PROTOCOL

TITLE:	**A PHASE IIIb, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SUBCUTANEOUS EMICIZUMAB IN PATIENTS FROM BIRTH TO 12 MONTHS OF AGE WITH HEMOPHILIA A WITHOUT INHIBITORS**
PROTOCOL NUMBER:	MO41787
VERSION NUMBER:	3
EUDRACT NUMBER:	2020-001733-12
IND NUMBER:	122954
NCT NUMBER:	NCT04431726
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
08-Aug-2021 09:05:27	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	See electronic date stamp on title page.
2	28 March 2021
1	29 May 2020

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol MO41787 has primarily been amended to update the schedule of activities (SOA) of the 7-year Long-Term Follow-Up (LTFU) period including the continuation of the data collection of the Bleed Medication Questionnaire data using the electronic handheld device (eBMQ), and the process of study drug dispensation clinic visits. The other changes include clarifications on the acceptable time window for the emicizumab injections; clarification on the derivation of the patient's age for the timing of the interim data review; clarification on the reporting of vitamin K in the eCRF, clarification on the inclusion criterion about adequate liver function, clarification on the possibility to collect the patient's body temperature temporally and clarification on the MRI assessment during the LTFU. Changes to the protocol in the order they appear in the document, along with a rationale for each change, are summarized below:

- It has been clarified that during the 7-year LFTU period, the BMQ data will be collected using an electronic handheld device given to parents/caregivers instead of a paper BMQ. The goal is to reduce the study burdens on parents/caregivers and site personnel in terms of BMQ data collection management with a unique process of BMQ data collection for the entire study duration (Sections 3.1, 4.3.2, 4.4., 4.5.2, 4.5.8.1, 4.5.8.2, 5.3.5.3 and Appendix 1 Tables 1–3).
- Language has been updated to clarify the derivation of the patient's age for the timing of the interim data review (Sections 3.1, 6.9.1 and 9.5).
- Language has been updated in the inclusion criteria (Section 4.1.1) to clarify the adequate hepatic function requirement for patients with benign neonatal hyperbilirubinemia and breastfed with milk. In the absence of any liver disease, the observation of high total bilirubin in newborns breastfed with milk may be physiologic and not pathologic; the condition of benign neonatal hyperbilirubinemia should not prevent milk breastfed newborns from participating in the study.
- Language has been updated in the exclusion criteria (Section 4.1.2) to clarify that the prior use of investigational or commercial emicizumab is not permitted.
- Language has been updated to clarify the process where the Medical Monitor is consulted by the Investigator for advice and to answer questions related to emicizumab administration, emicizumab up-titration and the use of other therapies during the study. The Investigator remains the decision-maker on medical decisions for patients on the study and the role of the Medical Monitor is to advise Investigators to ensure compliance with the protocol and to provide medical expertise for trial oversight and safety concern (Sections 4.3.1, 4.3.2, 4.4.2, and 5.1.2.1).
- Language has been updated in Section 4.3.2 to clarify the dosing schedule for a missed loading dose during the study:
  - If the scheduled dose (3mg/kg loading dose at Week 2, 3 or 4; 3 mg/kg QW up-titrated doses; 1.5 mg/kg QW during the 7-year LTFU period) is missed, 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.

  - If the scheduled dose (6.0 mg/kg Q4W during the 7-year LTFU period) is missed, emicizumab should be administered as soon as possible within a window of 14 days from the scheduled dosing date. If more than 14 days have elapsed, 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.

