PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF EMICIZUMAB IN PATIENTS WITH MILD OR MODERATE HEMOPHILIA A WITHOUT FVIII INHIBITORS**
PROTOCOL NUMBER:	BO41423
VERSION NUMBER:	3
EUDRACT NUMBER:	2019-002179-32
IND NUMBER:	122954
NCT NUMBER:	NCT04158648
TEST PRODUCT:	Emicizumab (RO5534262)
MEDICAL MONITOR:	[redacted], Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
18-Nov-2020 19:19:45	CMD	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	27 May 2019
2	20 December 2019

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol BO41423 has been amended to make minor changes, to correct errors, and to provide clarification. Changes to the protocol, along with a rationale for each change, are summarized below:

- Sections 2.2.2 and 4.5.7.4 now clarify the definition of target joint bleeds. The definition now includes unresolved target joints. An unresolved target joint is a target joint that does not fulfil the criterion of ≤ 2 bleeds into this joint within a consecutive 12-month period.
- Wording was corrected for consistency to state that the primary analysis will be conducted after 50 patients (not all patients) with moderate hemophilia A have completed 52 weeks of emicizumab treatment, are lost to follow-up, or have withdrawn, whichever occurs first (Section 3.1).
- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during IMP transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.4).
- The CRF page for entry of FVIII prophylaxis treatment in the week prior to enrollment was renamed (Section 4.4, Appendix 1).
- The protocol now clarifies that a mobile nurse may administer emicizumab or perform other assessments during home visits if necessary (Sections 4.5, 4.5.5, and Appendix 1).
- Language has been added to clarify that adverse events associated with special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.12).
- Language regarding investigator reporting of pregnancies has been clarified (Section 5.4.3.2).
- A sentence describing a secondary efficacy endpoint was removed (Section 6.5.2.2). This sentence was inadvertently carried over from previous HAVEN study protocols but does not apply to BO41423.
- Footnote g in Appendix 1 has been clarified to state that the Emipref (patient version) and EQ-5D-5L instruments will not be completed by patients < 12 years of age.
- Footnote h in Appendix 1 has been clarified to state that the Hemophilia Joint Health Score (HJHS) assessment will be performed for patients ≥ 4 years of age.
- Footnote g in Appendix 2 clarifies the timing for the screening sample for anti-FVIII antibodies and notes that results must be available before enrollment. In addition, it now states that local testing will not replace the central laboratory inhibitor testing performed at Week 1.

- The scoring numbers in tables in the Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) questionnaires have been removed (Appendices 4–6) because there were discrepancies with the scoring manual. The scoring is incorporated in the programming of the underlying algorithm.

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF EMICIZUMAB IN PATIENTS WITH MILD OR MODERATE HEMOPHILIA A WITHOUT FVIII INHIBITORS**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF EMICIZUMAB IN PATIENTS WITH MILD OR MODERATE HEMOPHILIA A WITHOUT FVIII INHIBITORS**
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EUDRACT NUMBER:	2019-002179-32
IND NUMBER:	122954
NCT NUMBER:	NCT04158648
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase III
INDICATION:	Mild or moderate hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients of all ages with mild (factor VIII [FVIII] level between $>5\%$ and $<40\%$) or moderate hemophilia A (FVIII level between $\geq 1\%$ and $\leq 5\%$) without inhibitors against FVIII whose bleeding phenotype warrants prophylactic treatment. Specific objectives and corresponding endpoints for the study are outlined below.

Safety Objective

The safety objective for this study is to evaluate the safety profile of emicizumab in patients with non-severe hemophilia A without inhibitors on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to WHO Toxicity Grading Scale
- Incidence of thromboembolic events
- Incidence of thrombotic microangiopathy
- Change from baseline in physical examination findings
- Change from baseline in and vital signs
- Change from baseline in ECG parameters
- Incidence of laboratory abnormalities
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to drug discontinuation
- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events
- Incidence and significance of anti-emicizumab antibodies
- Incidence of de novo development of FVIII inhibitors

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of emicizumab on the basis of the following endpoint:

- Number of treated bleeds over time (i.e., bleed rate)

Secondary Efficacy Objectives

The secondary efficacy objective for this study is to evaluate the efficacy of emicizumab on the basis of the following endpoints:

- Number of all bleeds (i.e., those treated and untreated with FVIII) over time
- Number of joint bleeds over time
- Number of target joint bleeds over time (target joints are defined as joints with ≥3 bleeds occurring in the same joint during the last 24 weeks *or unresolved target joints)*

  An unresolved target joint is defined as a target joint that does not fulfill the criterion of ≤2 bleeds into this joint within a consecutive 12-month period.
- Number of spontaneous bleeds over time (spontaneous bleed rate)
- Joint health, as assessed through use of the Hemophilia Joint Health Score at specified timepoints
- Health-related quality of life (HRQoL), as assessed through use of the Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) Questionnaire over time
- Preference for emicizumab compared with previous FVIII regimen, as assessed through use of the Emicizumab Preference Survey (EmiPref) at Week 17
- Effect of emicizumab prophylaxis treatment on physical activity compared with physical activity at baseline
- Effect of emicizumab prophylaxis treatment on menstruation heaviness and menstruation-related quality of life in female patients, as assessed through the use of the Menstrual Bleeding Questionnaire (MBQ) and the Menstruation Diary (MD) with the Pictorial Blood Assessment Chart (PBAC)

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the emicizumab PK profile on the basis of the following endpoint:

- Plasma concentration of emicizumab at specified timepoints

Immunogenicity Objective

The immunogenicity objective for this study is to evaluate the immune response to emicizumab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study
- Number and proportion of patients who develop anti-FVIII inhibitors (titer≥0.6 BU/mL) at specified timepoints

Biomarker Objective

The exploratory biomarker objective for this study is to investigate the effect of emicizumab on pharmacodynamic (PD) parameters, including but not limited to thrombin generation, FVIII activity, FVIII protein, D-dimer, and prothrombin fragment 1+2 (PF1+2) at regular intervals throughout the study and at times of treated bleeds. Changes over time in biomarkers related to bone and joint health may also be explored.

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with emicizumab on the basis of the following endpoint:

- Change from baseline in EuroQol 5-Dimension 5-level Questionnaire (EQ-5D-5L) index utility and visual analog scale scores at specified timepoints

Study Design

Description of Study

Study BO41423 is a multicenter, open-label, single-arm study designed to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients with mild or moderate hemophilia A without inhibitors against FVIII. Four loading doses of emicizumab 3 mg/kg will be administered subcutaneously once a week (QW) for 4 weeks followed by patient preference of one of the following maintenance regimens: 1.5 mg/kg QW, 3 mg/kg every 2 weeks (Q2W), or 6 mg/kg every 4 weeks (Q4W). The three maintenance dose regimens have shown equivalent average steady-state exposure, and demonstrated consistent efficacy and safety, and are approved in several countries for the treatment of Hemophilia A with or without FVIII inhibitors. As patients with mild or moderate Hemophilia A have residual FVIII levels of $\geq$1%, it is of interest to collect safety data over a longer time period. Therefore, in this study, the observation time to primary analyses was extended to approximately 52 weeks compared with prior Phase III studies investigating emicizumab.

Patients (or their legally authorized representative herein referred to as patient[s]) will choose the preferred emicizumab maintenance regimen (1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W) after consultation with his or her treating physician. The chosen regimen needs to be maintained throughout the study until completion of at least 52 weeks.

During the study, individual bleeds will be captured by the patient as the bleeds occur using a Bleed and Medication Questionnaire. Breakthrough bleeds will be treated with FVIII at the lowest dose expected to achieve hemostasis.

Female patients of childbearing potential will be administered two specific patient-reported outcome measures related to their menstruation (both questionnaires administered on paper): the MBQ will assess the menstrual bleed-related heaviness, pain, irregularity and quality of life; the Menstruation Diary (MD) with the PBAC will assess the use of sanitary products for menstruation (including the number of products used, the amount of bleeding, the occurrence and size of clots, and the number of episodes of heavy bleeding (flooding)).

HRQoL (CATCH and EmiPref) and health status (EQ-5D-5L) will be assessed as outlined in the schedule of activities. These measures will be captured either on paper questionnaires or on a site-based tablet available to patients during clinic visits.

Safety assessments will include physical examinations, vital signs, ECG, laboratory assessments (serum chemistry and hematology including complete blood count with differential), anti-drug antibodies (ADAs), and FVIII inhibitors. Adverse events will be captured on an ongoing basis, as they occur during the study.

Exploratory PD biomarkers (e.g., FVIII activity, thrombin generation) will be collected on a regular basis throughout the study and will be coupled with a PK assessment for days where PK and PD samples will be drawn.

Biomarkers related to thromboembolism (e.g., D-dimer, PF1+2) and immunologic biomarkers (i.e., anti-emicizumab antibodies) will be measured on a regular basis throughout the study.

Exploratory PD biomarkers and safety biomarkers will be collected within 24 hours but no later than 48 hours of a treated bleed.

After 24 weeks on prophylactic emicizumab, patients with suboptimal bleed control will be offered the option to increase their dose to 3 mg/kg QW, with approval from the Medical Monitor, if the protocol-defined criteria of suboptimal response is met.

Interim data reviews may be performed at various timepoints (e.g., for regulatory submissions), and the primary analysis for all patients will be conducted after 50 patients with moderate hemophilia A have completed 52 weeks of emicizumab treatment, are lost to follow-up, or have withdrawn, whichever occurs first. The primary analysis will occur at the specified time regardless if no patients with mild hemophilia A are enrolled; however, enrollment will be left open for patients with mild hemophilia A in order to enroll approximately 20 such patients. The total number of patients in the study might slightly exceed 70 patients depending on the number of female patients enrolled. Ideally, at least 5 female patients will be enrolled. If these are not

recruited within the pool of 70 patients, the enrollment will remain open until they are enrolled or until the cutoff date of primary analysis, whichever occurs sooner. Note that all patients will be included in the primary analysis irrespective of their follow-up time. After the primary analysis, patients will continue to receive emicizumab according to the Roche Policy on post study drug access until emicizumab is approved and accessible to patients commercially.

Patients who discontinue study drug prior to end of study will return to the clinic for a safety follow-up visit 24 weeks after the last dose of study drug. Patients who complete or discontinue from the study will return to the clinic for a study completion/discontinuation visit.

Number of Patients

Approximately 70 patients of all age groups will be enrolled in the study consisting of approximately 20 patients with mild and approximately 50 patients with moderate hemophilia A without FVIII inhibitors whose phenotype warrants prophylaxis. The total number of patients in the study might slightly exceed 70 patients depending on the number of female patients enrolled.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (signed by patient's legally authorized representative for patients who have not attained the age of majority)
- Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Willingness and ability to comply with schedules visits, treatment plans, laboratory tests and other study procedures
- Diagnosis of mild (FVIII level between $>5\%$ and $<40\%$) or moderate (FVIII level between $\geq 1\%$ and $\leq 5\%$) congenital Hemophilia A without FVIII inhibitors
- Weight ≥ 3 kg
- Need for prophylaxis based on investigator assessment
- A negative test for inhibitor (i.e., <0.6 BU/mL) within 8 weeks prior to enrollment
- No documented inhibitor (i.e., <0.6 BU/mL), FVIII half-life <6 hours, or FVIII recovery $<66\%$ in the last 5 years

  Patients who completed successful immune tolerance induction (ITI) at least 5 years before screening are eligible, provided they have had no evidence of inhibitor recurrence (permanent or temporary) as may be indicated by a detection of an inhibitor, FVIII half-life <6 hours or FVIII recovery $<66\%$ since completing ITI.
- Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks prior to enrollment
- Adequate hematologic function, defined as platelet count $\geq 100{,}000$ cells/µL and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function defined as total bilirubin $\leq 1.5 \times$ age-adapted upper limit of normal (ULN) (excluding Gilbert syndrome) and both AST and ALT $\leq 3 \times$ 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 $\leq 2.5 \times$ age-adapted ULN and creatinine clearance ≥ 30 mL/min by Cockroft-Gault formula
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

  Women must remain abstinent or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 24 weeks after the final dose of study drug.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

- Inherited or acquired bleeding disorder other than mild (FVIII level between >5% and <40%) or moderate (FVIII level between ≥1% and ≤5%) congenital hemophilia A
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, 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 during the emicizumab loading dose phase

  Surgeries in patients on emicizumab from Week 5 onwards are allowed.
- Known HIV infection with CD4 counts <200 cells/μL
- Concomitant disease, condition, significant abnormality on screening evaluation or laboratory tests, or treatment that could interfere with the conduct of the study, or that would in the opinion of the investigator, pose an additional unacceptable risk in administering study drug to the patient
- Receipt of any of the following:
  - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration with the exception of prior emicizumab prophylaxis (prior investigational or commercial emicizumab use is not an exclusion criterion)
  - A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
  - Any other investigational drug currently being administered or planned to be administered
- Inability to comply with the study protocol in the opinion of the investigator
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

End of Study

The end of this study is defined as the date when the last remaining patient has completed the last visit, as defined by the following criteria: completion of at least 52 weeks of emicizumab treatment during the study and either transfers to commercially available emicizumab or receives further emicizumab per Roche Global Policy on Continued Access to Investigational Medicinal Products OR completion of the end of study safety follow-up visit 24 weeks after discontinuing emicizumab OR withdrawal of consent OR lost to follow-up.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 27 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product for this study is emicizumab. The emicizumab dosing regimen to be tested is emicizumab 3 mg/kg SC QW for 4 weeks followed by a maintenance dose of either 1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W.

All patients with suboptimal control of bleeding as defined by the protocol will be offered the option to increase their emicizumab maintenance dose to 3 mg/kg QW, with approval from the Medical Monitor. Suboptimal response is defined as follows: $\geq$2 qualifying bleeds within 24 weeks while on prophylactic emicizumab.

Statistical Methods

Primary Analysis

The primary analysis will be performed after 50 patients with moderate hemophilia A have either completed 52 weeks of emicizumab treatment, are lost to follow-up, or have withdrawn prematurely, whichever occurs first. Data from all patients (including any female patients and any patients with mild hemophilia A) will be included in the primary analysis.

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 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.

Summaries will be presented overall, by dosing regimen, and, if applicable, by disease severity. Further details will be provided in the Statistical Analysis Plan.

The key efficacy objective is to characterize the efficacy of emicizumab based on the number of treated bleeds over time. The clinical effect of prophylactic emicizumab will be assessed via the annualized bleed rate estimated using a negative binomial regression model, which accounts for different follow-up times, with the number of bleeds from patients as a function of the time such that each patient who stays in the study is included as an offset in the model. A detailed description of the statistical methods and the summaries, if applicable, presented by dosing regimen and/or by disease severity for the efficacy analyses will be provided in the Statistical Analysis Plan.

Determination of Sample Size

The overall sample size of approximately 70 patients (approximately 50 patients with moderate disease, approximately 20 patients with mild disease) is based primarily on clinical considerations, taking into account the limited number of patients with non-severe hemophilia A. This sample size is expected to provide statistically robust point estimates with meaningfully narrow CIs in the overall group of enrolled patients, assuming the same efficacy across dosing regimens.

Optional Interim Analyses Reviews

Interim data reviews may be performed at various timepoints for regulatory submissions.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	annualized bleed rate
ADA	anti-drug antibody
aPCC	activated prothrombin complex concentrate
BMQ	Bleed and Medication Questionnaire
CATCH	Comprehensive Assessment Tool of Challenges in Hemophilia
DSC	daily step count
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EmiPref	Emicizumab Preference Survey
EQ-5D-5L	European Quality of Life 5-Dimension, 5-Level Questionnaire
FDA	Food and Drug Administration
FIXa	activated factor IX
FVIII	factor VIII
FX	factor X
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
HJHS	Hemophilia Joint Health Score
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITI	immune tolerance induction
IxRS	interactive voice or web-based response system
MBQ	Menstrual Bleeding Questionnaire
MD	Menstruation Diary
MN	mobile nursing
MVPA	moderate to vigorous physical activity
PBAC	Pictorial Blood Assessment Chart
PD	pharmacodynamic
PF1+2	prothrombin fragment 1+2
PK	pharmacokinetic
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks

Abbreviation	Definition
QW	once a week
RBR	Research Biosample Repository
rFVIIa	recombinant activated factor VII
SAP	Statistical Analysis Plan
TMA	thrombotic microangiopathy
ULN	upper limit of normal
VAS	visual analog scale
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HEMOPHILIA A AND DISEASE SEVERITY

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

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

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of the disease roughly correlates with the residual endogenous level of FVIII activity.

