- To evaluate the health status of patients according to EuroQoL 5-Dimension, 5–Level Questionnaire (EQ-5D-5L) scores after 24 weeks
- To assess preference for emicizumab regimen compared with previous regimen used
- To assess the number of days away from school/work
- To assess the number of days hospitalized

Safety Objectives

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

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

Pharmacokinetic Objective

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

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

Exploratory Pharmacodynamic Biomarker Objective

The exploratory PD biomarker objective is as follows:

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

Study Design

Description of Study

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

PK Run-In-Part

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

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

- To assess the number of days away from school/work
- To assess the number of days hospitalized

2.2.2 Safety Objectives

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

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

2.2.3 Pharmacokinetic Objective

The PK objective of this study is as follows:

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

2.2.4 Exploratory Pharmacodynamic Biomarker Objective

The exploratory PD biomarker objective is as follows:

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

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

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

3.1.1 PK Run-In Part

In the PK run-in part, a full PK profile will be measured in the first 6 enrolled patients during the first 4 weeks to characterize the pharmacokinetics of a single SC dose of 6 mg/kg emicizumab in patients with hemophilia A. After the first and second

emicizumab administration, an intense PK sampling will occur. A reduced PK sampling schedule will be used to characterize repeated Q4W SC administration from Week 9 to Week 21. After the sixth injection at Week 21, PK sampling frequency will be increased to characterize steady-state pharmacokinetics (see Appendix 2).

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

3.1.2 Expansion Part

An expansion phase will be conducted to further investigate the efficacy, pharmacokinetics, safety, and pharmacodynamics in a cohort of 40 patients. These patients will start with loading doses of 3 mg/kg QW × 4, followed by a maintenance dose of 6 mg/kg Q4W for at least 24 weeks overall. These patients will undergo PK sampling to investigate trough concentrations (C_{trough}) and samples (predose) will be drawn as per the schedule of assessments (see Appendix 2).

Single- and multiple-dose pharmacokinetics of emicizumab were characterized in Phase I and Phase II studies at doses up to 1 mg/kg and 3 mg/kg, respectively. After a single dose, the emicizumab plasma concentrations peaked 1–2 weeks after dosing. Plasma concentrations subsequently decreased with a mean elimination half-life ($t_{1/2}$) of 28.3–34.4 days, without clear differences among doses. Emicizumab exhibited linear PK, with exposure increasing in proportion to the dose. After multiple doses, 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 groups in which a single loading dose was administered and after approximately 24 weeks in the highest dose group, in which no initial loading dose was administered.

The exposure/response relationship of emicizumab (predicted plasma concentration at the time of bleeding event/bleeding event) was previously characterized with repeated time-to-event (RTTE) modeling. Simulations suggested that a median ABR of 1 is achieved for emicizumab trough plasma concentrations ≥ 16 μg/mL and a median ABR of 0 for emicizumab trough plasma concentrations ≥ 45 μg/mL. To achieve this level, once-weekly loading doses of 3 mg/kg for the first 4 weeks followed by QW maintenance doses of 1.5 mg/kg or Q2W maintenance doses of 3 mg/kg have been recommended for the other Phase III studies.

A dose of 6 mg/kg Q4W is equivalent in terms of cumulative dose to the dose levels of 1.5 mg QW or 3 mg/kg Q2W that are being evaluated in the other Phase III studies. Assuming linear PK up to 6 mg/kg, model-based simulations were used to explore whether a Q4W dosing regimen 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 ± 20.9 μg/mL and 1570 ± 447 day·μg/mL, respectively. While more than half of the patients would not be expected to have a trough level of ≥ 45 μg/mL at steady state, the simulated ABR distribution was similar to the planned dosing regimens of other Phase III studies. This Q4W dosing regimen is, therefore, expected to maintain similar efficacy to the QW and Q2W dosing regimens.

measurement of other coagulation or hemophilia-related factors as well. Finally, remaining plasma samples will be banked for future emicizumab-related research and will be stored for no longer than 5 years after study closure. No whole-blood samples will be collected except as used for local safety laboratory tests, and no DNA analysis will be performed in this study.

3.3.4 Rationale for Patient-Reported Outcome Assessments

HRQoL is an important outcome in the care of patients with hemophilia (Brown et al. 2009). HRQoL in patients with hemophilia is multifaceted and impacted by disease symptoms (i.e., pain, bleeding), treatment (i.e., prophylactic and on-demand), anxiety (around infusions), and limitations in daily activities.