- Language has been updated to simplify the process of study drug dispensation during the 7-year LFTU period to reduce the study burden on parents/caregivers. The study drug dispensation remains every 12 weeks from Week 53 where either parents/caregivers can pick-up emicizumab at study site or home shipment can be arranged. The decision is dependent on parents/caregivers preference and will be organized by site personnel (Sections 4.3.2, 4.5.3, and Appendix 1 Tables 2 and 4).
- It has been clarified that the receipt of vitamin K should be reported on the Concomitant Medications eCRF independently of the date of administration (Section 4.5.2 and Appendix 1 Table 1).
- It has been clarified that the patient's body temperature can also be collected temporally (Section 4.5.4 and Appendix 1 Tables 1–3).
- It has been clarified that the use of gadgets to facilitate the child's cooperation in staying still during the MRI assessment is encouraged, and that when needed the MRI assessment could be performed, over two visits around the scheduled date of the clinic visit on Years 5 and 8 respectively (Section 4.5.6 and Appendix 1 Table 2).
- It has been clarified that the name of the form to be used by the investigators to correct/delete eBMQ entries once verified with the parents/caregivers is named Data Clarification Request Form (Section 4.5.8.1).
- The definition of bleed type for the data analysis has been clarified for alignment with the other HAVEN studies of the HEMLIBRA program (Section 4.5.8.2).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IIIb, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SUBCUTANEOUS EMICIZUMAB IN PATIENTS FROM BIRTH TO 12 MONTHS OF AGE WITH HEMOPHILIA A WITHOUT 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 PHASE IIIb, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SUBCUTANEOUS EMICIZUMAB IN PATIENTS FROM BIRTH TO 12 MONTHS OF AGE WITH HEMOPHILIA A WITHOUT INHIBITORS**
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IND NUMBER:	122954
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TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase IIIb
INDICATION:	Severe hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

Study MO41787 will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab administered at 3 mg/kg every 2 weeks (Q2W) for a period of 52 weeks in previously untreated patients (PUPs) and minimally treated patients (MTPs) at study enrollment from birth to $\leq$12 months of age with severe hemophilia A (intrinsic FVIII level $<$1%) without FVIII inhibitors. After 1 year of treatment, patients will continue to receive emicizumab (1.5 mg/kg once a week [QW], 3 mg/kg Q2W, or 6 mg/kg every 4 weeks [Q4W]) over a 7-year long-term follow-up (LTFU) period, which will evaluate long-term safety of emicizumab and describe the natural history of these patients, including the preservation of joint health over time. Study MO41787 is a descriptive study with no formal hypothesis testing. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objective

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

- Number of treated bleeds over time (i.e., treated bleed rate)
- Number of all bleeds over time (i.e., all bleed rate)
- Number of treated spontaneous bleeds over time (i.e., treated spontaneous bleed rate)
- Number of treated joint bleeds over time (i.e., treated joint bleed rate)
- Joint health, as assessed through use of the Hemophilia Joint Health Score (HJHS) and magnetic resonance imaging (MRI) score of specific joints at specified timepoints only during the 7-year LTFU period

Safety Objective

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

- Incidence and severity of adverse events, with severity determined according to World Health Organization (WHO) Toxicity Grading Scale
- Incidence of thromboembolic events

- Incidence of thrombotic microangiopathy (TMA)
- Change from baseline in physical examination findings
- Change from baseline in vital signs
- Incidence of laboratory abnormalities
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to study drug discontinuation
- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

Pharmacokinetic Objective

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

- Plasma trough concentrations (C_{trough}) of emicizumab prior to study drug administration at the following timepoints:
  - Q2W during Weeks 1–9
  - Q4W during Weeks 13–53

Additional PK samples will be obtained from patients who require up-titration (only if up-titration occurs during the first year of emicizumab treatment).

Additional PK samples will be obtained in case of clinical suspicion of anti-drug antibody (ADA) development during the 7-year LTFU period.

Biomarker Objective

The biomarker objective for this study is to investigate the effect of emicizumab on pharmacodynamic (PD) parameters, including aPTT, thrombin generation (TG), and reported FVIII activity, as well as FIX antigen and FX antigen (emicizumab substrates) levels prior to study drug administration at the following timepoints:

- Q2W during Weeks 1–9
- Q4W during Weeks 13–53

Additional biomarker samples will be obtained in patients who require up-titration (only if up-titration occurs during the first year of emicizumab treatment).

Additional biomarker samples will be obtained in case of clinical suspicion of ADA development during the 7-year LTFU period.

Biomarkers related to bone and joint health will be assessed at specified timepoints only during the 7-year LTFU period.

Immunogenicity Objective

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

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

Additional ADA samples will be obtained from patients who require up-titration (only if up-titration occurs during the first year of emicizumab treatment).

Additional ADA samples will be obtained in case of clinical suspicion of ADA development during the 7-year LTFU period.