Severity of hemophilia A is largely defined by either clinical bleeding symptoms or residual plasma FVIII activity levels. A widely used classification system is based on plasma FVIII activity, with a FVIII level between $>5\%$ and $<40\%$ of normal considered to be mild disease, a level between $\geq 1\%$ and $\leq 5\%$ to be moderate disease, and a level $<1\%$ to be severe disease (White et al. 2001). Approximately 63% of people with hemophilia A have a moderate (19%) or severe (44%) form, leading to frequent bleeding events (bleeds) with the sequelae of musculoskeletal complications (e.g., arthropathy), local functional deficits, hemorrhagic shock, neurocognitive defects, or even death (World Federation of Hemophilia 2017). Although classifications based exclusively on residual FVIII levels are often proportionally manifested in clinical presentations of types and numbers of bleeding episodes, phenotypic heterogeneity exists such that a subset of non-severe patients exhibit a severe bleeding phenotype (Di Minno et al. 2013) and therefore may require prophylactic treatment. Indeed, the predictive value of residual FVIII levels to define severity of hemophilia has been recently called into question, with traditional classification of patients into mild, moderate, and severe categories being

recognized as inadequate in directing the management of patients with hemophilia. A recent International Society on Thrombosis and Haemostasis guidance (Mancuso et al. 2018) now recommends development of criteria for "clinically severe hemophilia" which would inform treatment strategies (e.g., prescribing prophylaxis vs. on-demand regimens based on bleeding phenotype instead of on residual clotting factor activity alone). Therefore, no a priori criteria can be defined and the decision which patient warrants prophylaxis remains with the treating physician, as it is currently.

Joint bleeding is a hallmark of hemophilia A, mostly involving large synovial joints such as the knees, elbows, and ankles (Bolton-Maggs and Pasi 2003). Repeated hemarthrosis causes inflammation and synovial degeneration leading to chronic arthropathy, a common and major complication in patients with hemophilia (Raffini and Manno 2007). Whereas patients with mild and moderate disease generally report a significantly lower number of joint bleeds compared with those with severe hemophilia, there are patients with non-severe disease who present with recurrent articular bleeds. Accordingly, hemophilic arthropathy with its associated morbidity is observed in about 30% of non-severe patients (Soucie et al. 2004; Den Uijl et al.2009, 2011). A national survey from the Netherlands, which included 1066 patients with hemophilia A showed that 43% of patients with moderate hemophilia had joint damage, with 32% of cases having multiple sites of articular impairment (Soucie et al. 2004; Den Uijl et al.2009, 2011). Of 470 patients with mild disease, 11% of patients required orthopedic aids such as crutches and walking sticks and 7% of patients reported chronic joint pain. These data suggest that arthropathy, although uncommon, is debilitating for patients with mild disease who experience chronic hemarthrosis (Ling et al. 2011).

The body of literature describes a well-recognized group of patients with non-severe hemophilia A whose significant bleeding phenotype results in hemophilic complications and thus justifies routine prophylactic treatment. This is illustrated best by a recent report on 3,315 patients with non-severe hemophilia A that revealed a 6-month joint bleed rate >0.8 in adults and adolescents with FVIII level of 10% (Soucie et al. 2018). Accordingly, in current practice, the decision to initiate prophylaxis in patients with non-severe hemophilia A relies on the clinical judgment of the treating physician, based on the bleeding phenotype of the patient.

Primary prophylaxis is beneficial for patients with non-severe hemophilia A who present with more severe bleeding patterns. Indeed, prophylactic replacement therapy is used by approximately 30% of patients with non-severe hemophilia A (Di Minno et al. 2013; Den Uijl et al. 2014). A recent survey described the treatment and bleeding patterns in adult and pediatric patients across centers and registries from Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom. Overall, of 342 patients with moderate hemophilia A, approximately one third to one half of patients received regular prophylaxis without significant difference across age groups (Berntorp et al. 2017). Similarly, a recent survey in Australia revealed that 25% of patients with moderate hemophilia A receive regular prophylaxis (Mason et al. 2018). A recent report from the

UK National Haemophilia Database is consistent with these results and provides a unique nationwide view of treatment of patients with moderate hemophilia A. Of 864 patients, 273 (31.6%) patients had a significant bleeding phenotype and kept a regular treatment diary. Complete data was available for 154 individuals, of whom 68.8% used FVIII prophylaxis regularly. The median annualized bleed rate (ABR) for this group was 3 (1.0–7.0), of which 24% of patients experiencing no bleed (Scott et al. 2019).

1.2 BACKGROUND ON EMICIZUMAB

1.2.1 Molecule and Preclinical Data

Emicizumab (also known as ACE910, RO5534262, and HEMLIBRA®) is a recombinant, humanized, bispecific, immunoglobulin G4 monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of FVIII. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of SC administration, removing the need for venous access. Finally, because of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of this antibody, use of emicizumab enables a dosing interval of once a week (QW), every 2 weeks (Q2W), or every 4 weeks (Q4W).

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

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

A subgroup of the cynomolgus monkeys treated with repeat doses of emicizumab showed the formation of anti-emicizumab antibodies (which is expected with humanized monoclonal antibodies) with few animals also showing antibodies with neutralizing potential. Aspects of acute as well as repeat-dose toxicity including local tolerance assessment were evaluated in cynomolgus monkeys in 4-, 13-, and 26-week SC dose toxicity studies (at doses up to 30 mg/kg QW) and a 4-week IV dose toxicity study (at doses up to 100 mg/kg QW). No toxicologically relevant changes attributable to SC or IV administration of emicizumab were observed; the no-observed-adverse-effect level

was the highest tested dose in each toxicity study. These in vitro studies are consistent with in vivo results of repeat-dose toxicology studies. In these experiments, normo-coagulative monkeys with 100% FVIII activity were exposed to repeat doses and showed no prothrombotic effects in any organs or tissues even at supra-therapeutic levels of emicizumab (Roche Report Numbers: 1060133, 1060134, 1060140, and 1060168). This nonclinical model provides a more extreme condition than prophylaxis treatment of patients with non-severe disease whose residual FVIII activities are far below 100%.

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

1.2.2 Clinical Experience

Currently available experience with emicizumab in humans includes data from three completed Phase I studies (ACE001JP, JP29574, and YP39308); one completed Phase I/II extension study (ACE002JP) in patients with hemophilia A; and five ongoing Phase III studies in adults and adolescent patients with hemophilia A with inhibitors (BH29884, MO39182), without inhibitors (BH30071), and with or without inhibitors (BO39182 and YP39309); and two ongoing Phase III studies in pediatric patients with (BH29992) and without (JO39881) inhibitors.

Based on the Phase III program, emicizumab gained approval in many countries, including the United States and is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adults and children with hemophilia A (congenital FVIII deficiency) with or without FVIII inhibitors and can be used in all age groups. In the European Union, the label is restricted to patients with severe hemophilia A (FVIII level $<1\%$). Refer to U.S. Prescribing Information and Summary of Product Characteristics for full details on approved indications.

Refer to the RO5543262 (Emicizumab) Investigator's Brochure for details on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

To investigate emicizumab prophylaxis in patients with mild or moderate hemophilia A, this study will evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients with mild (FVIII level between $>5\%$ and $<40\%$) or moderate hemophilia A (FVIII level between $\geq 1\%$ and $\leq 5\%$) without inhibitors against FVIII whose bleeding phenotype warrants prophylactic treatment.

In patients who experience multiple spontaneous bleeds (regardless of their specific FVIII level), a prophylactic approach is beneficial as it will prevent the occurrence of bleeds and their consequences. Given the clinically meaningful efficacy of emicizumab in the prevention of bleeds and the major benefit it offers over available agents,

emicizumab is considered an appropriate option in the medical armamentarium for individuals with non-severe hemophilia A who require prophylaxis.

Patients with non-severe hemophilia A experience bleeds because of reduced FVIII activity and consequently inefficient formation of the intrinsic tenase complex. Physiologically, the coagulation system is in a dynamic balance between a tendency to bleed and the tendency to clot, which should provide adequate hemostasis without thrombotic events. In patients with hemophilia, the balance tips towards bleeding, whereas in patients with thrombophilia it tips towards thrombosis. As described above, by its very nature, emicizumab is intended for routine prophylaxis for prevention of bleeds. As such, patients with non-severe hemophilia A who will use emicizumab are those patients for whom routine prophylaxis is indicated by clinical symptoms. These individuals are suffering from a severe bleeding phenotype, reflecting a coagulation balance markedly slanted towards propensity to bleed despite residual FVIII activity.

Regarding the theoretical risk of thrombotic complications in patients receiving emicizumab prophylaxis in addition to constant residual low FVIII activity, the Sponsor considered characteristics of the patient population, emicizumab biochemical properties, and in vitro and in vivo data, as well as available clinical experience. Together, these data do not point to an increased risk of thrombosis in patients with non-severe hemophilia A treated with emicizumab.

When considering the coagulation potential of the combination of FVIII and emicizumab, it is important to account for their different biochemical characteristics. Although emicizumab facilitates the intrinsic tenase reaction, its affinity for FIXa or FX is at least 10-fold lower than that of FVIIIa. Additionally, kinetic analysis of FIXa-catalyzed FX activation demonstrates that the rate of tenase reaction in the presence of emicizumab is 1/44 of the reaction rate in the presence of FVIIIa, suggesting that while emicizumab mimics FVIIIa, its enzymatic kinetics are not as strong as FVIIIa (Kitazawa et al. 2017). These properties of emicizumab safeguard against the risk of a synergistic effect in thrombin generation with FVIIIa.

In line with these characteristics, in vitro data indicate that while emicizumab is highly effective in increasing generation of thrombin in the presence of 1 IU/dL or 10 IU/dL of FVIII (FVIII levels akin to patients with mild and moderate hemophilia), the level of thrombin generation in these conditions is a fraction of the thrombin generated in the presence of normal FVIII concentration. Importantly, at 100 IU/dL FVIII (normal levels), emicizumab does not add to the generation of thrombin, beyond the effect of FVIII (Roche Report No. 1060118). Similarly, Nogami et al. (2018) recently reported the results of clot waveform analysis demonstrating a decreasing contribution of emicizumab in the presence of increasing FVIII. They further demonstrated that the combination of 40% FVIII activity with 100 µg/mL emicizumab yields a lower Ad|min1| (an adjustment of the minimum transmittance in the clot waveform to 0% in the immediate postcoagulation phase, as detailed in Nogami et al. 2018) than 100% FVIII alone. This illustrates that

even in the presence of normal plasma FVIII activity levels, addition of emicizumab is unlikely to increase the risk of clotting. The coagulation potential of the combination of FVIII and emicizumab is unlikely to exceed 100% FVIII activity whereas, hypothetically, administering excess FVIII may expose a patient to thrombogenic supraphysiologic FVIII levels.

These data are consistent with the mechanistic understanding that FVIII and emicizumab compete for the same targets in the coagulation system, and therefore, the combination has a limited additive potential. This is in contrast with the combination of emicizumab and bypassing agents, or the combination of FVIII or bypassing agents with inhibitors of endogenous regulators of coagulation (e.g., antithrombin) that exert their effect at different levels of the coagulation cascade and synergistically enhance the coagulation potential (Pasl et al. 2017). Therefore, the Sponsor believes that emicizumab is a safe option for individuals with non-severe hemophilia A whose bleeding phenotype warrants prophylaxis and considers the benefit-risk profile of emicizumab in patients with mild or moderate hemophilia A in line with the benefit-risk profile of emicizumab as established in the Phase III studies undertaken in patients with severe hemophilia A or hemophilia A with inhibitors.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients of all ages with mild (FVIII level between $>5\%$ and $<40\%$) or moderate hemophilia A (FVIII level between $\geq 1\%$ and $\leq 5\%$) without inhibitors against FVIII whose bleeding phenotype warrants prophylactic treatment. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety profile of emicizumab in patients with non-severe hemophilia A without inhibitors on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to WHO Toxicity Grading Scale
- Incidence of thromboembolic events
- Incidence of thrombotic microangiopathy (TMA)
- Change from baseline in physical examination findings
- Change from baseline in and vital signs
- Change from baseline in ECG parameters
- Incidence of laboratory abnormalities
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to drug discontinuation
- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

- Incidence and significance of anti-emicizumab antibodies
- Incidence of de novo development of FVIII inhibitors

2.2 EFFICACY OBJECTIVES

2.2.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of emicizumab on the basis of the following endpoint:

- Number of treated bleeds over time (i.e., bleed rate)

2.2.2 Secondary Efficacy Objectives

The secondary efficacy objective for this study is to evaluate the efficacy of emicizumab on the basis of the following endpoints:

- Number of all bleeds (i.e., those treated and untreated with FVIII) over time
- Number of joint bleeds over time
- Number of target joint bleeds over time (target joints are defined as joints with ≥3 bleeds occurring in the same joint during the last 24 weeks *or unresolved target joints)*

  An unresolved target joint is defined as a target joint that does not fulfil the criterion of ≤2 bleeds into this joint within a consecutive 12-month period.
- Number of spontaneous bleeds over time (spontaneous bleed rate)
- Joint health, as assessed through use of the Hemophilia Joint Health Score (HJHS) at specified timepoints
- Health-related quality of life (HRQoL), as assessed through use of the Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) Questionnaire over time
- Preference for emicizumab compared with previous FVIII regimen, as assessed through use of the Emicizumab Preference Survey (EmiPref) at Week 17
- Effect of emicizumab prophylaxis treatment on physical activity compared with physical activity at baseline
- Effect of emicizumab prophylaxis treatment on menstruation heaviness and menstruation-related quality of life in female patients of childbearing potential, as assessed through the use of the Menstrual Bleeding Questionnaire (MBQ) and the Menstruation Diary (MD) with the Pictorial Blood Assessment Chart (PBAC) over time

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the emicizumab PK profile on the basis of the following endpoint:

- Plasma concentration of emicizumab at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to emicizumab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study
- Number and proportion of patients who develop anti-FVIII inhibitors (titer≥0.6 BU/mL) at specified timepoints

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to investigate the effect of emicizumab on PD parameters, including but not limited to thrombin generation, FVIII activity, FVIII protein, D-dimer, and prothrombin fragment 1+2 (PF1+2) at regular intervals throughout the study and at times of treated bleeds. Changes over time in biomarkers related to bone and joint health may also be explored.

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with emicizumab on the basis of the following endpoint:

- Change from baseline in EuroQol 5-Dimension 5-level Questionnaire (EQ-5D-5L) index utility and visual analog scale (VAS) scores at specified timepoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study BO41423 is a multicenter, open-label, single-arm study designed to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients with mild or moderate hemophilia A without inhibitors against FVIII. Four loading doses of emicizumab 3 mg/kg will be administered subcutaneously QW for 4 weeks followed by patient preference of one of the following maintenance regimens: 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W. The three maintenance dose regimens have shown equivalent average steady-state exposure, and demonstrated consistent efficacy and safety, and are approved in several countries for the treatment of Hemophilia A with or without FVIII inhibitors. As patients with mild or moderate Hemophilia A have residual FVIII levels of ≥1%, it is of interest to collect safety data over a longer time period. Therefore, in this study, the observation time to primary analyses was extended to approximately 52 weeks compared with prior Phase III studies investigating emicizumab.

Approximately 70 patients of all age groups will be enrolled, approximately 20 patients with mild (FVIII level between >5% and <40%) and *approximately* 50 patients with moderate (FVIII level between ≥1% and ≤5%) hemophilia A, without FVIII inhibitors whose phenotype warrants prophylaxis.

Patients (or their legally authorized representative herein referred to as patient[s]) will choose the preferred emicizumab maintenance regimen (1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W) after consultation with his or her treating physician. The chosen regimen needs to be maintained throughout the study until completion of at least 52 weeks.