The goal of measuring HRQoL is to quantify the benefit of treatment from the patient perspective. Previous studies with adolescent patients treated with prophylactic regimens 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 in adults treated with prophylactic regimens (Stasyshyn et al. 2014).

The inclusion of HRQoL measures in the current study will allow for the longitudinal assessment of the impact of prophylactic treatment with emicizumab in adolescents and adults with hemophilia A and an evaluation of any changes from their baseline assessment.

The study will also include a measure designed to capture patient preference with 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 inconvenient, and have a goal of achieving a “normal life” (Cimino et al. 2014). The inclusion of a fit-for-purpose preference survey after treatment with emicizumab will provide information on whether SC is preferred to IV administration and explore potential underlying reasons.

4. MATERIALS AND METHODS

4.1 PATIENTS

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

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (consent/assent will be taken as appropriate)

- Aged ≥ 12 years
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the patient-reported outcome (PRO) questionnaires and bleed diaries through the use of an electronic device
- Body weight ≥ 40 kg at screening
- Diagnosis of severe congenital hemophilia A or hemophilia A with FVIII inhibitors
- Patients using rFVIIa or willing to switch to rFVIIa as primary bypassing agent for the treatment of breakthrough bleeds
- FVIII inhibitor test during screening with titer results available prior to first administration of study drug
- Patients without FVIII inhibitors (< 0.6 BU/mL*; < 1.0 BU/mL only for laboratories with an historical sensitivity cutoff for inhibitor detection of 1.0 BU/mL*) who completed successful ITI must have done so at least 5 years before screening and must have no evidence of inhibitor recurrence (permanent or temporary) indicated by detection of an inhibitor > 0.6 BU/mL *(> 1.0 BU/mL only for laboratories with an historical sensitivity cutoff for inhibitor detection of 1.0 BU/mL)* since ITI
- For patients to be enrolled into PK run-in cohort:

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

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

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

assessments during the study may be performed by an MN professional at the patient's home or another suitable location, such as his or her school or office, to improve access and convenience for patients participating in the study. The Sponsor may select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor will be responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. For adolescents (i.e., 12–17 years of age), an Informed Assent Form will be completed instead. Parents or legally authorized representatives of adolescents will also complete an Informed Consent Form.

All screening evaluations must be completed within 4 weeks prior to the first dose and reviewed to confirm that patients meet all eligibility criteria before enrollment. 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 prior ITI, anaphylaxis, or known thrombophilia. It should also include all medication taken in the 4 weeks prior to enrollment (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies). Finally, all bleed information (i.e., start date, cause, type, location), number of school/work days missed, and number of days hospitalized during the 24 weeks prior to study entry should be documented.

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, respiratory, gastrointestinal, and neurological systems, height, and weight. Any abnormality identified during screening should be recorded on

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 health-related quality of life 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 (8–17 years) containing 35 items was selected for adolescents in 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 7), is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D-5L will be utilized in this study for economic modeling.

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).

Patient Preference

Patient preference 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 or bypassing agents (episodic or prophylaxis) prior to study entry and SC emicizumab during the study. 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 will complete this questionnaire at Week 17 on emicizumab.

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. Bleeds related to procedure/surgery are not associated with any trauma except procedure/surgery-induced trauma.

Patients (or their legally authorized representative) will complete a bleed/medication questionnaire weekly and whenever a bleed occurs via an electronic, handheld device. 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. If the electronic, handheld device is not available, a paper questionnaire might be used. Investigators will review the bleed and bleed medication data as per the schedule of assessments (see Appendix 1) and have the option to correct or complete these in agreement with the patient via a Data Request Form process or via a Web-based portal, once implemented. The Sponsor will have view-access only but will do a review of the bleed and bleed medication data as per the Medical Data Review Plan.

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)

[redacted]

For more details please refer to Investigator Brochure.

These events should be reported as serious adverse events or adverse events of special interest, see Section 5.2.3.

5.1.2.5 *Life-Threatening Bleeding Due to Unreliable Standard Coagulation Tests and Inhibitor Assays in the Setting of 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 t1/2 of emicizumab, these effects on coagulation assays may persist for up to 6 months after the last dose.

There is a risk of life-threatening bleeding due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab in the market setting by practitioners, particularly for emergency care practitioners.

Table 1 Guidelines for Management of Specific Adverse Events (cont.)