Study Design

Description of Study

Study MO41787 is a Phase IIIb, multicenter, open-label, single-arm study of emicizumab in PUPs and MTPs at study enrollment from birth to $\leq$12 months of age with severe hemophilia A (intrinsic FVIII level $<$1%) without FVIII inhibitors. The study is designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab administered at

3 mg/kg Q2W for 52 weeks. After 1 year of treatment, patients will continue to receive emicizumab (1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W) over a 7-year LTFU period under this study frame. Study MO41787 is a descriptive study with no formal hypothesis testing.

Approximately 50 patients from birth to ≤12 months of age and weighing ≥3 kg at time of informed consent will be recruited. A minimum of 20 patients from birth to <3 months of age and a maximum of 30 patients from ≥3 months to ≤12 months of age will be enrolled. Once the 30 patients from ≥3 months to ≤12 months of age have been recruited, no additional patients in this age group will be enrolled. The recruitment of patients from birth to <3 months of age will remain open until 20 patients in this age group are enrolled.

Initially, all patients will receive four loading doses of 3 mg/kg emicizumab SC QW for 4 weeks followed by the maintenance dosing regimen 3 mg/kg SC Q2W for a total of 52 weeks. Starting from Week 17 of treatment with emicizumab, individual patients may have their dose up-titrated to 3 mg/kg SC QW if they experience suboptimal bleeding control. At the Week 53 clinic visit following consultation with the treating physician, parents/caregivers may elect for their child to continue with the maintenance 3-mg/kg SC Q2W dosing regimen or to switch to the maintenance 1.5-mg/kg SC QW or 6-mg/kg SC Q4W dosing regimen for the subsequent 7-year LTFU period. During the study, patients will be treated with emicizumab until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria specified in the protocol, whichever occurs first. Patients who discontinue study treatment prior to the end of the study (with the exception when the reason for discontinuation is the patient switching to commercial emicizumab product) will return to the clinic for a safety follow-up visit, 24 weeks after the final dose of study drug.

Safety assessments will include physical examinations, vital signs, and safety laboratory assessments (serum chemistry and hematology) performed as specified in the schedule of activities. Adverse events will be recorded on an ongoing basis as they occur during the study. All patients in this study will undergo PK assessments. Blood samples will also be collected to assess the PD properties of emicizumab (i.e., aPTT, TG, reported FVIII activity), to assess FIX and FX antigen levels, to assess immunogenicity (i.e., anti-emicizumab antibodies and anti-FVIII antibodies), as well as to assess bone and joint biomarkers.

During the study, individual bleeds will be recorded by the parents/caregivers as the bleeds occur using a Bleed and Medication Questionnaire (BMQ). Breakthrough bleeds will be treated with FVIII at the lowest dose expected to achieve hemostasis. When a bleed occurs, parents/caregivers will be required to report bleed information details (e.g., date and time, location, and reason) and medication details including the reason for the use of FVIII (e.g., treatment for bleed, prior to surgery or short-term prophylaxis prior to activity), agent, date, time, and dose on the BMQ. During the *entire study duration,* information on bleeds, hemophilia medications for bleeds, and emicizumab doses will be collected using an electronic BMQ (eBMQ) on an electronic handheld device given to parents/caregivers.

The primary analysis will be performed when the last patient has completed 52 weeks in the study, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first. An interim analysis to review safety, efficacy, pharmacokinetics, pharmacodynamics, and immunogencity data will be performed when the 10th patient from birth to <3 months of age at *the time of informed consent has completed* 24 weeks in the study*, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first*. All patients will be included at the time of the interim analysis irrespective of their age and time in the study. The interim analysis will be performed by the Sponsor's study team. An Internal Monitoring Committee (IMC) and Scientific Overview Committee (SOC) (as needed) will review the interim analysis reports generated by the Sponsor's study team.

The 7-year LTFU period will evaluate long-term safety of emicizumab and describe the natural history of this population including the preservation of joint health over time. Joint health will be assessed through the use of MRI of knees, ankles and elbows, the HJHS, bone and joint biomarkers complemented with physical examination of the joints.