During the study, individual bleeds will be captured by the patient as the bleeds occur using a Bleed and Medication Questionnaire (BMQ). Patients will be asked on a weekly basis to record whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a bleed (e.g., prior to surgery or short-term prophylaxis prior to increased activity) has been given. Breakthrough bleeds will be treated with FVIII at the lowest dose expected to achieve hemostasis. When a bleed has occurred, patients will be required to report bleed information details (e.g., site, type, day, time) and medication details including reason for the use of FVIII (e.g., treatment of a bleed, preventative dose before activity), agent, start time, dose, route of administration, and number of infusions needed to treat the bleed via the BMQ.

HRQoL (CATCH and EmiPref) and health status (EQ-5D-5L) will be assessed as outlined in the schedule of activities. These measures will be captured either on paper questionnaires or on a site-based tablet available to patients during clinic visits. Female patients of childbearing potential will be administered two specific patient-reported outcome measures related to their menstruation (both questionnaires administered on paper): the MBQ will assess the menstrual bleed-related heaviness, pain, irregularity and quality of life; the Menstruation Diary (MD) with the PBAC will assess the use of sanitary products for menstruation (including the number of products used, the amount of bleeding, the occurrence and size of clots, and the number of episodes of heavy bleeding (flooding)).

Safety assessments will include physical examinations, vital signs, ECG, laboratory assessments (serum chemistry and hematology including complete blood count with differential), anti-drug antibodies (ADAs), and FVIII inhibitors. Adverse events will be captured on an ongoing basis, as they occur during the study.

Exploratory PD biomarkers (e.g., FVIII activity, thrombin generation) will be collected on a regular basis throughout the study and will be coupled with a PK assessment for days where PK and PD samples will be drawn. For pediatric patients, see Section 4.5.5 regarding blood draw volumes.

Biomarkers related to thromboembolism (e.g., D-dimer, PF1+2) will be measured on a regular basis throughout the study. For pediatric patients, see Section 4.5.5 regarding blood draw volumes.

Exploratory PD biomarkers and safety biomarkers will be collected within 24 hours but no later than 48 hours of a treated bleed.

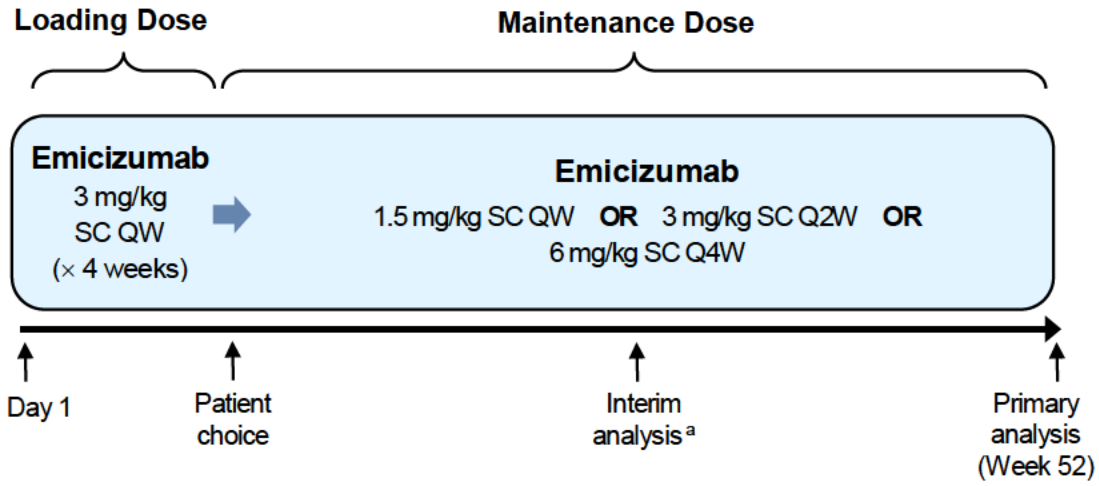
After 24 weeks on prophylactic emicizumab, patients with suboptimal bleed control will be offered the option to increase their dose to 3 mg/kg QW, with approval from the Medical Monitor, if the protocol-defined criteria of suboptimal response is met (see Section 4.3.2).

Interim data reviews may be performed at various timepoints (e.g., for regulatory submissions), and the primary analysis for all patients will be conducted after 50 patients with moderate hemophilia A have completed 52 weeks of emicizumab treatment, are lost to follow-up, or have withdrawn, whichever occurs first. The primary analysis will occur at the specified time regardless if no patients with mild hemophilia A are enrolled; however, enrollment will be left open for patients with mild hemophilia A in order to enroll approximately 20 such patients. The total number of patients in the study might slightly exceed 70 patients depending on the number of female patients enrolled. Ideally, at least 5 female patients will be enrolled. If these are not recruited within the pool of 70 patients, the enrollment will remain open until they are enrolled or until the cutoff date of primary analysis, whichever occurs sooner. Note that all patients will be included in the primary analysis irrespective of their follow-up time. After the primary analysis, patients will continue to receive emicizumab according to the Roche Policy on post study drug access until emicizumab is approved and accessible to patients commercially.

Patients who discontinue study drug prior to end of study will return to the clinic for a safety follow-up visit, 24 weeks after the last dose of study drug. Patients who complete or discontinue from the study will return to the clinic for a study completion/discontinuation visit (see Appendix 1 and Appendix 2).

Figure 1 presents an overview of the study design. The schedules of activities are provided in Appendix 1 and Appendix 2.

Figure 1 Study Schema



QW = once a week; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: Patients who discontinue study drug prior to end of study will return to the clinic for a safety follow-up visit 24 weeks after the final dose of study drug.
[a] Interim data reviews may be performed at various timepoints.

3.2 END OF STUDY AND LENGTH OF STUDY

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

- Completion of at least 52 weeks of emicizumab treatment during the study and either transfers to commercially available emicizumab or receives further emicizumab per Roche Global Policy on Continued Access to Investigational Medicinal Products

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

  OR
- Withdrawal of consent

  OR
- Lost to follow-up

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 27 months.

The length of the study for an individual patient will include the following:

- Screening period up to 4 weeks

- Treatment period at least 52 weeks
- For patients who discontinue emicizumab, safety follow-up visit 24 weeks after discontinuation of emicizumab

3.3 RATIONALE FOR STUDY DESIGN

The Sponsor proposes a single-arm, multicenter, Phase III trial that will enroll patients of all ages with mild or moderate hemophilia A. The study will use approved dosing regimens at the choice of the patient following consultation with the treating physician. The study will assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in patients with non-severe hemophilia A, as emicizumab has not been tested in patients without FVIII inhibitors with residual FVIII levels of $\geq 1\%$.

3.3.1 Rationale for Emicizumab Dose and Schedule

The three maintenance dose regimens have shown equivalent average steady-state exposure, and demonstrated consistent efficacy and safety, and are approved in several countries for the treatment of Hemophilia A with or without FVIII inhibitors. As patients with mild or moderate Hemophilia A have residual FVIII levels of $\geq 1\%$, it is of interest to collect safety data over a longer time period. Therefore, in this study, the observation time to primary analyses was extended to approximately 52 weeks compared with prior Phase III studies investigating emicizumab.

Patients in consultation with investigators will be allowed to choose the dosing regimen that is most appropriate for them as follows:

- Loading dose of 3 mg/kg SC QW $\times 4$ weeks followed by one of the following:
  - Maintenance dose of 1.5 mg/kg SC QW
  - Maintenance dose of 3 mg/kg SC Q2W
  - Maintenance dose of 6 mg/kg SC Q4W

3.3.2 Rationale for Patient Population and Analysis Groups

This study will include patients of all ages with mild or moderate hemophilia A without inhibitors against FVIII who warrant FVIII prophylaxis. As it has been shown that primary prophylaxis is beneficial for patients with non-severe hemophilia A who present with more severe bleeding patterns and prophylactic replacement therapy is used by approximately 30% of patients with non-severe hemophilia A, the efficacy and safety of emicizumab prophylaxis in these patients will be evaluated. The majority of patients enrolled will be of moderate severity (approximately 50 patients) as bleeding phenotypes that warrant prophylaxis in patients with mild disease are rare. The cutoff date of the primary analysis will be the observation time of 52 weeks after the last patient with moderate disease has been enrolled to reduce the risk of significant timeline prolongation because of potential difficulties in recruiting patients with mild hemophilia A who warrant FVIII prophylaxis. The primary analysis will occur at the specified time regardless if no patients with mild hemophilia A are enrolled; however, enrollment will be left open for patients with mild hemophilia A in order to enroll approximately 20 such

patients. Ideally, at least 5 female patients will be enrolled. If these are not recruited within the pool of 70 patients, the enrollment will remain open until they are enrolled or until the cutoff date of primary analysis, whichever occurs sooner. Note that all patients will be included in the primary analysis regardless of their follow-up time.

3.3.3 Rationale for Pharmacokinetic Assessments

PK assessments allow for confirming that plasma concentrations are consistent within the expected concentration ranges observed in previous emicizumab Phase III studies that were effective and safe. Additionally, influence of various demographic (e.g., body weight) or clinical factors (e.g., ADA) on exposure in individual patients may be investigated. Therefore, samples for measurement of emicizumab concentrations in plasma will be collected at designated timepoints.

3.3.4 Rationale for Immunogenicity Assessments

Monitoring of immune response is important for biologics as development of ADAs may affect the safety and/or efficacy of emicizumab. Samples for measurement of anti-emicizumab antibodies will therefore be collected at regular timepoints. In case of ADA positivity, further investigations will be conducted to assess their neutralizing potential, either via visual inspections of the PK and PD profiles or, if available, via testing on a neutralizing antibody assay.

De-novo development of FVIII inhibitors in patients with emicizumab will be monitored during the study. Although the development of de novo FVIII antibodies during treatment with emicizumab is unexpected, occurrence of these would impact the management of breakthrough bleeds requiring the need of bypassing agents.

3.3.5 Rationale for Biomarker Assessments

Samples to assess biomarkers to measure the PD effect of emicizumab on hemostasis will be collected at the same time as PK samples at all clinic visits. These will assess evidence of biologic activity and safety of emicizumab in patients with non-severe hemophilia A with residual endogenous FVIII levels of $\geq 1\%$.

The PD biomarkers include, but are not limited to, coagulation assays such as thrombin generation, and FVIII activity assays. These assays have shown in previous Phase I/III studies to exhibit a dose-response relationship to emicizumab concentration (for more information, refer to the RO5543262 [Emicizumab] Investigator's Brochure).

Two thrombin generation assays will be run, one using FXIa triggering reagent, which is more sensitive and has been used in previous emicizumab clinical studies, and one using tissue factor as triggering reagent, which is more commonly used and enables viewing data in the context of other analyses.

Endogenous and exogenous FVIII activity will be measured using a chromogenic assay containing bovine coagulation factors that is insensitive to emicizumab as well as using a

chromogenic assay containing human coagulation factors. FVIII protein levels will also be measured using an immunoassay.

Serum and plasma will be collected periodically for the assessment of bone and joint health-related biomarkers, which may include, but not be limited to, procollagen type 1 amino-terminal propeptide, C-terminal telopeptide of collagen 1, osteoprotegerin, and soluble RANK-L. Samples for the analysis of bone and joint markers need to be collected under fasting conditions (see Appendix 1).

One blood sample will be collected for clinical genotyping and may be used to analyze FVIII mutations and potentially other coagulation-related gene polymorphisms.

3.3.6 Rationale for Patient-Reported Outcome Assessments

HRQoL is an important outcome in the care of patients with hemophilia (Brown et al. 2009), and its measurement in clinical trials quantifies the benefit of treatment from the perspective of the patient. HRQoL in patients with hemophilia is multifaceted and affected by disease symptoms (e.g., pain, bleeding), treatment (prophylactic, on demand, side effects), limitation on daily functioning, anxiety/depression, etc.

The newly developed CATCH instrument addresses the need for a content-valid, fit-for-purpose, hemophilia-specific, self-reported questionnaire to capture the benefit of modern therapies and breakthrough therapies in development (Regnault et al. 2019; see Section 4.5.7.2).

The study will also include a measure, the EmiPref, designed to capture patient preference with regard to treatment and will be completed by patients ≥12 years of age. Additionally, for patients younger than 18 years of age, the patient's caregiver will be asked to fill out the EmiPref (caregiver version). For patients <12 years old, only the caregiver will fill out the EmiPref (caregiver version). Previous studies noted that patients have expressed preference for treatments that do not have negative effects (e.g., pain that results from infusions), are not time consuming, are not associated with high treatment burden, and have a goal of achieving a "normal life" (Cimino et al. 2014). Previous Phase III studies documented patient preference for emicizumab compared with prior treatment (Mahlangu et al. 2018; Pipe et al. 2019).

For female patients with bleeding disorders, menorrhagia has shown to adversely affect their HRQoL (Shankar et al. 2008). In order to assess the potential impact of emicizumab prophylaxis treatment on menorrhagia, this study will include two PRO measures for female patients of childbearing potential, the MBQ and the MD. The MBQ is a validated measure for menorrhagia and is widely used in clinical practice to assess impact on menstrual bleed-related heaviness, pain, irregularity, and quality of life (Matteson et al. 2015). The MD will use a PBAC, which has been shown to be a reliable method for assessing blood loss (Higham et al. 1990).

3.3.7 Rationale for Physical Activity Assessment

This study provides an opportunity to evaluate whether physical activity of patients treated with emicizumab change during the course of treatment. Accelerometer-based instruments provide a patient-independent, objective-movement count. Despite the gold standard of global activity assessment being the direct measurement of activity-related energy expenditure, there is evidence that acceleration measurements from the wrist can be used to estimate energy expenditure accurately and relatively precisely (Staudenmayer et al. 2015). Weighing these considerations, an objective assessment using an accelerometer that is worn on the wrist will focus on, but is not limited to, measuring changes in amount of moderate to vigorous physical activity (MVPA) and daily step count (DSC) as reliably derived outcome measures (Staudenmayer et al. 2015; Kendall et al. 2019).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 70 patients of all age groups will be enrolled in the study consisting of approximately 20 patients with mild and approximately 50 patients with moderate hemophilia A without FVIII inhibitors whose phenotype warrants prophylaxis.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (signed by patient's legally authorized representative for patients who have not attained the age of majority)
- Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Willingness and ability to comply with schedules visits, treatment plans, laboratory tests and other study procedures
- Diagnosis of mild (FVIII level between $>5\%$ and $<40\%$) or moderate (FVIII level between $\geq 1\%$ and $\leq 5\%$) congenital Hemophilia A without FVIII inhibitors
- Weight ≥ 3 kg
- Need for prophylaxis based on investigator assessment
- A negative test for inhibitor (i.e., <0.6 BU/mL) within 8 weeks prior to enrollment
- No documented inhibitor (i.e., <0.6 BU/mL), FVIII half-life <6 hours, or FVIII recovery $<66\%$ in the last 5 years

  Patients who completed successful immune tolerance induction (ITI) at least 5 years before screening are eligible, provided they have had no evidence of inhibitor recurrence (permanent or temporary) as may be indicated by a detection of an inhibitor, FVIII half-life <6 hours or FVIII recovery $<66\%$ since completing ITI (Antun et al. 2015).

- Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks prior to enrollment
- Adequate hematologic function, defined as platelet count $\geq$100,000 cells/µL and hemoglobin $\geq$8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function defined as total bilirubin $\leq 1.5 \times$ age-adapted upper limit of normal (ULN) (excluding Gilbert syndrome) and both AST and ALT $\leq 3 \times$ 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 $\leq 2.5 \times$ age-adapted ULN and creatinine clearance $\geq$30 mL/min by Cockroft-Gault formula
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

  Women must remain abstinent or use contraceptive methods that result in a failure rate of $<$1% per year during the treatment period and for at least 24 weeks after the final dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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 mild (FVIII level between $>$5% and $<$40%) or moderate (FVIII level between $\geq$1% and $\leq$5%) congenital hemophilia A
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, 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 during the emicizumab loading dose phase

  Surgeries in patients on emicizumab from Week 5 onwards are allowed.
- Known HIV infection with CD4 counts <200 cells/μL
- Concomitant disease, condition, significant abnormality on screening evaluation or laboratory tests, or treatment that could interfere with the conduct of the study, or that would in the opinion of the investigator, pose an additional unacceptable risk in administering study drug to the patient
- Receipt of any of the following:
  - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration with the exception of prior emicizumab prophylaxis (prior investigational or commercial emicizumab use is not an exclusion criterion)
  - A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
  - Any other investigational drug currently being administered or planned to be administered
- Inability to comply with the study protocol in the opinion of the investigator
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a single-arm, open-label study. After initial written informed consent/assent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number from an interactive voice or web-based response system (IxRS) and indicate the maintenance treatment regimen chosen. The time between screening and enrollment of eligible patients should be ≤ 4 weeks; otherwise, patients must be re-screened to determine if they continue to meet the inclusion and exclusion criteria.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is emicizumab.