Event	Actions to Be Taken
Coagulation Disorder and Risk of Bleeding	• 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.

- 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)

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 mild, moderate, or severe, or according to the World Health Organization [WHO] toxicity grading scale; 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 3 and Appendix 4)
- 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 initiation of study drug**, 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 initiation of study drug, all adverse events will be reported until the patient completes his or her last study visit. 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 3) will be used for assessing adverse event severity (WHO 2003). Table 2 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 2 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 an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into:

- 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

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 are judged to be related to study drug injection should be captured as an "injection-site reaction" on the Adverse Event eCRF. Associated signs and symptoms (e.g., injection-site erythema or injection-site rash) should be recorded on the dedicated Injection-Site Reaction eCRF. If a patient experiences both a local and systemic reaction to the same administration of study drug, each reaction should be recorded separately on the Adverse Event eCRF. Only for local injection-site reactions should the dedicated Injection-Site Reaction eCRF be used to capture the individual signs/symptoms.

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 × 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 whether 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).

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).

- 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 Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for all sites

Medical Monitor	[redacted], Ph.D.
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Roche Medical Responsible:	[redacted], M.D.
Telephone No.:	[redacted]
Mobile 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 Responsible (listed above and/or on the Roche Medical Emergency List), 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 and Medical Responsible 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 Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. 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 Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 24 weeks after the last dose of study drug. 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 QW 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, so contraception use by male patients is not required for participation in the study. Therefore, 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).

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

The Sponsor will promptly evaluate all serious adverse events (see Section 5.2.2) 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:

- RO5534262 (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

No formal hypothesis testing is planned for this study. All analyses will be descriptive. The 6 run-in patients will be analyzed separately from the expansion cohort.

6.1 DETERMINATION OF SAMPLE SIZE

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

The overall sample size of 40 patients in the expansion cohort is based primarily on clinical considerations taking into account the limited number of patients with hemophilia A. *A sample size of 40 patients is expected to provide statistically robust point estimates with meaningfully narrow confidence intervals.*

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.4.2 Patient-Reported Outcomes

Scale scores for the Haemo-QoL-SF and the Haem-A-QoL will be calculated for each assessment, with change scores being examined for the assessments over the course of 24 weeks. These will be summarized descriptively.

The proportion of patients preferring emicizumab after 17 weeks of treatment will be presented along with the reasons for that choice. Summary statistics of the number of days away from school and days hospitalized will be presented.

6.5 SAFETY ANALYSES

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

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

For clinical laboratory data, summary statistics will be presented. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale (WHO 2003).

6.6 PHARMACOKINETIC ANALYSES

PK Run-In Cohort

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

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

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

Expansion Cohort

For all patients, predose (trough) plasma concentrations of emicizumab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

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

6.7 IMMUNOGENICITY ANALYSES

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

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized. Patients are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

6.8 EXPLORATORY ANALYSES

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

6.9 INTERIM ANALYSIS

6.9.1 Planned Interim Analysis

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

centralized database at the vendor of the electronic handheld devices. The data from the electronic devices are available for view access only via secure access to a Web portal provided by the vendor. 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 electronic handheld 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 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, electronic handheld device records, 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.

Appendix 1
Schedule of Assessments (cont.)

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

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

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

[b] In order to characterize pharmacokinetics, it is mandatory *for* assessments *to* be performed on the exact visit day until Week 25; no deviation from visit day is acceptable until Week 25, deviations of ±2 days are acceptable thereafter *until safety follow-up visit. Safety follow-up visit should be performed 24 weeks after discontinuation of emicizumab, deviation of +7 days is acceptable. The safety follow- up visit will not be performed for patients who transfer to an extension study or to commercial emicizumab.*

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

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

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

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

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

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

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

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

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

[c] 8 hours postdose on Day 1.