Number of Patients

Approximately 50 patients from birth to ≤12 months of age and weighing ≥3 kg at time of informed consent will be enrolled with a minimum of 20 patients from birth to <3 months of age and a maximum of 30 patients from ≥3 months to ≤12 months of age. Once the 30 patients from ≥3 months to ≤12 months of age have been recruited, no additional patients in this age

group will be enrolled. The recruitment of patients from birth to <3 months of age will remain open until 20 patients in this age group have been enrolled.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Written informed consent obtained from parent or legally authorized representative (latest approved version by Ethics Committee [EC]/Institutional Review Board [IRB]) prior to any study-specific assessments or procedures being performed
- Age from birth to ≤ 12 months at time of informed consent
- Body weight ≥ 3 kg at time of informed consent

  Patients with a lower body weight can be enrolled after they have reached a body weight of 3 kg.

  Premature babies (gestational age <38 weeks) may be enrolled as long as they have reached a body weight of 3 kg. For premature babies, the corrected gestational age should be reported.
- Mandatory receipt of vitamin K prophylaxis according to local standard practice
- Diagnosis of severe congenital hemophilia A (intrinsic FVIII level $<1\%$)
- A negative test for FVIII inhibitor (i.e., <0.6 Bethesda units [BU]/mL) locally assessed during the 2-week screening period for all patients
- No history of documented FVIII inhibitor (i.e., <0.6 BU/mL), FVIII drug-elimination half-life <6 hours, or FVIII recovery $<66\%$
- PUPs or MTPs (i.e., up to 5 days of exposure with hemophilia-related treatments such as plasma-derived FVIII, recombinant FVIII, fresh frozen plasma, cryoprecipitate, or whole blood products)
- Documentation of the details of the hemophilia-related treatments received since birth
- Documentation of the details of the bleeding episodes since birth
- For patients from birth to <3 months of age at the time of study entry: no evidence of active intracranial hemorrhage (ICH), as confirmed by a negative cranial ultrasound at screening irrespective of delivery mode
- Adequate hematologic function, defined as platelet count $\geq 100{,}000/\mu L$ ($\geq 100 \times 10^9$cells/L) and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at screening
- Adequate hepatic function, defined as total bilirubin $\leq 1.5 \times$ the age-specific upper limit of normal (ULN) (excluding patients with Gilbert syndrome *and patients with benign neonatal hyperbilirubinemia because of breastfeeding*) and both AST and ALT$\leq 3 \times$ the age-specific ULN at screening
- Adequate renal function, defined as a serum creatinine $\leq 1.5 \times$ the age-specific ULN

  Note: When the serum creatinine is $\geq 1.5 \times$ ULN, creatinine clearance by Schwartz estimation must be >70 mL/min/1.73 m^2.
- For parents/caregivers: willingness and ability to comply with the study protocol requirements, scheduled visits, treatment plans, laboratory tests, completion of applicable questionnaires, and other study procedures

Exclusion Criteria

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

- Inherited or acquired bleeding disorder other than severe hemophilia A
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study
- Receipt of any of the following:
  - *Prior use of emicizumab prophylaxis including investigational or commercial emicizumab*

  - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 drug-elimination half-lives of last drug administration
  - A non–hemophilia-related investigational drug within the last 30 days or 5 drug-elimination half-lives, whichever is shorter
  - An investigational drug concurrently
- Current active severe bleed, such as ICH
- Planned surgery (excluding minor procedures, e.g., circumcision, CVAD placement) during the study
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA, such as thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome) in the investigator's judgment
- Previous or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis in patients for whom anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Any hereditary or acquired maternal condition that may predispose the patient to thrombotic events (e.g., inherited thrombophilias antiphospholipid syndrome)
- Other diseases (e.g., certain autoimmune diseases) that may increase risk of bleeding or thrombosis
- Known infection with HIV, hepatitis B virus, or hepatitis C virus
- Serious infection requiring antibiotics or antiviral treatments within 14 days prior to screening
- Concurrent disease, treatment, abnormality in clinical laboratory tests, vital signs measurements, or physical examination findings that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
- Unwillingness of the parent or caregiver to allow receipt of blood or blood products, or any standard-of-care treatment for a life-threatening condition
- Any other medical, social, or other condition that may prevent adequate compliance with the study protocol in the opinion of the investigator

End of Study

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., last patient, last visit), as demonstrated by any one of the following: completed the last visit of the LTFU period, completed the end of study safety follow-up visit 24 weeks after discontinuing emicizumab, switched to commercial emicizumab product, withdrew consent, or was lost to follow-up.