4.3.1 Study Treatment Formulation, Packaging, and Handling

Emicizumab will be supplied by the Sponsor as a sterile liquid for SC injection; it contains no preservatives and requires storage at 2°C−8°C (do not freeze and protect from light). Single-use vials contain 30 or 150 mg (nominal) of emicizumab at pH 6.0. The drug product is formulated in 150 mmol/L arginine, 0.5 mg/mL poloxamer 188, and 20 mmol/L histidine−aspartic acid buffer (pH 6.0). Because emicizumab is administered on a weight-based dosing regimen, two vial strengths will be supplied for this study differing from each other only in emicizumab concentration: nominal vial strength 150 mg (150 mg/mL, 1.0 mL) and nominal vial strength 30 mg (30 mg/mL, 1.0 mL). The less concentrated formulation will enable safe SC weight-based volume dosing of small children with sufficient precision. The excipient composition and primary packaging is identical for all configurations. For further information on the formulation and handling of emicizumab, refer to the RO5543262 (Emicizumab) Investigator's Brochure.

To minimize the number of injections for patients in certain weight categories, the administration per single injection of up to 2 mL of drug product solution will be permitted. This will require pooling of emicizumab drug product solution from up to two 1-mL vials into a single syringe using a new transfer needle for each vial. The detailed procedure for vial pooling is described in the Instructions for Use. It is important to note that vials of different emicizumab concentrations must not be combined in the same syringe.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1. The emicizumab dosing regimen to be tested is emicizumab 3 mg/kg SC QW for 4 weeks followed by a maintenance dose of either 1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W.

All patients with suboptimal control of bleeding as defined by the protocol will be offered the option to increase their emicizumab maintenance dose to 3 mg/kg QW, with approval from the Medical Monitor. Suboptimal response is defined as follows:

- $\geq$2 qualifying bleeds within 24 weeks while on prophylactic emicizumab

A qualifying bleed is defined as spontaneous, verified by investigator (e.g., by imaging or physical examination), and occurring while on prophylactic emicizumab at steady state (after Week 5). If the investigator believes that a specific patient warrants dose escalation on the basis of a different reason, he or she may discuss the case with the Medical Monitor for consideration and potential approval.

An increase of the emicizumab dose to 3 mg/kg QW can occur at the next scheduled emicizumab administration of the initial regimen (i.e., 1 week from the last dose of a QW regimen, 2 weeks from the last dose of a Q2W regimen, and 4 weeks from the last dose of a Q4W regimen).

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Any cases of overdose, medication error, drug abuse, or drug misuse of study drug will be determined from emicizumab data entered into the electronic, handheld device (see Section 5.3.5.12 for details).

Patients will be observed for a minimum of 60 minutes after the first three doses as described in Section 3.1.

Patients (≥7 years of age) capable to self-administer study drug will be able to perform home administration of emicizumab provided they did not experience prior clinically significant hypersensitivity reactions with emicizumab. For home administration, patients/caregivers will be required to complete in-person instructional training, using the Instructions for Use document, on how to administer emicizumab as an SC injection. Patients/caregivers need to observe at least one SC injection performed by the healthcare provider (HCP) and successfully administer at least one SC injection while being observed by an HCP prior to starting home administration. Each site will have the discretion to provide additional training if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject emicizumab correctly, study drug may be administered by a trained home nursing professional at the patient's home or another suitable location.

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

Patients/caregivers should administer emicizumab on the scheduled dosing days. On days when blood is to be collected, patients will receive emicizumab after samples are drawn in the clinic. On the other days, for patients receiving emicizumab 1.5 mg/kg QW who miss a scheduled dose, emicizumab should be administered as soon as possible within a window of 3 days from the scheduled dosing date. If more than 3 days have passed, the missed dose should be skipped, and the next dose of emicizumab should be taken at the next scheduled time resuming the original dosing schedule. For patients receiving emicizumab 3 mg/kg Q2W who miss a scheduled dose, emicizumab should be administered as soon as possible within a window of 7 days from the scheduled dosing date. If more than 7 days have passed, the missed dose should be skipped, and the next dose of emicizumab should be taken at the next scheduled time resuming the original dosing schedule. For patients receiving emicizumab 6 mg/kg Q4W who missed a dose, emicizumab should be administered as soon as possible but no later than 14 days from the scheduled dosing date. If more than 14 days have

passed, the missed dose should be skipped, and the next dose of emicizumab should be taken at the next scheduled time resuming the original dosing schedule.

All emicizumab dosing should be clearly documented on the handheld device during patient's visits in clinic and when the patient is out of the clinic.

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

4.3.3 Investigational Medicinal Product Accountability

Emicizumab, the only IMP in this study, is required for completion of this study and will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. *The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMP received and that any discrepancies have been reported and resolved before use of the IMP. The IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.*

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Continued Access to Emicizumab

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

A patient will be eligible to receive Roche IMP (emicizumab) after completing the study if all of the following conditions are met:

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

A patient will not be eligible to receive Roche IMP (emicizumab) after completing the study if any of the following conditions are met:

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

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

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

4.4 CONCOMITANT THERAPY AND PROHIBITED THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 4 weeks prior to enrollment to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. Medications taken to treat a bleed (e.g., FVIII) will be reported only via the BMQ, except for FVIII taken in the week prior to starting emicizumab by patients who will continue their prior FVIII prophylaxis until the second loading dose of emicizumab. For these patients only, FVIII treatment taken in the week prior to the first dose of emicizumab will be recorded on the *Hemophilia History Medication 7 Days Prior to Enrollment* eCRF page.

4.4.1 Permitted Therapy

Patients will be permitted to use the following concomitant drugs and therapies during the study:

- Regular FVIII prophylaxis may continue until the second emicizumab loading dose to avoid bleeds before adequate emicizumab levels are reached. Concomitant routine FVIII prophylaxis is otherwise not permissible during the study.
- For the treatment of breakthrough bleeds, FVIII should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase patients' coagulation potential, the doses required to achieve hemostasis may be lower than FVIII doses used prior to the study.

  Exact dose and schedule of FVIII should be discussed with patients at the beginning and throughout the study. Repeat dosing of VIII should be performed only under medical supervision and consideration should be given to verifying bleeds prior to repeated dosing.
- Other drugs intended to control bleeds (e.g., bypassing agents, DDAVP, or antifibrinolytics) are permitted. However the use of aPCC should be avoided unless no other treatment options/alternatives are available. If aPCC is indicated in a patient receiving emicizumab prophylaxis, the initial dose should not exceed 50 U/kg and laboratory monitoring is recommended (including but not restricted to renal monitoring, platelet testing, and evaluation of thrombosis). If bleeding is not controlled with the initial dose of aPCC up to 50 U/kg, additional aPCC doses should be administered under medical guidance or supervision with consideration made to laboratory monitoring for the diagnosis of TMA or thromboembolism and verification of bleeds prior to repeated dosing. The total aPCC dose should not exceed 100 U/kg in the first 24-hours of treatment. Treating physicians must carefully weigh the risk of TMA and thromboembolism against the risk of bleeding when considering aPCC treatment beyond a maximum of 100 U/kg in the first 24-hours.
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc. that are not considered to result in systemic exposure are permitted.
- Drugs to treat an existing medical condition ongoing at study entry that does not violate the eligibility criteria (e.g., anti-retroviral therapy for HIV infections) are permitted.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited for at least 4 weeks prior to initiation of study treatment, during the study, and until last observation.

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

  However, drugs intended to control bleeding episodes or used in the context of surgeries or injuries (e.g., concussion) to prevent deterioration are allowed.

- Systemic immunomodulators (e.g., rituximab, interferon) other than anti-retroviral therapy
- Elective surgery during the emicizumab loading phase (prior to Week 5)
- Use of other investigational drug

Use of concomitant prophylactic regimen with FVIII or bypassing agents is prohibited during the study.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 and Appendix 2. All activities should be performed and documented for each patient.

If a breakthrough bleed occurs outside of a hospital visit and requires treatment, collection of a blood sample should occur within 30 minutes–24 hours but no later than 48 hours after treatment for the bleed has been administered. In such a case, to avoid requiring patients to return to the study site for a blood draw, this sample collection may be performed by a mobile nursing (MN) professional at the patient's home or another suitable location to improve access and convenience for patients participating in the study. *In addition, if a patient or caregiver needs assistance with injecting emicizumab correctly, emicizumab may be administered by a MN professional.*

The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is 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. The schedule of activities (see Appendix 1 and Appendix 2) will specify which assessments may be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent/assent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent/Assent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed 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, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, procedures, use of alcohol and drugs of abuse within the past year, and medical allergies will be recorded at baseline. In particular, sites should record whether the patient has any history of prior ITI, anaphylaxis, or known thrombophilia. For female patients, fertility status, and menstruation and menorrhagia history data will be recorded at baseline. In addition, all medications (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies) used by the patient within 4 weeks prior to enrollment will be recorded. All bleed information (i.e., start date, cause, type, location) during the 24 weeks prior to study entry should be documented.

Demographic data will include age, sex, and self-reported race/ethnicity. Race and ethnicity are standard data points in clinical trials conducted by Roche, collected as part of the demographics, as there is potential that diseases might affect racial groups differently.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. The HJHS (see Appendix 3) will be performed as part of physical examination as per the schedule of activities (see Appendix 1)

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

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. Deviations from the schedule of assessments of ± 2 days are acceptable; however, pre-dose 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: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and absolute differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width
- Chemistry panel (serum or plasma): sodium, potassium, glucose, BUN, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, albumin, ALP, ALT, AST, LDH, and CPK
- Coagulation tests (aPTT, PT/INR)
- Pregnancy test

  All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and within 7 days prior to initiation of study medication, if applicable. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

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

- Plasma samples for PK analysis
- Plasma samples for immunogenicity assessment (ADA)
- Plasma samples for anti-FVIII antibody measurement (inhibitor titer)
- Plasma samples for PD biomarker assessments (FVIII activity, FVIII protein level, thrombin generation, and others as listed in Appendix 2).
- Plasma aliquot for assessment of fibrinogen, D-dimer, and PF1+2
- Plasma and serum samples for bone and joint biomarkers
- Blood sample for clinical genotyping

In the event of coagulation factor product treatment for breakthrough bleeds, plasma samples should be collected within 30 minutes–24 hours (but no later than 48 hours) of initial coagulation factor product administration and sent to the central laboratory (see below) for monitoring of emicizumab pharmacokinetics, fibrinogen, FVIII activity (bovine and human coagulation factor chromogenic assays), D-dimer, PF1+2, and thrombin generation (two triggering agents; see Section 3.3.5).

A blood sample for clinical genotyping will be collected at pre-dose on Day 1 (see Appendix 2). DNA obtained from blood may be analyzed for FVIII mutations and potentially other coagulation-related gene polymorphisms (see Section 3.3.5). If the sample is missed on Day 1, it can be collected at any other scheduled visit. Only one clinical genotyping sample is required per patient. If the patient gives consent, the remainder of the clinical genotyping samples (blood) and their derivatives (DNA) will be

stored under the Research Biosample Repository (RBR) policy, otherwise the remainder will be destroyed.

For the pediatric population, assessments that require blood draws should be monitored closely to ensure that institutional mandates regarding total sample blood volumes are followed. In situations where no institutional guidance is available, the following limits should be used and have been included in the design of the sampling program: No more than 1% of the total blood volume should be taken at one time and no more than 3% of the total blood volume should be taken over a 30-day period (total blood volume is defined as 80–90 mL/kg [European Union 2008]). Thus, blood sampling timepoints and volumes follow the Ethics Committee (EC) guideline on Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population (European Union 2008). In situations where the total volume of blood drawn might exceed the limits stated above, clinical (safety) laboratory assessments should be prioritized. Any remaining permitted blood volume should be collected for PK and immunogenicity samples, followed by PD samples/safety biomarkers. Refer to the laboratory manual for detailed weight-based blood sampling guidelines.

In certain instances, blood draws*, emicizumab administration, or other assessments* may be performed by an MN professional (see Section 4.5).

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling Manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research or RBR (see Section 4.5.9), biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.6 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following parameters will be obtained (and reported by the instrument): uncorrected QT interval, RR interval, heart rate, QT interval corrected through use of Bazett's formula, QT interval corrected through use of Fridericia's formula based on the machine readings of the individual ECG tracings, PR duration and QRS interval, and T- and U-wave morphology.

Any ECG changes that are associated with symptoms or lead to a change in study treatment or concomitant treatment, or discontinuation from study treatment must be reported as an adverse event on the adverse event eCRF. The ECG may be repeated if investigator deems it appropriate. During the study, the Sponsor may request copies of ECGs to be submitted to the Sponsor or a Central Vendor. Centralized ECG reading and interpretations will not be performed unless safety concerns arise.

4.5.7 Clinical Outcome Assessments

PRO data will be collected through use of the following instruments: BMQ, CATCH, EmiPref, EQ-5D-5L, MBQ, and MD with the PBAC.

4.5.7.1 Data Collection Methods for Clinical Outcome Assessments

The BMQ, CATCH, EmiPref, and EQ-5D-5L will be collected electronically using two devices (BMQ collected at home on a handheld device given to the patient/caregiver; the other questionnaires collected at site on a tablet). In addition, for female patients of childbearing potential, the MBQ and MD with PBAC will be collected on paper. These instruments will be translated into the local language as appropriate.

For the BMQ data, the patient will be provided with a handheld device (see Section 4.5.7.3). The handheld device to capture bleed data, emicizumab use, and other hemophilia medication use during study treatment via the BMQ will be

provided/performed/during the Week 1 visit at the study site and will be used by the patient for the duration of the study to enter bleed and medication data weekly at a minimum. Patients who withdraw from emicizumab treatment will continue to record bleeds and hemophilia medication administration until they complete the safety follow-up visit. For the collection of the CATCH, EQ-5D-5L, and EmiPref, a site-based tablet will be used.

The devices will be pre-programmed to enable the BMQ (see Section 4.5.7.3), CATCH, EQ-5D-5L, and EmiPref at each specified timepoint (see Appendix 1). The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel. If the electronic data collection system becomes unavailable, the Sponsor may instruct sites to collect PRO data (bleed data, emicizumab use, hemophilia medication use, and HRQoL) on paper, and once electronic data entry is available, all information will need to be entered and submitted electronically.

For female patients of childbearing potential, the MBQ will be self-administered on paper at the site during the clinic visits on Day 1 and subsequently every 4 weeks. The MD with PBAC will be completed on paper by patients at home. The MD with PBAC will be given to patients on Day 1 and should be completed monthly on days of menstruation. The patient should return the completed MD with PBAC to the site personnel during the next clinic visit. All MBQ and MD data will be entered into the study database by site personnel.

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see Appendix 1) and at home when appropriate. At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

Patients should be given the following instructions for completing PRO instruments at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.

- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 15 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.7.2 Description of Clinical Outcome Assessment Instruments

Comprehensive Assessment Tool of Challenges in Hemophilia

CATCH is a newly developed, validated instrument to measure the effect of hemophilia and its treatment on pediatric (aged 8–17 years) and adult patients (aged ≥18 years), and caregivers of pediatric patients (Regnault et al. 2019). The adult and pediatric versions of CATCH are composed of seven domains, and the caregiver version of CATCH is composed of two domains. Each domain constitutes a set of specific items and overall items that help to assess the overall impact of the disease on a given domain. The current versions of the CATCH can be administered electronically. The instructions for completion are within the body of the questionnaire to allow participants to complete it independently.

The adult version covers concepts including daily activity risk perception and impact (48 items), social activity risk perception and impact (22 items), recreational activity risk perception and impact (32 items+larger bank of additional items), work impact (10 items), preoccupation (10 items), treatment burden (8 items), and pain (5 items) (see Appendix 4). The pediatric version includes concepts of daily activity risk perception and impact (38 items), social activity risk perception and impact (16 items), recreational activity risk perception and impact (34 items+larger bank of additional items), school impact (11 items), preoccupation (3 items), treatment burden (7 items), and pain (2 items) (see Appendix 5). For recreational activities, patients only respond to those items that are relevant to them. On average, the adult and pediatric versions take 15–20 minutes to complete. The caregiver version comprises concepts related to preoccupation (13 items) and treatment burden (8 items), and takes approximately 5 minutes to complete (see Appendix 6).