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

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

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

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

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

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

Appendix 3
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

LIVER ENZYMES continued				
Amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	> 5.0 × ULN
CHEMISTRIES				
Hyponatremia	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

Expansion Part

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

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

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

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

Emicizumab is intended for prophylactic use only (i.e., not to treat bleeds that have already occurred). There is clinical experience in the ongoing Phase I/II clinical studies with the treatment of over 60 breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents. FVIII, aPCC, or recombinant activated factor VII (rFVIIa) do not interfere with emicizumab PK assessments and no safety signals have been observed when breakthrough bleeds were treated with standard-of-care regimens during Phase I/II studies. However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), *3* events of TMA and 2 thromboembolic events were observed in patients who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds. Therefore, it is recommended that breakthrough bleeds in the inhibitor population are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided. *In addition, caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients who are receiving emicizumab, and the use of anti-fibrinolytics is prohibited in conjunction with aPCC or Byclot®.*

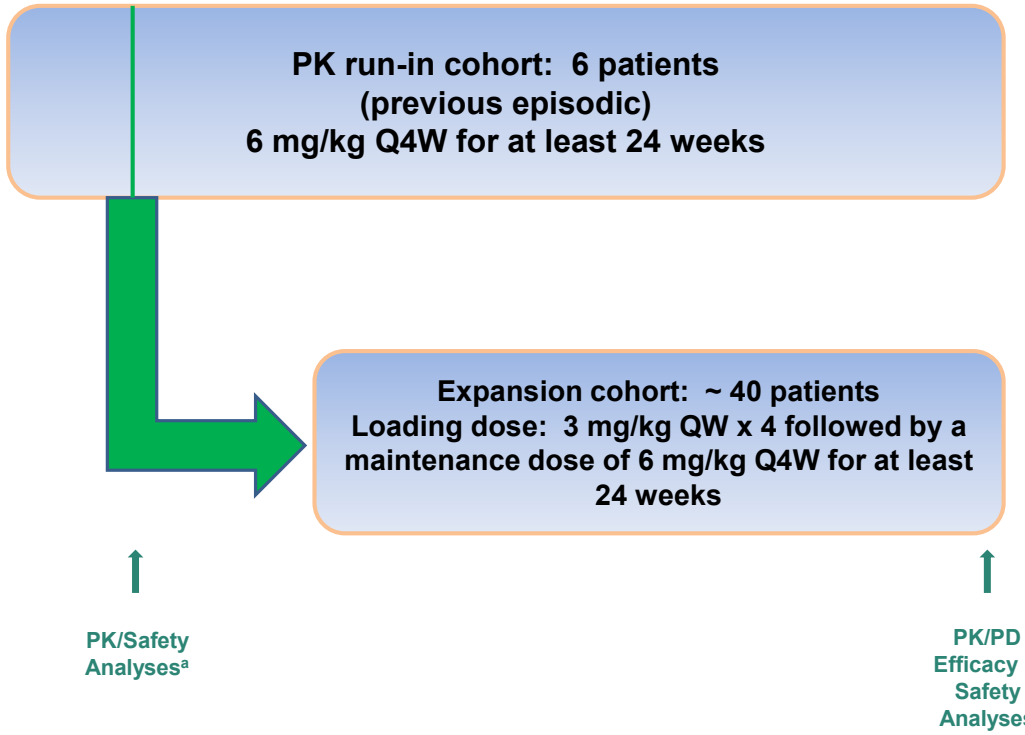
Therefore, a washout period of 72 hours prior to the first emicizumab dose in this study is required for patients receiving prior aPCC or Byclot. Also a washout period of 72 hours for patients who were previously receiving ITI is required prior to the first emicizumab administration. Patients may require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

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

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

Breakthrough bleeds will be treated with appropriate coagulation products with either FVIII (non-inhibitor patients) or rFVIIa (inhibitor patients) at the lowest expected dose to achieve hemostasis and captured as they occur. When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed (e.g., other than emicizumab in case of breakthrough bleeds). The reason for the use

