients on Emicizumab (cont.)

central (second aliquot) laboratory monitoring of prothrombin fragment 1+2, fibrinogen, and D-dimer. If the test for prothrombin fragment 1+2 is not available at the site, the sample should be sent 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 unscheduled visit electronic Case Report Forms (eCRFs).

Appendix 10

Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.