The items in the CATCH versions are scored on ordinal scales (3–4 points for pediatric version, 4–5 points for adults and caregiver versions), with an 11-point numeric rating scale for pain. All CATCH raw scores are obtained by calculating the mean of the item scores for all items within the corresponding concept and applying a linear

transformation. The transformed scores range from 0 to 100 scale with higher scores indicating higher perceived risk or effect.

EQ-5D-5L

The EQ-5D-5L is a validated, self-report, health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 7). 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 VAS that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete and will be completed by patients 12 years of age and older. It will be used in this study for informing pharmacoeconomic evaluations.

Emicizumab Preference Survey

Patient preference will be assessed through the EmiPref (see Appendix 8 and Appendix 9). Patients and/or caregivers will be asked to report which treatment regimen they would prefer to continue to receive or administer after having been treated with or administered IV FVIII prior to study entry and SC emicizumab during the study. Patients and/or caregivers who express a preference will then be asked to identify which reasons may have influenced their decision and indicate the top three reasons for this choice. This assessment will be performed at Week 17 when patients have gained sufficient experience with SC injection of emicizumab, while still reliably recalling their experience with prior therapy.

Menstrual Bleeding Questionnaire and Menstruation Diary

For females with bleeding disorders, menorrhagia can further diminish their health-related quality of life (Shankar et al. 2008). Menorrhagia is defined subjectively as excessive or prolonged loss of blood on a regular cyclical basis or objectively as menstrual blood loss $\geq$80 mL for the whole period (Higham et al. 1990).

All female patients of childbearing potential will be asked to complete two PROs, the MBQ and MD (See Appendix 13 and Appendix 14).

- The MBQ is a validated measure for menorrhagia and is widely used in research and clinical practice to assess impact on the menstrual bleed-related heaviness, pain, irregularity, and quality of life (Matteson et al. 2015). The MBQ is a 20-item measure covering four aspects regarding heavy menstrual bleeding: heaviness (8 items), quality of life (8 items), irregularity (1 item), and pain (1 item).
- The MD will use a PBAC, which has shown good correlation with menstrual blood loss (Higham et al. 1990). The PBAC is a chart that records the occurrence and size of clots, and the number of episodes of heavy bleeding (flooding), as well as depicts the amount of blood loss during a cycle. When summed, the weighted scores for light, moderate, or severe blood loss determine a PBAC score for each cycle.

4.5.7.3 Bleed and Medication Questionnaire

Patients (or their legally authorized representative) will complete a BMQ whenever a bleed occurs or at least on a weekly basis (retrospective reporting for last 7 days) via an electronic, handheld device. For each bleed episode, the patient will provide information regarding bleed start date and time, reason, type, location, and associated symptoms (only collected for muscle and joint bleeds in patients 12 years of age and older). Hemophilia medications and reason for treatment (e.g., bleed, surgery, physical activity) will also be collected through the use of the BMQ. 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 activities (see Appendix 1) and will have the option to correct or complete the BMQ 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 perform a review of the bleed and bleed medication data as per the Medical Data Review Plan.

4.5.7.4 Bleed Definitions and Reporting

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/Factor IX subcommittee of the International Society of Thrombosis and Hemostasis, and similar to that used in a recent clinical study, will be used in this study (Blanchette et al. 2014; Mahlangu et al. 2014) as follows:

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

Definition of Bleed Sites

Bleed sites are defined as follows:

- 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) *or as an unresolved target joint. An unresolved target joint is defined as a target joint that does not fulfil the criterion of $\leq$2 bleeds into this joint within a consecutive 12-month period (Blanchette et al. 2014).*

- Joint bleeds: defined as bleeds with bleed type “joint bleed” reported via the BMQ 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 BMQ)
- Other (sites as per the BMQ)

Definitions of Bleed Types

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 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: For example, hematomas resulting from any surgery or invasive procedure (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) would not be considered a bleed related to procedure/surgery. Such bleeds are not associated with any trauma except procedure/surgery-induced trauma.

Reporting of Bleed Data

Patients will complete a BMQ weekly and whenever a bleed occurs via an electronic, handheld device. For each bleeding episode, the patient 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 BMQ. 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 perform a review of the bleed and bleed medication data as per the Medical Data Review Plan 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.

Reporting of Menstrual Bleed and Menstruation Diary Data

All female patients of childbearing potential will be asked to complete the following paper questionnaire and diary:

- MBQ in the clinic on Day 1 and subsequently every 4 weeks to document the menstrual bleed-related heaviness, pain, irregularity, and quality of life during the past month (See Appendix 13).
- MD with the PBAC to document at home the use of menstrual products during the past month (including the number of products used, the amount of bleeding, the occurrence and size of clots, and the number of episodes of heavy bleeding (flooding)). The MD with PBAC will be given to patients on Day 1 and should be completed monthly on days of menstruation (See Appendix 14). The patient should return the completed MD with PBAC to the site personnel during the next clinic visit.

All MBQ and MD data will be entered into the study database by site personnel.

4.5.8 Physical Activity Assessments

Patients (≥5 years of age) should wear the study device continuously (24 hr/day) every day for designated 2-week periods during the study (see Appendix 1) as follows: Weeks 1–2, Weeks 12–13, Weeks 24–25, Weeks 36–37, and Weeks 48–49. Patients will be instructed to wear the accelerometer on the wrist for 14 consecutive days. Patients will be instructed to charge the device.

Accelerometry data will be collected passively using the study device and uploaded regularly to provide continuous measures of, but not limited to, MVPA and DSC; in addition, further analyses may be performed.

An activity count is a measure of the acceleration that is measured by the device. The number of hours the device is worn each day will also be derived from the activity counts data.

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the

development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board (IRB) or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site.

4.5.9.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to emicizumab, diseases, or drug safety:

- Leftover blood samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.9.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

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

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

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

4.5.9.5 Consent to Participate in the Research Biosample Repository

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

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.9.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a safety follow-up visit 24 weeks after the final dose of study drug (see Appendix 1 and Appendix 2 for additional details).

4.6.2 Patient Discontinuation from the Study

Patients will return to the clinic for a study completion visit as per the schedule of activities (see Appendix 1 and Appendix 2).

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 patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study 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.

4.6.4 Site Discontinuation

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 approved for the treatment of hemophilia A including mild and moderate disease in several countries; however, the clinical development in patients with mild or moderate hemophilia A without FVIII inhibitors is ongoing, as emicizumab was not tested in this population before. The safety plan for patients in this study is on the basis of clinical experience with emicizumab in completed and ongoing studies. The anticipated important safety risks for emicizumab are outlined below. Refer to the RO5543262 (Emicizumab) Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Emicizumab

5.1.1.1 Injection-Site Reactions

Injection-site reactions have been observed in patients with hemophilia A. These local injection-site reactions included erythema, hematoma, rash, discomfort, pain, and pruritus and were mostly of mild and moderate intensity. Further details for observed injection-site reactions are available in the RO5543262 (Emicizumab) Investigator's Brochure. Directions for emicizumab administration should be followed, as outlined in Section 3.3.1 and Section 4.3.2.

5.1.1.2 Hypersensitivity Reaction, Anaphylaxis, and Anaphylactoid Reaction

Because emicizumab is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions, may occur. In completed and ongoing clinical studies of emicizumab, no severe hypersensitivity reactions have been reported. These events should be reported as serious adverse events or adverse events of special interest as described in Section 5.4.2.

HCPs administering study medication in the clinic must be trained in the appropriated administration procedures; must be able to recognize the signs and symptoms associated with potential hypersensitivity, anaphylactic, and anaphylactoid reactions; and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al.

2006; see Appendix 10 and Appendix 11). HCPs should also instruct patients how to recognize the signs and symptoms of hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an HCP or seek emergency care in case of any occurrence. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should any of these reactions occur.

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

5.1.1.3 Hypercoagulation and Thromboembolic Events

A total of four thromboembolic events have been observed in 3 patients receiving emicizumab. There was one event of Grade 1 device occlusion (non-serious) reported in 1 patient (Study BH29884). The event resolved and was assessed by the investigator as not related to emicizumab. In addition, 2 patients experienced a total of three serious adverse events of thromboembolic event in Study BH29884. One patient developed a cavernous sinus thrombosis after repeated use of supratherapeutic doses of aPCC, and the event was considered related to emicizumab and aPCC. Another patient developed extensive skin necrosis on the right shin and local skin necrosis on the left shin due to superficial thrombophlebitis after administering aPCC. Ultrasound showed a superficial thrombophlebitis of the right saphenous vein and investigator considered the skin necrosis due to the thrombophlebitis and was assessed as being related to emicizumab and with use of aPCC. Refer to the RO5543262 (Emicizumab) Investigator's Brochure for further details.

Thromboembolic events should be reported as serious adverse events or adverse events of special interest as described in Sections 5.2.2 and 5.2.3. HCPs should educate patients to recognize signs and symptoms of potential thromboembolism (i.e., dyspnea, chest pain, leg pain, or swelling; or if in the head, headache, numbness in the face, eye pain or swelling, or vision impairment) and ensure that they understand the importance of seeking appropriate medical attention. Patients will also receive two alert cards to remind them of this information and instructions should thromboembolism be suspected.

5.1.1.4 Thrombotic Microangiopathy

TMA is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, central nervous system, etc.

Three cases of TMA were reported in Study BH29884. All cases were assessed as being related to study treatment and occurred after recent concomitant aPCC use. This

study will be conducted in patients without FVIII inhibitors, and aPCC is therefore not expected to be used for the treatment of breakthrough bleeds. For further details on TMAs, refer to the RO5543262 (Emicizumab) Investigator's Brochure.

Any TMA event should be reported as an adverse event of special interest and also as a serious adverse event, if it meets criteria for such (see Sections 5.2.2 and 5.2.3).

5.1.1.5 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 Table 1). In one-stage assays, emicizumab is associated with a supraphysiologically 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. Furthermore, 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 as to which tests can be used and how the test results can be interpreted.

Because of the long half-life 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.

However, as of June 2018, no instances of under-treatment for bleeding events due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab were reported by patients receiving emicizumab prophylaxis in clinical trials.

5.1.2 Management of Patients Who Experience Adverse Events

See Table 1 for guidelines for management of patients who experience adverse events.

Table 1 Guidelines for Management of Patients Who Experience Adverse Events

Event	Actions to Be Taken
Injection-site reaction	• Injection-site reactions should be treated as clinically indicated. • Emicizumab should not be injected into areas where the skin is red, bruised, tender, or hard or into areas where there are moles or scars. • In the clinic setting, patients will be monitored for signs of injection-site reactions during the period immediately following injections. Patients will be given guidance on reporting injection-site reactions when administering drug at home or after they leave the clinic.
Hypersensitivity reaction, anaphylaxis, and anaphylactoid reaction	• Suspected cases should be fully evaluated and treated as clinically indicated. • Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) and resuscitation equipment must be available for immediate use during the initial administrations in the infusion center, clinic, or hospital. • If a patient has symptoms of anaphylaxis or severe hypersensitivity, administration of study drug must be immediately stopped and treatment of the reaction be initiated. • The investigator should contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk to determine if and when the patient should resume taking emicizumab and discuss the patient's continued study participation. If the patient continues in the study, the next two scheduled doses must be in a monitored setting with at least a 60-minute observation period and resuscitation treatment immediately available. After each of these two doses in the clinic, the site will call the patient 24 hours after each dose to assess status of the patient. • Investigators may order any pertinent laboratory tests, including an unscheduled anti-drug antibody, in the event any of these reactions occur.

Table 1 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Actions to Be Taken
Thrombotic microangiopathy	• Breakthrough bleeds will be treated with FVIII at the lowest dose expected to achieve hemostasis (see Sections 3.1 and 4.4.1). • HCPs should be vigilant for patients who exhibit signs/symptoms consistent with TMA and immediately begin work-up and treatment, as per local guidelines. • If a patient has a TMA event, further administration of study drug should be interrupted. Decision to resume emicizumab after an event of TMA must be discussed with and approved by the Medical Monitor.
Hypercoagulation and thromboembolic events	• HCPs should be vigilant for patients who exhibit signs/symptoms consistent with thromboembolic events and immediately begin work-up and treatment, as per local guidelines. • If a patient has a thromboembolic event, further administration of study drug should be interrupted. Decision to resume emicizumab after a thromboembolic event must be discussed with and approved by the Medical Monitor.
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.

FVIII=factor VIII; HCP=healthcare provider; TMA=thrombotic microangiopathy.

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) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

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 National Cancer Institute Common Terminology Criteria for Adverse Events; 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). Adverse events of special interest for this study are as follows:

- 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 Appendix 10)
- Thromboembolic events
- Microangiopathic hemolytic anemia or TMA (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.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in 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 12) will be used for assessing adverse event severity. 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 consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of 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. If possible, avoid ambiguous terms such as "systemic reaction." 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

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.

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

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

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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., ALP 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).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) 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 the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

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

5.3.5.8 Deaths

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

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

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

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Hemophilia

Medical occurrences or symptoms of deterioration that are anticipated as part of hemophilia should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in terms of severity (e.g., increased number of doses of FVIII to stop bleeds with emicizumab, in the absence of neutralizing anti-emicizumab antibodies, compared with before study entry), frequency of bleeds, or nature of hemophilia at any time during the study. When recording an unanticipated worsening of hemophilia on the Adverse Event eCRF, it is important to convey that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia"). A clinically significant bleed (i.e., Intracranial, retroperitoneal) does not by itself constitute loss of efficacy, unless it is associated with features indicating worsening of the underlying hemophilia phenotype.

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event.

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

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

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For emicizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with emicizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.

- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor:	[redacted] 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 paper Clinical Trial 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 emailing the form using the fax number or email 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 final 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 paper Clinical Trial 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 emailing the form using the fax number or email 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 serious adverse events that occur 24 weeks after the final dose of study treatment 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 *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the final dose of study drug. A paper 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 emailing the form using the fax number or email 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 plasma concentration (7 ng/mL) and the estimated maternal maximum concentration (for all dosing regimens: 1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W, and up-titrated to 3 mg/kg QW) 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

A spontaneous 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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity 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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

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 trial-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, email, 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 final dose of study drug), 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 emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- RO5543262 (Emicizumab) Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis will be performed after 50 patients with moderate hemophilia A have either completed 52 weeks of emicizumab treatment, are lost to follow-up, or have withdrawn prematurely, whichever occurs first. Data from all patients (including any female patients and any patients with mild hemophilia A) will be included in the primary analysis.

6.1 DETERMINATION OF SAMPLE SIZE

The overall sample size of approximately 70 patients (approximately 50 patients with moderate disease, approximately 20 patients with mild disease) is based primarily on clinical considerations, taking into account the limited number of patients with non-severe hemophilia A. This sample size is expected to provide statistically robust point estimates with meaningfully narrow CIs in the overall group of enrolled patients, at

the time of the primary analysis or at earlier timepoints appropriate for regulatory submissions (see Section 6.10), assuming the same efficacy across dosing regimens.

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 discontinuation 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.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, and self-reported race/ethnicity) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall (all patients), by dosing regimen, and, if applicable, by disease severity. Menstruation history will be summarized descriptively for female patients. Further details will be provided in the Statistical Analysis Plan (SAP).

6.4 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 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.

Summaries will be presented overall, by dosing regimen, and, if applicable, by disease severity. Further details will be provided in the SAP.

6.5 EFFICACY ANALYSES

6.5.1 Primary Efficacy Endpoint

The key efficacy objective is to characterize the efficacy of emicizumab based on the number of treated bleeds over time. The definition of a treated bleed is described in Section 4.5.7.3.

The clinical effect of prophylactic emicizumab will be assessed via the ABR estimated using a negative binomial regression model, which accounts for different follow-up times, with the number of bleeds from patients as a function of the time such that each patient who stays in the study is included as an offset in the model.

The number of bleeds resulting from the model will be annualized for each patient using the following formula:

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

The mean and median ABR based on the above formula using the observed numbers of bleeds instead of the number resulting from the model will also be calculated. In the case where the negative binomial model does not converge, the alternative derivations of the ABR will be used as the sole method of analysis.