Figure 1 Study Schema



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

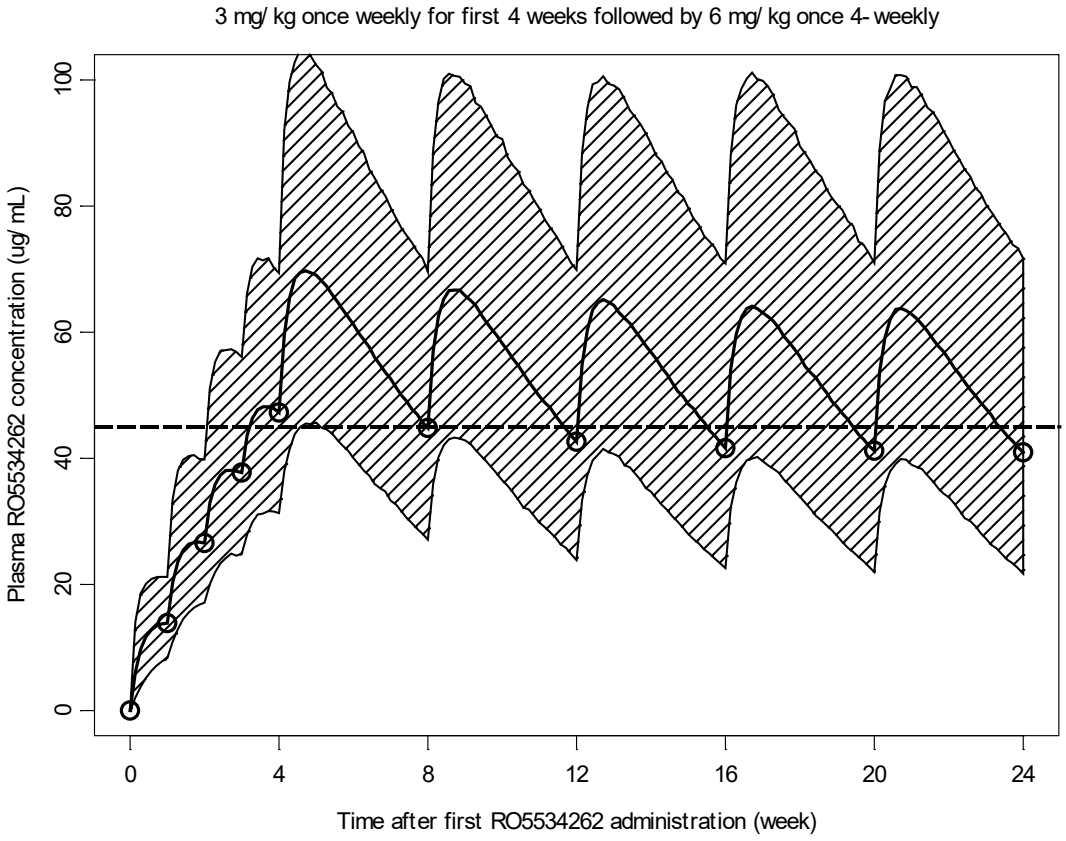
[a] Analysis will occur when last patient enrolled in the PK run-in cohort has been in the study for 6 weeks.

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

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

Physical examinations, vital signs, ECG, and laboratory assessments will be performed as detailed in the schedule of assessments (see Appendix 1) and will be the same for all patients receiving emicizumab, regardless of whether they are enrolled in the PK run-in cohort or the expansion cohort. Adverse events will be captured on an ongoing basis, as they occur during the study.

Figure 2 Simulated Plasma Emicizumab Concentration over Time (Q4W Dosing)



Q4W = every 4 weeks.

Notes: Once-weekly loading dose of 3 mg/kg for first 4 weeks followed by every 4 weeks maintenance dose of 6 mg/kg was applied.

X-axis = time after first emicizumab administration (week).

Y-axis = plasma emicizumab concentration (μg/mL).

Dots and solid line = simulated median plotted at each trough sampling timepoint.

Shaded area = simulated 5- to 95-percentile range.

Broken line = target exposure level of 45 μg/mL.

Overall, a Q4W dosing regimen with 6 mg/kg is expected to provide favorable safety and efficacy in patients with hemophilia A with or without inhibitors.

3.3.2 Rationale for Patient Population

This study will include patients with hemophilia A, irrespective of the presence of FVIII inhibitors. The mode of action of emicizumab is identical in the inhibitor and non-inhibitor populations, and data from Phase I/II studies did not show a difference in pharmacokinetics, safety, or efficacy between patients with or without inhibitors against FVIII. Ideally, a representative variety of patients with hemophilia A should be enrolled

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. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of <1% per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide

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

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
- Ongoing or planned ITI therapy; patients in whom ITI has failed will be eligible with a 72-hour washout period prior to the first emicizumab administration
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment
- Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Known HIV infection with CD4 counts <200 cells/μL

  HIV infection with CD4 counts ≥200 cell/μL permitted
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy

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, if appropriate.

4.5.4 Vital Signs

Vital signs will include measurement of heart and respiratory rate, temperature, and systolic and diastolic blood pressure 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. On days of study drug administration, laboratory samples should be drawn before the administration of study drug. In the PK run-in, no deviation from defined drug administration visits is allowed until Week 25. Deviations from the schedule of assessments of ±2 days are acceptable after Week 25 in the PK run-in cohort. For the expansion cohort, deviations from the schedule of assessments of ±2 days are acceptable; however, predose PK and PD sample collection and drug administration should coincide.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- 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, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase)
- 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.