A detailed description of the statistical methods and the summaries, if applicable, presented by dosing regimen and/or by disease severity for the efficacy analyses will be provided in the SAP.

6.5.2 Secondary Efficacy Endpoints

6.5.2.1 Bleed Endpoints

The clinical effect of prophylactic emicizumab on the secondary bleed endpoints of all bleeds (i.e., those treated and untreated with coagulation factors), joint bleeds, target joint bleeds, and spontaneous bleeds (see Section 4.5.7.3 for bleed definitions) will be analyzed in the same manner as for the primary analysis.

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.

6.5.2.2 Health-Related Quality-of-Life, Patient Preference, Joint Health, Activity, Menstruation Heaviness, and Menstruation-Related Quality of Life

With regards to the PRO secondary objectives, scores by each domain for the CATCH will be computed for each assessment with changes in scores examined for the assessments over time, and these will be summarized descriptively. Patient compliance with the CATCH will be summarized at each assessed timepoint.

For the EmiPref, the proportion of patients/caregivers preferring emicizumab after 17 weeks of treatment will be presented along with the reasons for that choice. Patient/caregivers compliance with the EmiPref will be summarized for Week 17.

For the activity assessment and HJHS, descriptive analyses will be presented by timepoints. All enrolled subjects who contribute to valid activity data (e.g., at least 8 days of wearing the device within a 14-day observation period) will be analyzed for

activity. The definition of valid activity data and the handling of missing values will be provided in the SAP.

Relative change from baseline (Weeks 1–2 period) at Weeks 13 (Weeks 12–13 period), 25 (Weeks 24–25 period), 37 (Weeks 36–37 period), and 49 (Weeks 48–49 period) in mean MVPA and DSC will be calculated and summarized. Subject-level data will also be presented at each timepoint.

MBQ will be summarized descriptively over time, including change from baseline for individual subscales (heaviness, quality of life, irregularity, and pain) and total score. PBAC scores will be summarized descriptively over time. If the number of female patients of childbearing potential is too low to provide reliable summaries, the data will listed and presented in individual patient plots where applicable.

6.6 PHARMACOKINETIC ANALYSES

Pre-dose (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 may also be used to analyze the dose-concentration-time data of emicizumab following SC administration and estimate population PK parameters. If conducted, these analyses will be reported in a dedicated report.

6.7 IMMUNOGENICITY ANALYSES

6.7.1 Anti-Emicizumab Antibodies

The immunogenicity analyses for emicizumab antibodies will include patients with at least one pre-dose and one post-dose 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 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.

6.7.2 Factor VIII Inhibitors

The number and proportion of patients who develop anti-FVIII inhibitors (titer ≥0.6 BU/mL) following study drug administration will be summarized.

6.8 BIOMARKER ANALYSES

Change over time in PD parameters (e.g., parameters derived from thrombin generation, FVIII activity, and protein levels) will be presented using summary statistics (e.g., arithmetic and geometric means, median, range, standard deviations, and coefficients of variation). Bone and joint health (if applicable, presented by HJHS categories at baseline) may also be explored in the same manner. Association of *FVIII* mutations and other coagulation-related gene polymorphisms with safety, efficacy, PK, and PD endpoints may be explored and reported descriptively.

6.9 HEALTH STATUS UTILITY ANALYSES

Absolute values and change from baseline in EQ-5D-5L health utility index-based and VAS scores at specified timepoints will be summarized descriptively.

6.10 OPTIONAL INTERIM ANALYSES REVIEWS

Interim data reviews may be performed at various timepoints for regulatory submissions. The results of each of these analyses will be documented in an interim Clinical Study Report.

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. Central laboratory 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.

PRO data will be collected through the use of an electronic device provided by a vendor and tablet at the clinic (see Section 7.3 for details). In the event that the electronic device is unavailable, the paper version provided to investigators should be completed,

and once electronic data entry is available, all information will need to be entered and submitted electronically.

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 that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure portal provided by the vendor. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

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

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review 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, patient-reported outcomes, 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 trial.

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

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form, 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") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient

to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

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

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 20 sites globally will participate to enroll approximately 70 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

	Screening [a]		Treatment																Week >49 to Study Completion	Safety FU [b]	Study Completion/ Discon. [c]
Week	–	–	1	2	3	4	5	9	13	17	21	25	29	33	37	41	45	49			
Day [d]	–28 to –1	–7 to –1	1	8	15	22	29	57	85	113	141	169	197	225	253	281	309	337			
Informed consent	x [e]																				
Demographic data	x																				
Medical history and baseline conditions [f]	x																				
PROs, HRQoL (CATCH) [g]			x						x			x			x			x	Q12W		x
Patient-reported outcomes (EmiPref) [g]										x											
Health status (EQ-5D-5L) [g]			x						x			x			x			x	Q12W		x
Joint health (HJHS) [h]		x										x						x	Q24W		x
Activity [i]			Weeks 1–2, Weeks 12–13, Weeks 24–25, Weeks 36–37, and Weeks 48–49																		
Vital signs [j]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q12W		x
Weight	x		x				x	x	x	x	x	x	x	x	x	x	x	x	Q12W		x
Height [k, l]			x						x			x			x			x	Q12W		
Complete physical examination [m]	x								x			x			x			x	Q12W		x
ECG [n]	x						x					x						x	Q12W		x
Hematology [o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q12W		x

Appendix 1: Schedule of Activities (cont.)

	Screening [a]		Treatment																Week >49 to Study Completion	Safety FU [b]	Study Completion/ Discon. [c]
Week	–	–	1	2	3	4	5	9	13	17	21	25	29	33	37	41	45	49			
Day [d]	–28 to –1	–7 to –1	1	8	15	22	29	57	85	113	141	169	197	225	253	281	309	337			
Chemistry [p]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q12W		x
Local coagulation tests (aPTT, PT/INR)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x
Pregnancy test [q]		x	x				x	x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x
Emicizumab administration [r]			x	x	x	x	To be administered QW, Q2W, or Q4W depending on regimen															
Samples for PK, PD, ADA, and biomarkers	See Appendix 2.																				
BMQ [s]			QW and on days of bleed																		
BMQ review [t]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q4W	x	x
MBQ [u]			x				x	x	x	x	x	x	x	x	x	x	x	x	Q4W	x	x
MD with PBAC [u]			Monthly																Monthly	x	x
Concomitant medications	x [v]	x [v]	x [v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q4W	x	x
Adverse events [w]	x	x	Ongoing																		

ADA = anti-drug antibody; BMQ = Bleed Medication Questionnaire; CATCH = Comprehensive Assessment Tool of Challenges in Hemophilia; Discon. = discontinuation; eCRF = electronic Case Report Form; EmiPref = Emicizumab Preference Survey; EQ-5D-5L = European Quality of Life 5-Dimension, 5-Level Questionnaire; FU = follow-up; FVIII = factor VIII; HJHS = Hemophilia Joint Health Score; HRQoL = health-related quality of life; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcome; QW = once a week; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; UV = unplanned visit; MBQ = Menstrual Bleeding Questionnaire; MD = Menstruation Diary; PBAC = Pictorial Blood Assessment Chart

Notes: All study visits and assessments should be performed within ±2 days of the scheduled visit, until safety follow-up visit. Safety follow-up visit should be performed 24 weeks after discontinuation of emicizumab; deviation of ±7 days is acceptable. Safety follow-up visit will not be

performed for patients who transfer to commercial emicizumab. On treatment days, all assessments should be performed prior to emicizumab dosing, unless otherwise specified. On treatment days, all PRO assessments, when applicable, should be performed prior to any study intervention.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study drug will return to the clinic for a safety follow-up visit 24 weeks after their final dose of study drug.

[c] Study completion/discontinuation visit occurs when the patient completes 52 weeks of emicizumab treatment in the study and either transfer to commercially available emicizumab or receive further emicizumab per Roche Global Policy on Continued Access to Investigational Medicinal Products; OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation; OR patient has withdrawn consent; OR patient is lost to follow-up.

[d] Assessments can deviate from planned schedule by ±2 days until safety follow-up visit. Safety follow-up visit should be performed 24 weeks after discontinuation of emicizumab; deviation of +7 days is acceptable. Safety follow-up visit will not be performed for patients who transfer to commercial emicizumab.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

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

[g] Questionnaire will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment. For patients younger than 18 years of age, the patient's caregiver will also be asked to fill out the EmiPref (caregiver version). For patients <12 years old: only the caregiver will fill out the EmiPref (*caregiver version); the EmiPref (patient version) and EQ-5D-5L will not be completed.*

[h] HJHS will be performed as part of the physical examination *for patients ≥4 years of age.*

[i] Applicable to patients ≥5 years of age. Accelerometer should be worn on the wrist continuously for 24 hr/day for 14 days at each 2-week period indicated.

[j] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[k] Height assessment at Day 1 only for adults.

[l] Height assessments for adolescents at Day 1 and ideally at all drug administration and PK sampling visits at the investigational site, but at least Q12W (repeated assessments).

[m] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[n] If screening ECG is abnormal, repeat at Week 1. ECGs will also be performed: once during Weeks 4–8 and once 24 and 49 weeks after starting emicizumab.

[o] Pre-dose: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and absolute differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width will be 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.

[p] Pre-dose: sodium, potassium, glucose, BUN, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, albumin, ALP, ALT, AST, LDH and CPK will be 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.

[q] All women of childbearing potential (including those who have had a tubal ligation) will be required to have a negative serum pregnancy test result at screening and within 7 days prior to initiation of study medication (Day –7 to Day –1). If applicable, urine pregnancy tests will be performed at the scheduled visits, except for Weeks 2–4. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. If the serum pregnancy test is positive, further administration of emicizumab should be discontinued.

[r] *Emicizumab may be administered by a mobile nursing professional.*

[s] Bleed information for each bleed (start date and time, reason, type, location, and associated symptoms (only collected for muscle and joint bleeds in patients 12 years of age and older)) 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 final study drug administration). Emicizumab doses should be recorded by the patient in the BMQ starting on Day 1.

[t] Investigator review of bleed information.

[u] All female patients of childbearing potential will be asked to provide the start and end dates of menstruation that will be recorded on eCRF and to complete the MBQ and the MD with PBAC, both on paper. The MBQ will be self-administered in the clinic on Day 1 and subsequently every 4 weeks; the MD with PBAC will be completed by patients at home. The MD with PBAC will be given to patients on Day 1 and should be completed monthly on days of menstruation. The patient should return the completed MD with PBAC to the site personnel during the next clinic visit. The MD with PBAC is a monthly form that will be given in multiple copies to the patients to cover the length of the study.

[v] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 4 weeks prior to enrollment to the study completion/discontinuation visit. FVIII taken during the week prior to starting emicizumab (i.e., week prior to Day 1) will also be collected on the *Hemophilia History Medication 7 Days Prior to Enrollment* eCRF page for patients who will continue their prior FVIII prophylaxis during the first week of the study.

[w] 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. Adverse events will be collected on an ongoing basis throughout the study. Injection-site reactions will be collected on a separate form from the adverse event form. After initiation of study drug, all adverse events will be reported until 24 weeks after the final dose of emicizumab. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Assessments	Screening	Treatment Period																Week >49 to Study Completion	Safety FU Visit	Study Completion/ Discon. [a]
Week		1	2	3	4	5	9	13	17	21	25	29	33	37	41	45	49			
Day	–28 to –1	1	8	15	22	29	57	85	113	141	169	197	225	253	281	309	337			
Blood sample for genotyping [b, c, f]		x																		
Emicizumab PK (plasma) [b]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x
Emicizumab ADA (plasma) [b, d]		x				x		x			x		x		x		x	Q12W	x	x
PD and safety biomarkers (plasma) [b, e, f]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x
Anti-FVIII antibodies [f]	x [g]	x						x			x			x			x	Q12W	x	x
Plasma and serum sample for bone and joint biomarkers [h, f]		x									x						x			x
Plasma samples following treatment with coagulation factor product [i]		Monitoring for procoagulant effect [i]																		

ADA = anti-drug antibody; Discon. = discontinuation; FU = follow-up; FXIa = factor XIa; FVIII = factor VIII; PD = pharmacodynamic; PK = pharmacokinetic; Q12W = every 12 weeks; TGA = thrombin generation assay.

Note: All study visits and assessments during the treatment period should be performed within ± 2 days of the scheduled date until safety follow-up visit. Safety follow-up visit should be performed 24 weeks after discontinuation of emicizumab; deviation of ± 7 days is acceptable. Safety follow-up visit will not be performed for patients who transfer to commercial emicizumab. On treatment days, all assessments should be performed prior to emicizumab dosing, unless otherwise specified. On treatment days, all PRO assessments, when applicable, should be performed prior to any study intervention,

[a] Study completion/discontinuation visit occurs when the patient completes 52 weeks of emicizumab treatment in the study and either transfers to commercially available emicizumab or receives further emicizumab per Roche Global Policy on Continued Access to Investigational Medicinal Products; OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation; OR patient has withdrawn consent; OR patient is lost to follow-up.

[b] Samples should always be drawn pre-dose.

[c] If the sample is missed on Day 1, it can be collected at any other scheduled visit.

[d] ADA samples may also be drawn if hypersensitivity event occurred or at any time (unscheduled) in the investigator's judgment.

[e] PD markers include FVIII activity (bovine and human coagulation factor chromogenic assays), FVIII protein, and thrombin generation (FXIa- and tissue factor triggered TGAs). Safety markers include, but are not limited to, fibrinogen, D-dimer, and prothrombin fragment 1+2.

[f] Samples will only be collected if the permitted blood volumes allow (based on patient body weight as described in Section 4.5.5). Refer to the laboratory manual for details.

[g] At screening, the evaluation for anti-FVIII antibodies will be performed locally and documented on eCRF to confirm the negative testing for inhibitor as per inclusion criteria. *This sample 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 Week 1.*

[h] Collect after fasting overnight in patients ≥ 12 years of age.

[i] Following treatment with coagulation factor product, sample should be collected *for* central laboratory monitoring of emicizumab pharmacokinetics, fibrinogen, FVIII activity (bovine and human coagulation factor chromogenic assays), D-dimer, prothrombin fragment 1 + 2, and thrombin generation (FXIa- and tissue factor-triggered TGAs) within 24 hours (but no later than 48 hours) of initial coagulation factor product use. If a breakthrough bleed occurs outside of a hospital visit and requires treatment, collection of a blood sample should occur within 30 minutes–24 hours but no later than 48 hours after treatment for the bleed has been administered. In such a case, to avoid requiring patients to return to the study site for a blood draw, this sample collection may be performed by a mobile nursing professional at the patient's home or another suitable location to improve access and convenience for patients participating in the study.

Appendix 3
Hemophilia Joint Health Score

Subject ID #:_____ Name of physiotherapist:_____

Assessment #: _____ Date: _____
yyyy / mm / dd

Time: _____

Hemophilia Joint Health Score 2.1 – Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Duration (swelling)		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Muscle Atrophy		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Crepitus on motion		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Flexion loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Extension loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint pain		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Strength		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Total												

Sum of Joint Totals + ☐

Global Gait Score ☐
(☐ NE included in Gait items)

HJHS Total Score = ☐

NE = Non-Evaluable

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

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

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

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

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

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

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

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

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

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

General comments:

_____
_____
_____
_____
_____
_____

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

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

Appendix 4
Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH): Adult

HEMOPHILIA IMPACT INSTRUMENT - Adult

You are now starting the main survey. There are a number of different parts – you can see which part you are on by looking at the status bar at the top of the page.

The survey will ask you questions about how hemophilia affects different aspects of your life. We realize some of the questions may seem repetitive, but very much appreciate your time and consideration. Please answer all questions.

General question about lifestyle:
How would you rate the level of restriction in your lifestyle, due to hemophilia?

1 Not restricted at all	2	3	4	5	6	7	8	9	10 Extremely restricted

Daily activities: Please indicate how risky each of the following activities is for you in terms of causing a bleed and how often your hemophilia impacts your ability to do each activity.