In the event of use of a bypassing agent, the following local laboratory tests will be performed within 24–48 hours of initial bypassing agent *administration* so the investigator may monitor for potential thromboembolic events and thrombotic microangiopathy: platelet count, serum creatinine, LDH, and schistocytes. A plasma

4.5.8 Bleed Definitions

Definition of a Bleed

For the purpose 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 be utilized in this study (Blanchette et al. 2014; Mahlangu et al. 2014).

- An event is considered a bleed if coagulation factors are administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.). An additional definition of all reported bleeds (irrespective of treatment with coagulation factors) will be applied for a separate analysis.
- 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 $\leq$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.

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 $\geq$3 bleeds into the same joint over the last 24 weeks prior to study entry)
- Joint bleeds *are* defined as *bleeds with bleed type "joint bleed" reported via the bleed/medication questionnaire* with *at least one* of the following *symptoms*:

  Increasing swelling or warmth of the skin over the joint

  Increasing pain

  Progressive loss of range of motion or difficulty in using the limb as compared with baseline
- Muscle bleeds (sites as per the bleed/medication questionnaire)
- Other (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." The determination of what constitutes "strenuous" or "overuse" will be at the discretion of the patient. For

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. Patients participating in the PK run-in cohort who withdraw from the study will be replaced if they withdraw prior to being in the study for 6 weeks. Patients participating in the expansion cohort who withdraw at any time will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience the following:

- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

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:

- The 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
- 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 the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Emicizumab is currently in clinical development and is not approved. Thus, the complete safety profile is not known at this time. The safety plan for this study is

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 April 2017, no instances of under-treatment of bleeding events due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab were observed.

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 cannot be detected 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

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 cause 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 A.

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 A, "hemophilia A 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.

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.

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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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 24 weeks after the last dose of study drug or rollover to an extension study), if the event is believed to be related to prior study drug treatment.

These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, 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.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

6.4 EFFICACY ANALYSES

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

6.4.1 Efficacy Endpoints

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

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

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

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

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

The clinical effect of prophylactic emicizumab on the number of bleeds, joint bleeds, target joint bleeds, spontaneous bleeds and all bleeds (i.e., those treated and untreated with coagulation factors) over time will be evaluated (see Section 2.2.1).

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

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

A detailed description of the statistical methods that will be used for the efficacy analyses will be provided in the Statistical Analysis Plan.

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

6.9.2 Optional Interim Analysis

Additional interim data reviews may be performed at various timepoints to support regulatory submissions.

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.

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

Patient-reported data will be collected electronically with use of electronic devices. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted electronically in real-time to a

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, electronic PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 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).

8.2 INFORMED CONSENT

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

Appendix 1
Schedule of Assessments (cont.)

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

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

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

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

[l] For any dose increase (i.e., 3 mg/kg QW), an ECG should be obtained after 4–8 weeks *and 24 weeks after* dose *up-titration, as well as at study completion/ early termination*.

[m] Predose (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width), performed locally. Laboratory assessments completed at the screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator. *If patients undergo up-titration of their dose after ≥ 24 weeks on emicizumab, an additional blood draw for safety laboratory assessments should be performed within the first 4 weeks after up-titration.*

[n] Predose (sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase), performed locally. Laboratory assessments completed at the screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator. *If patients undergo up-titration of their dose after ≥ 24 weeks on emicizumab, an additional blood draw for safety laboratory assessments should be performed within the first 4 weeks after up-titration.*

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

[p] 6 mg/kg Q4W emicizumab.

[q] Bleed information (start date and time, reason, type, location, and associated symptoms of each bleed) and medication for bleeds (breakthrough bleeds) should be reported by the patient via an electronic handheld device when a bleed occurs or at least on a weekly basis (retrospective reporting for last 7 days). If the patient discontinues study treatment, bleed and bleed medication data should be provided by the patient until the safety follow-up visit (24 weeks after last study drug administration). *Emicizumab doses should be recorded by the patient in the bleed/medication questionnaire starting from Day 1.*

[r] Investigator review of bleed information.

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

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

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

Appendix 3
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

CHEMISTRIES continued				
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
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 1–2 g loss/day	4 + or > 1.0% or > 10 g/L 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