		How risky do you think [this activity] is for you?			How often does hemophilia impact your ability to do [this activity]?			
	No risk	Low risk	Moderate risk	High risk	Never	Rarely	Sometimes	Most of the time
Typing a text message								
Talking on the phone								
Washing your face								
Brushing your teeth								
Washing the dishes								
Drying your whole body after a shower or bath								

		How risky do you think [this activity] is for you?			How often does hemophilia impact your ability to do [this activity]?			
	No risk	Low risk	Moderate risk	High risk	Never	Rarely	Sometimes	Most of the time
Playing video games with a controller								
Playing video games that require you to move your body								
Putting on a shirt								
Putting on a tie or closing the top button of a shirt								
Putting on socks and shoes								
Getting in and out of a car								
Doing your weekly grocery shopping								
Walking inside the house								
Walking outside								
Sleeping								
Doing the laundry								
Cooking								
Walking up one flight of stairs								
Walking down one flight of stairs								

		How risky do you think [this activity] is for you?			How often does hemophilia impact your ability to do [this activity]?			
	No risk	Low risk	Moderate risk	High risk	Never	Rarely	Sometimes	Most of the time
Standing for a long time								
Gardening/yard work								
Carrying heavy objects								

Overall, how risky are *daily activities* for you in terms of causing a bleed?
☐ No risk ☐ Low risk ☐ Moderate risk ☐ High risk

Overall, how often does hemophilia have an impact on your ability to do *daily activities*?
☐ Never ☐ Rarely ☐ Sometimes ☐ Most of the time

Social activities: Please indicate how risky each of the following activities is for you in terms of causing a bleed and how often your hemophilia impacts your ability to do each activity.

	How risky do you think [this activity] is for you?				How often does hemophilia impact your ability to do [this activity]?			
	No risk	Low risk	Moderate risk	High risk	Never	Rarely	Sometimes	Most of the time
Going out to an activity where you will be sitting (movie, play, church, etc.)								
Playing board games								
Going out to an activity that requires walking (museum, etc.)								
Going out to a bar								
Shopping for clothes								
Travelling locally in a car								

	How risky do you think [this activity] is for you?				How often does hemophilia impact your ability to do [this activity]?			
	No risk	Low risk	Moderate risk	High risk	Never	Rarely	Sometimes	Most of the time
Travelling long distances in a car or airplane								
Making plans with friends								
Keeping plans (not cancelling)								
Sexual activity								
Playing rough with kids								

Overall, how risky are *social activities* for you in terms of causing a bleed?
☐ No risk ☐ Low risk ☐ Moderate risk ☐ High risk

Overall, how often does hemophilia have an impact on your ability to do *social activities*?
☐ Never ☐ Rarely ☐ Sometimes ☐ Most of the time

Recreational activities: Please indicate whether you do the following activities on a regular basis.

☐	Fishing
☐	Swimming
☐	Doing yoga
☐	Golfing
☐	Playing tennis
☐	Woodworking
☐	Dancing
☐	Hiking
☐	Camping
☐	Canoeing/Kayaking
☐	Riding a stationary bicycle
☐	Riding a bicycle
☐	Running on a treadmill or elliptical trainer
☐	Running outside
☐	Hunting
☐	Rock climbing
☐	Surfing
☐	Volleyball
☐	Frisbee ®
☐	Soccer
☐	Baseball
☐	Basketball
☐	Squash/racquetball
☐	Karate or judo
☐	Weight lifting
☐	Nordic/cross country skiing
☐	Downhill skiing
☐	Skateboarding
☐	Scuba diving
☐	Ice hockey
☐	Football
☐	Rugby

Recreational activities: Please indicate whether there are any activities on this list you do NOT do because of your hemophilia.

☐	Fishing
☐	Swimming
☐	Doing yoga
☐	Golfing
☐	Playing tennis
☐	Woodworking
☐	Dancing
☐	Hiking
☐	Camping
☐	Canoeing/Kayaking
☐	Riding a stationary bicycle
☐	Riding a bicycle
☐	Running on a treadmill or elliptical trainer
☐	Running outside
☐	Hunting
☐	Rock climbing
☐	Surfing
☐	Volleyball
☐	Frisbee®
☐	Soccer
☐	Baseball
☐	Basketball
☐	Squash/racquetball
☐	Karate or judo
☐	Weight lifting
☐	Nordic/cross country skiing
☐	Downhill skiing
☐	Skateboarding
☐	Scuba diving
☐	Ice hockey
☐	Football
☐	Rugby

For those activities that you do, please indicate how risky each of the following activities is for you in terms of causing a bleed and how often your hemophilia impacts your ability to do each activity.

	How risky do you think [this activity] is for you?				How often does hemophilia impact your ability to do [this activity]?			
	No risk	Low risk	Moderate risk	High risk	Never	Rarely	Sometimes	Most of the time
Activities are populated based on those chosen above								

Overall, how risky are *recreational activities* for you in terms of causing a bleed?

☐ No risk ☐ Low risk ☐ Moderate risk ☐ High risk

Overall, how often does hemophilia have an impact on your ability to do *recreational activities*?

☐ Never ☐ Rarely ☐ Sometimes ☐ Most of the time

Work items

How often does hemophilia impact your ability to…	*Never*	*Rarely*	*Sometimes*	*Most of the time*
1. …work full time?				
2. …work on the days you planned to work (i.e., not cancel or call in sick)?				
3. …complete a full work day or work shift (i.e., not come in late, go home early, or cut the work day short)?				
4. …physically do your job?				
5. …get your work done?				
6. …travel to and from your workplace?				
7. …move around your workplace?				
8. …concentrate on tasks at work?				

Because of hemophilia, how often…	*Never*	*Rarely*	*Sometimes*	*Most of the time*
9. …do you modify the way you do your tasks at work?				

Overall, how often does hemophilia impact your ability to work?

☐ Never ☐ Rarely ☐ Sometimes ☐ Most of the time

College items

Because of your hemophilia, how often…	*Never*	*Rarely*	*Sometimes*	*Most of the time*
1. …do you miss class?				
2. …do you get to class late or need to leave class early?				
3. …do you modify the way you do your tasks at school?				
How often does hemophilia impact your ability to…				
4. …attend college full time?				
5. …attend all of your scheduled classes?				
6. …get your school work done?				
7. …get around campus?				
8. …concentrate at school?				
9. …participate in extracurricular activities?				

Overall, how often does hemophilia impact your ability to go to school and/or do schoolwork?

☐ Never ☐ Rarely ☐ Sometimes ☐ Most of the time

In a typical day, how often do these statements apply to you?

	Never	Rarely	Sometimes	Often	Always
1. Hemophilia is in the back of my mind					
2. Because of my hemophilia, I plan ahead when I do something out of my usual routine					
3. I think about whether something I am about to do may cause a bleed					
4. I think about my hemophilia before I make a decision to do something					
5. I make sure the people I spend time with are aware of how to help me if I get a severe bleed					
6. Because of my hemophilia, I'm very careful about everything I do					
7. I'm forced to think about hemophilia more than I would like					
8. I am anxious in situations that I think could cause a bleed					
9. I worry about the long-term consequences of my hemophilia					

Overall, in a typical day, how often do you think about hemophilia?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

The following questions are about your hemophilia treatment.

Do you give yourself your hemophilia treatment or does someone else do it for you?

☐ **I give the treatment to myself**
☐ **Someone else does it for me**

	How much are you bothered by	**Not at all**	**A little**	**Moderately**	**Quite a bit**	**Extremely**
1.	Preparing your hemophilia treatment for administration?					
2.	Taking your hemophilia treatment with you while traveling?					
3.	Having to take your hemophilia treatment before physical activities?					
4.	The frequency of hemophilia treatments?					
5.	The type of needle used for your hemophilia treatment?					
6.	Physically giving yourself or receiving your hemophilia treatment?					
7.	The pain when hemophilia treatment is administered?					

	How much of a problem for you…	**Not at all**	**A little**	**Moderately**	**Quite a bit**	**Extremely**	**Not Applicable;** I am not on prophylaxis treatment
8.	is it to stick to your hemophilia treatment schedule?						

Overall, how much are you bothered by your hemophilia treatment?
☐ Not at all ☐ A little ☐ Moderately ☐ Quite a bit ☐ Extremely

The following questions are about your level of pain over the past 7 days. Please check the box that corresponds to your level of pain.

Did you get a bleed in the **past 7 days?** ☐ **Yes** ☐**No[if NO they do not receive the question below]** If **yes,** please rate your pain by picking the number that best describes your pain associated with the bleed.										
0 (no pain)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (pain as bad as you can imagine)**
Do you have **target joints?** ☐ **Yes** ☐**No[if NO they do not receive the question below]** If **yes,** please rate your pain by picking the number that best describes your pain in your target joint(s) over the past 7 days										
0 (no pain)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (pain as bad as you can imagine)**
Please rate your pain by picking the number that best describes your pain **at its WORST** over the **past 7 days**										
0 (no pain)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (pain as bad as you can imagine)**
Please rate your pain by picking the number that best describes your pain **at its LEAST** over the **past 7 days**										
0 (no pain)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (pain as bad as you can imagine)**
Please rate your pain by picking the number that best describes your pain **on the AVERAGE** over the **past 7 days**										
0 (no pain)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (pain as bad as you can imagine)**

Appendix 5
Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH): Pediatric

HEMOPHILIA IMPACT INSTRUMENT – Pediatric

You are now starting the main survey. There are a lot of different parts – you can see which part you are on by looking at the status bar at the top of the page.

General question

Thinking about your hemophilia, how often can you do what you want at school or with friends?

1 Never	2 Sometimes	3 Often	4 Always

Daily activities: Please tell us how likely you would be to have a bleed when doing each activity and how often your hemophilia makes it hard to do each activity.

	Would you have a bleed if you were to do this activity?			Because of your hemophilia, is it hard for you to do this activity?			
	No	Maybe	Yes	Never	Sometimes	Often	Always
Typing a text message							
Talking on the phone							
Washing your face							
Brushing your teeth							
Drying your whole body after a shower/bath							
Sitting on the floor when watching TV or playing							
Playing video games with a controller							
Playing video games that require moving your body							
Putting on a shirt							
Putting on socks and shoes							

	Would you have a bleed if you were to do this activity?			Because of your hemophilia, is it hard for you to do this activity?			
	No	Maybe	Yes	Never	Sometimes	Often	Always
Getting in and out of a car							
Walking inside the house							
Walking outside							
Sleeping							
Walking up one flight of stairs							
Walking down one flight of stairs							
Standing for a long time							
Carrying heavy objects (like a box of toys or pile of books)							

Overall, would you have a bleed from doing *daily activities*?
☐ No ☐ Maybe ☐ Yes

Overall, does hemophilia make it hard for you to do your *daily activities*?
☐ Never ☐ Sometimes ☐ Often ☐ Always

Social activities: Please tell us how likely you would be to have a bleed when doing each activity and how often your hemophilia makes it hard to do each activity.

	Would you have a bleed if you were to do this activity?			Because of your hemophilia, is it hard for you to do this activity?			
	No	Maybe	Yes	Never	Sometimes	Often	Always
Going out to an activity where you would be sitting (like the movies)							
Playing with friends inside							

	Would you have a bleed if you were to do this activity?			Because of your hemophilia, is it hard for you to do this activity?			
	No	Maybe	Yes	Never	Sometimes	Often	Always
Going out to an activity where you would be moving your body (like a playground)							
Shopping for clothes							
Playing with friends outside							
Travelling short distances in a car (like to a friend's house)							
Travelling long distances (like a few hours away in a car or on an airplane)							

Overall, would you have a bleed from doing *social activities*?

☐ No ☐ Maybe ☐ Yes

Overall, does hemophilia make it hard for you to do your *social activities*?

☐ Never ☐ Sometimes ☐ Often ☐ Always

Recreational activities: Please check off any activities on this list that you do regularly.

☐	Swimming
☐	Golfing
☐	Ping pong®
☐	Archery
☐	Tennis
☐	Dancing
☐	Climbing trees
☐	Riding a scooter
☐	Riding a bicycle
☐	Riding horses
☐	Ice skating
☐	Rollerblading

☐	Playing paintball
☐	Running outside
☐	Hunting
☐	Frisbee®
☐	Kickball
☐	Fencing
☐	Dodgeball
☐	Water polo
☐	Wakeboarding
☐	Snowboarding
☐	Rock climbing
☐	Soccer
☐	Baseball
☐	Basketball
☐	Lacrosse
☐	Volleyball
☐	Squash/racquetball
☐	Bouncy houses
☐	Jumping on trampolines
☐	Nordic/cross country skiing
☐	Downhill skiing
☐	Gymnastics
☐	Karate or Judo
☐	Parkour
☐	Wrestling
☐	Boxing
☐	Kickboxing
☐	Weightlifting
☐	Skateboarding
☐	Ice hockey
☐	Flag football
☐	Tackle football
☐	Rugby

Recreational activities: Please check off any activities on this list that you DO NOT DO because of your hemophilia.

☐	Swimming
☐	Golfing
☐	Ping pong®
☐	Archery
☐	Tennis
☐	Dancing
☐	Climbing trees
☐	Riding a scooter

☐	Riding a bicycle
☐	Riding horses
☐	Ice skating
☐	Rollerblading
☐	Playing paintball
☐	Running outside
☐	Hunting
☐	Frisbee®
☐	Kickball
☐	Fencing
☐	Dodgeball
☐	Water polo
☐	Wakeboarding
☐	Snowboarding
☐	Rock climbing
☐	Soccer
☐	Baseball
☐	Basketball
☐	Lacrosse
☐	Volleyball
☐	Squash/racquetball
☐	Bouncy houses
☐	Jumping on trampolines
☐	Nordic/cross country skiing
☐	Downhill skiing
☐	Gymnastics
☐	Karate or Judo
☐	Parkour
☐	Wrestling
☐	Boxing
☐	Kickboxing
☐	Weightlifting
☐	Skateboarding
☐	Ice hockey
☐	Flag football
☐	Tackle football
☐	Rugby

For those activities that you do, please tell us how likely you would be to have a bleed when doing each activity and how often your hemophilia makes it hard to do each activity.

	Would you have a bleed if you were to do this activity?			Because of your hemophilia, is it hard for you to do this activity?			
Activities are populated based on those chosen above	No	Maybe	Yes	Never	Sometimes	Often	Always

Overall, would you have a bleed from doing *recreational activities*?

☐ No ☐ Maybe ☐ Yes

Overall, does hemophilia make it hard for you to do your *recreational activities*?

☐ Never ☐ Sometimes ☐ Often ☐ Always

School items

Because of your hemophilia, how often…	*Never*	*Sometimes*	*Often*	*Always*
1. …do you miss school?				
2. …do you get to class late or need to leave class early?				
Because of your hemophilia, is it hard for you to…				
3. … participate in gym class?				
4. … stay at school for a full school day?				
5. … get around school (i.e. move from one class to another)?				
6. …travel to and from school?				
7. …concentrate on tasks at school?				
8. …get your work done at school?				
9. …get your homework done?				
10. …participate in after school activities?				

Overall, how often does hemophilia make it hard for you to go to school and/or do schoolwork?

☐ Never ☐ Sometimes ☐ Often ☐ Always

How careful are you about your hemophilia? Please answer thinking of the past 7 days.

		Never	Sometimes	Often	Always
1.	I am more careful than other kids when doing activities				
2.	I avoid activities that could make me bleed				

Overall, how often do you think about hemophilia?

☐ Never ☐ Sometimes ☐ Often ☐ Always

How do you feel about your hemophilia treatments?

How much do you like or dislike…	Dislike a lot	Dislike a little	Like a little	Like a lot
1. …how your hemophilia treatment gets into your body?				
2. …where the needle is inserted into your body?				
3. …how often you have to take your hemophilia treatment?				
4. …having to take extra treatments for your hemophilia (more than usual)				
5. …how long each hemophilia treatment takes from start to finish?				
6. …what your body feels like when you get hemophilia treatment (e.g. pain from needles)?				

Overall, how much do you like or dislike your hemophilia treatment?

☐ Dislike a lot ☐ Dislike a little ☐ Like a little ☐ Like a lot

How much does your body hurt? Please answer thinking of the past 7 days.

Did you get a bleed in the **past 7 days?** □ **Yes** □ **No [if NO they do not receive the question below]** If **yes,** how much did the bleed hurt?										
0 (no hurt)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (a lot of hurt)**
What is the **WORST** that your body has hurt over the **past 7 days?**										
0 (no hurt)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (a lot of hurt)**

Did you complete these questions on your own or did you get help from a grown up?

☐ Completed on my own ☐ Got help from a grown up

Appendix 6
Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH): Caregiver

Caregiver

The following questions ask about what it is like to have a child with hemophilia. Please pick the answer that best applies to you.

Because my child has hemophilia…		**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
1.	Hemophilia is in the back of my mind.					
2.	I feel like I need to be 'on call' 24 hours a day (always available).					
3.	I feel like I need to organize my life around the disease.					
4.	I worry about my child when I'm not with him/her.					
5.	My relationship with family members is impacted negatively (including my other children and/or spouse).					
6.	I have to cancel plans with my friends.					
7.	I worry about my child's future.					
8.	I feel stressed about controlling my child's physical activity to prevent a bleed.					
9.	I feel stressed about the unpredictability of bleeds.					
10.	I worry that my child won't tell me when he or she has a bleed.					
11.	I worry that my child won't adhere to his/her treatment plan.					
12.	I feel like I need to watch my child closely.					

Overall, how often do you think about your child's hemophilia?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

The following questions are about tasks related to treatment and caring for a child with hemophilia

Do you administer your child's treatment or do they do it themselves? [If child administers own treatment, parent will not get Q4]

☐ **I administer my child's treatment**

☐ **My child administers his/her own treatment**

How much of a problem for you…		Not at all	A little	Moderately	Quite a bit	Extremely
1.	…is it to restrict your child from doing activities that he/she wants to do?					
2.	…is it to ask your child to stop an activity if he/she needs to treat his/her hemophilia?					
3.	… is the time it takes for hemophilia treatment?					
4.	… is it to physically give your child treatment for hemophilia (keeping them still, finding a vein)?					
5.	… is the frequency of hemophilia treatment?					
6.	… is storing your child's hemophilia treatment supplies?					
7.	… is deciding whether to treat your child's hemophilia or have them miss an activity?					

Overall, how much of a problem for you is your child's hemophilia treatment?

☐ Not at all ☐ A little ☐ Moderately ☐ Quite a bit ☐ Extremely

Appendix 7
EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L)

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

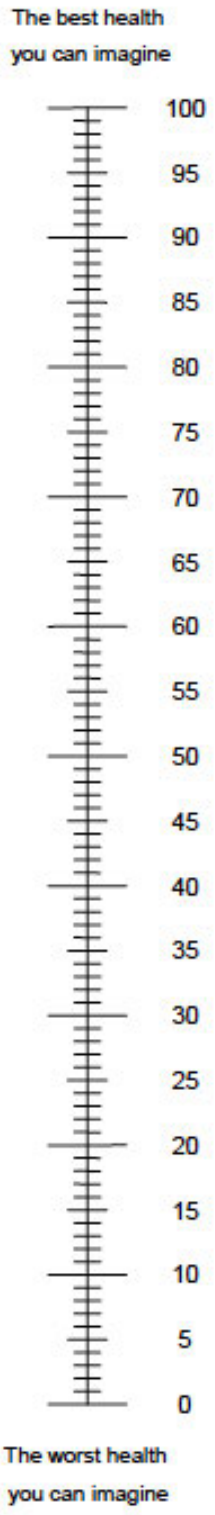
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Appendix 8
Emicizumab Preference Survey (EmiPref): Patient

Instructions: You have been treated with intravenous (IV) factor VIII or bypassing agent (your old hemophilia treatment) and prophylactic subcutaneous (SC) emicizumab (the new study drug treatment). Please complete the following questions based on your experience with these treatments.

There are no right or wrong answers and your responses will not influence your continued participation in the study or treatment with emicizumab.

1. Which of the treatments would you prefer to take as the treatment for your hemophilia? (Mark ONLY one response)

	Prefer my old hemophilia treatment (IV)
	Prefer the new study drug treatment (SC)
	Have no preference

If you indicated a preference, please complete question 2.

If you did not have a preference, you do not need to complete questions 2.

2. Below are some factors that may have influenced your treatment preference. Please indicate which factors had an influence on YOUR preference. Please indicate YES (this influenced my preference) or NO (this did not influence my preference) for each item.

   On those you said YES to, please rank the top 3 in order of importance (1 being the "most important" reason for your preference).

	Yes	No	Importance rank
Route of administration (IV or SC) was easier			
Pain associated with treatment was less			
Worry about finding a vein was less			
Concern over port use/infection was less			
Administration was easier			
Able to keep treatment at room temperature			
Time to administer treatment was shorter			
The frequency of treatments was lower			
Effect on other activities (work, school, sports, social interactions) was less			
Impact on family members and friends was less			
Worries about having a bleed were less			
Quality of life, in general, was better			
It was easier to take every dose my doctor recommended			
Made me feel more 'normal'			

3. Please add any additional information about your experience with the study drug (SC emicizumab).

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Appendix 9
Emicizumab Preference Survey (EmiPref): Caregiver

Instructions: Your child has been treated with intravenous (IV) factor VIII (your child's old hemophilia treatment) and prophylactic subcutaneous (SC) emicizumab (the new study drug treatment). Please complete the following questions based on your experience with these treatments.

There are no right or wrong answers and your responses will not influence your child's continued participation in the study or treatment with emicizumab.

1. Which of the treatments would you prefer your child to take as the treatment for your child's hemophilia? (Mark ONLY one response)

	Prefer my child's old hemophilia treatment (IV)
	Prefer the new study drug treatment (SC)
	Have no preference

If you indicated a preference, please complete question 2.

If you did not have a preference, you do not need to complete questions 2.

2. Below are some factors that may have influenced your treatment preference. Please indicate which factors had an influence on YOUR preference. Please indicate YES (this influenced my preference) or NO (this did not influence my preference) for each item.

   On those you said YES to, please rank the top 3 in order of importance (1 being the "most important" reason for your preference).

	Yes	No	Importance rank
Route of administration (IV or SC) was easier			
Pain associated with treatment was less			
Worry about finding a vein was less			
Concern over port use/infection was less			
Administration was easier			
Able to keep treatment at room temperature			
Time to administer treatment was shorter			
The frequency of treatments was lower			
Effect on other activities (work, school, sports, social interactions) was less			
Impact on family members and friends was less			
Worries about having a bleed were less			
Quality of life, in general, was better			
It was easier to take every dose my child's doctor recommended			
Made my child feel more 'normal'			

3. Please add any additional information about your child's experience with the study drug (SC emicizumab).

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Appendix 10
Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network [1]. Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue/uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

   - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure [2]
   - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

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

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

Appendix 11
Anaphylaxis Precautions

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

REQUIRED EQUIPMENT AND MEDICATION

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

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

PROCEDURES

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

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

Appendix 12
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	< 6.5 g/dL
Absolute neutrophil count	1000–1500/mm^3	750–999/mm^3	500–749/mm^3	< 500/mm^3
Platelets	75,000–99,999/mm^3	50,000–74,999/mm^3	20,000–49,999/mm^3	< 20,000/mm^3
Prothrombin time (PT)	1.01–1.25 × ULN	1.26–1.5 × ULN	1.51–3.0 × ULN	> 3 × ULN
Activated partial thromboplastin (APPT)	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3 × ULN	> 3 × ULN
Fibrinogen	0.75–0.99 × LLN	0.50–0.74 × LLN	0.25–0.49 × LLN	< 0.25 × LLN
Fibrin split product	20–40 mcg/mL	41–50 mcg/mL	51–60 mcg/mL	> 60 mcg/mL
Methemoglobin	5–9.9%	10.0–14.9%	15.0–19.9%	> 20 %
LIVER ENZYMES				
AST (SGOT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
ALT (SGPT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
GGT	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Alkaline phosphatase	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	> 5.0 × ULN

Appendix 12: WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
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
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

Appendix 12: WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CHEMISTRIES (cont.)				
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
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires treatment
Hypertension	transient increase. > 20 mmHg; no Rx required	recurrent, chronic, increase > 20 mmHg, Rx required	requires acute Rx; no hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1–2 units transfused	massive blood loss; > 3 units transfused

Appendix 12: WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
RESPIRATORY				
Cough	transient; no Rx	treatment-associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx < 70%–79% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50%–69% (or peak Flow)	no normalization with bronchodilator; FEV_1 25%–49% (or peak flow retractions)	cyanosis: $FEV_1 < 25\%$ (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3–4 loose stools/day	5–7 loose stools/day	orthostatic hypotension or > 7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
NEURO AND NEUROMUSCULAR				
Neuro-cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization

Appendix 12: WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

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

Appendix 13 Menstrual Bleeding Questionnaire

Menstrual Bleeding Questionnaire

These questions ask for details about your period. Periods can be different from month to month. Please make sure you read all of the options. For this questionnaire, period refers to any bleeding that you have from your vagina, even if it is irregular.

Some of the questions may sound similar. Just read through each question carefully and give your best answer.

You may have other medical problems that could affect your answers. Please try to focus on questions and answers **ONLY** as they relate to your period.

During the past month, did you have ANY bleeding?

Yes..... [ ]

No..... [ ]

If you answered "YES" continue to question 1.
If you answered "NO" skip to question 12.

1. During the past month, how would you describe your periods?

Very Light.....	[ ]
Light.....	[ ]
Moderate.....	[ ]
Heavy.....	[ ]
Very Heavy.....	[ ]

Instructions for questions 2, 3, and 4.

"High absorbency" sanitary products mean any type of tampon or a pad that is NOT a thin pantyliner.

"Soaked" means completely or almost completely stained and filled with blood.

2. On your heaviest day of bleeding during the past month, how many high absorbency sanitary products did you soak (either completely or almost completely)?

0.....	[ ]
1-4.....	[ ]
5-8.....	[ ]
9-12.....	[ ]
13-16.....	[ ]
More than 16.....	[ ]

Menstrual Bleeding Questionnaire (MBQ)

Matteson KA, Scott DM, Raker CA, Clark MA. The development and validation of a patient centered outcome measure for heavy menstrual bleeding: The Menstrual Bleeding Questionnaire (MBQ). BJOG 2015;122(5):681-9. PMID: 25675842

3. During the past month, how often did you need to wear either an incontinence brief or more than one high absorbency sanitary product (either more than one pad, a pad and a tampon, more than one tampon) at a time to contain your bleeding?

Never..... [ ]
1-3 times..... [ ]
4-6 times..... [ ]
7-10 times..... [ ]
11 times or greater..... [ ]

4. During the past month, how many times have you had an episode of bleeding that soaked through your "outer" clothes (pants, skirt, dress)?

Never..... [ ]
1-3 times..... [ ]
4-6 times..... [ ]
Greater than 6 times..... [ ]

5. During the past month, how many times did you need to get out of bed in the middle of night (or during sleep hours) to change your sanitary products?

Never..... [ ]
1-3 times..... [ ]
4-6 times..... [ ]
7-10 times..... [ ]
11 times or greater..... [ ]

6. During the past month, how many times did you pass blood clots (clumps of blood)?

Never..... [ ]
1-3 times..... [ ]
4-6 times..... [ ]
Greater than 6 times..... [ ]

7. During the past month, how often did passing blood clots (clumps of blood) stain your clothing?

Never..... [ ]
1-3 times..... [ ]
4-6 times..... [ ]
Greater than 6 times..... [ ]

Menstrual Bleeding Questionnaire (MBQ)
Matteson KA, Scott DM, Raker CA, Clark MA. The development and validation of a patient centered outcome measure for heavy menstrual bleeding: The Menstrual Bleeding Questionnaire (MBQ). BJOG 2015;122(5):681-9. PMID: 25675842

8. Please fill in the following statement about pain related to your period. During the past month, my period was associated with…

No pain..... [ ]

Slight pain..... [ ]

Moderate pain..... [ ]

Severe pain..... [ ]

9. During the past month, how many weeks did your periods last?

1 week or less out of 4 weeks..... [ ]

More than 1 week, less than 2 weeks out of 4 weeks..... [ ]

More than 2 weeks, less than 3 weeks out of 4 weeks..... [ ]

More than 3 weeks out of 4 weeks..... [ ]

10. During the past month, on how many days do you think your work at your job suffered because you were bleeding?

I am currently not working outside of the home..... [ ]

Never, my bleeding does not affect my work..... [ ]

1-3 days..... [ ]

4-8 days..... [ ]

9-12 days..... [ ]

13 days or more..... [ ]

11. During the past month, on how many days did you miss work because you were bleeding?

I am currently not working outside of the home..... [ ]

Never, my bleeding does not affect my work schedule..... [ ]

1-3 days..... [ ]

4-8 days..... [ ]

9-12 days..... [ ]

13 days or more..... [ ]

Menstrual Bleeding Questionnaire (MBQ)

Matteson KA, Scott DM, Raker CA, Clark MA. The development and validation of a patient centered outcome measure for heavy menstrual bleeding: The Menstrual Bleeding Questionnaire (MBQ). BJOG 2015;122(5):681-9. PMID: 25675842

12. During the past month, on how many days did you avoid family activities (grocery shopping, household chores) when you thought you would be bleeding?

Never	[ ]
1-3 days	[ ]
4-8 days	[ ]
9-12 days	[ ]
13 days or more	[ ]

13. During the past month, when would you carry sanitary products (pads, tampons) with you (in your pocket, in your bag)?

Every day, in case I had any bleeding	[ ]
On the days when I had bleeding and on days when I guessed that I might have bleeding	[ ]
Only on the days that I had bleeding	[ ]

14. During the past month, on how many days did you avoid social activities (such as getting together with friends, going shopping for fun, going sight-seeing) when you thought you would be bleeding?

Never	[ ]
1-3 days	[ ]
4-8 days	[ ]
9-12 days	[ ]
13 days or more	[ ]

15. During the past month, on how many days did you plan <u>your</u> activities (work, social, or family) based on whether or not there was a bathroom nearby?

Never	[ ]
1-3 days	[ ]
4-8 days	[ ]
9-12 days	[ ]
13 days or more	[ ]

Menstrual Bleeding Questionnaire (MBQ)

Matteson KA, Scott DM, Raker CA, Clark MA. The development and validation of a patient centered outcome measure for heavy menstrual bleeding: The Menstrual Bleeding Questionnaire (MBQ). BJOG 2015;122(5):681-9. PMID: 25675842

16. During the past month, on how many days did you bring extra clothes with you (to work, out shopping) in case you had staining from your period?

Never..... [ ]
1-3 days..... [ ]
4-6 days..... [ ]
Greater than 6 days..... [ ]

17. During the past month, on how many days did you choose what to wear based on whether or not you were bleeding?

Never..... [ ]
1-3 days..... [ ]
4-8 days..... [ ]
9-12 days..... [ ]
13 days or more..... [ ]

18. On a scale of 0-10, with 0 being no concern at all and 10 being extremely concerned, please rate your overall concern about bleeding staining your clothes.

_____

19. During the past month, would you say that your period start date was…

Completely predictable..... [ ]
Somewhat predictable..... [ ]
Not at all predictable..... [ ]

20. During the past month, would you say that your period end date was…

Completely predictable..... [ ]
Somewhat predictable..... [ ]
Not at all predictable..... [ ]

Menstrual Bleeding Questionnaire (MBQ)
Matteson KA, Scott DM, Raker CA, Clark MA. The development and validation of a patient centered outcome measure for heavy menstrual bleeding: The Menstrual Bleeding Questionnaire (MBQ). BJOG 2015;122(5):681-9. PMID: 25675842

Appendix 14 Menstruation Diary

Study Number: **Subject Number:**

Site Number: **Date of Study Enrollment:**

Each row represents a day of the month. Please count the number of sanitary pads and/or tampons you used each day (24 hours period), if any. The light, medium, and heavy columns indicate how stained each item was with blood. If you used both a pad and tampon simultaneously and both sanitary items were stained with blood, please include both items in the diary.

If you passed any clots, please indicate this on the relevant days and the approximate size (small = close to the size of penny; large = close to the size of a quarter).

If you experienced any episodes of 'flooding'/overflowing/staining of clothing or underwear, please indicate the number of episodes on the relevant days.

If you also experienced bleeding between periods that required sanitary protection, please record the items on the relevant days.

Please do not write anything in the Score column.

Month: _____

	Pads			Tampons			Clots		Flooding Episodes	Score
Date	Light 	Medium 	Heavy 	Light	Medium	Heavy	Small	Large		TO BE COMPLETED BY STUDY STAFF ONLY
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
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