Length of Study

The length of the entire study from screening of the first patient to the last patient completing the LTFU period will be approximately 10 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Patients treated with emicizumab will receive a loading dose of 3 mg/kg SC QW for the first 4 weeks (on Day 1 of each week) followed by a maintenance dose of 3 mg/kg SC Q2W at Week 5 (on Day 1 of each 2-week period). Patients will receive prophylactic emicizumab during their participation in the study for 52 weeks. After the first 52 weeks of treatment with emicizumab, switching to other dosing regimens (1.5 mg/kg SC QW or 6 mg/kg SC Q4W) will be permitted for the 7–year LTFU period.

Statistical Methods

Primary Analysis

No formal hypothesis testing is planned for the study. All the analyses will be descriptive. No adjustment for multiplicity of endpoints will be considered. Further details will be provided in the Statistical Analysis Plan.

Determination of Sample Size

The sample size for this study is based on recruitment feasibility and clinical considerations rather than on statistical considerations, taking into account the limited number of pediatric patients from birth to $\leq$12 months of age, especially patients younger than 3 months with hemophilia A without inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in this population.

During the study, a re-assessment of the initially specified sample size based on enrollment consideration may be performed.

Interim Analyses

An interim data review will occur when the 10th patient *aged* $<$3 months *at the time of informed consent has completed* 24 weeks in the study*, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first*, with the aim of having an early look at the totality of the data (particularly safety) in the youngest population. All patients will be included at the time of the interim analysis irrespective of their age and time in the study. The interim analysis will be performed by the Sponsor's study team. The evaluation of the interim data review will be performed on the safety and efficacy endpoints as well as on the pharmacokinetics, pharmacodynamics, and immunogenicity results. The IMC and SOC (as needed) will review the interim analysis reports generated by the Sponsor's study team.

Additional interim analyses may be conducted at an intermediate timepoint during the LTFU period between the primary analysis and the end of the study.

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
BU	Bethesda units
CDC	Centers for Disease Control and Prevention
C_{trough}	trough concentration
CVAD	central venous access device
EC	Ethics Committee
eBMQ	electronic Bleed and Medication Questionnaire
eCRF	electronic Case Report Form
EDC	electronic data capture
eObsRO	electronic observer-reported outcome
FDA	Food and Drug Administration
FII	factor II
FIX	factor IX
FVII	factor VII
FVIII	factor VIII
FX	factor X
HCP	health care provider
HIPAA	Health Insurance Portability and Accountability Act
HJHS	Hemophilia Joint Health Score
HTC	Hemophilia Treatment Center
IA	interim analysis
ICH	intracranial hemorrhage
IFU	Instructions for Use
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IPSG	International Prophylaxis Study Group
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LTFU	long-term follow-up
MRI	magnetic resonance imaging
MTP	minimally treated patient
ObsRO	observer-reported outcome
PD	pharmacodynamic
PK	pharmacokinetic
pop-PK	population-pharmacokinetic

Abbreviation	Definition
PUP	previously untreated patient
Q2W	every 2 weeks
Q4W	every 4 weeks
QV	$quarterly\ visit$
QW	once a week
rFVIIa	recombinant activated factor VII
SOC	Scientific Overview Committee
TG	thrombin generation
TMA	thrombotic microangiopathy
UDC	Universal Data Collection
ULN	upper limit of normal
WFH	World Federation of Hemophilia

1. BACKGROUND

1.1 BACKGROUND ON HEMOPHILIA A IN INFANTS

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 *F8* 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 future mother who is a carrier will have a 50% chance to receive a mutated *F8* gene; thus, hemophilia A could be transmitted to one-half of the boy infants, and one-half of girl infants will be carriers.

Diagnosis of hemophilia A in newborns and infants is prompted by known maternal carrier status, positive family history, or the occurrence of bleeds. Accurate knowledge regarding maternal carrier status and the ability to elicit a family history of hemophilia are crucial to identify affected individuals before and at birth and to propose an optimal management of the disease. Diagnosis following a bleed occurs in 30%–40% of the cases in infants: Patients bleeding remains the single most common manifestation leading to the diagnosis of hemophilia (Kulkarni et al. 2009, 2017; Kenet et al. 2010). Precise laboratory assessment, including adapted coagulation assays for small blood volumes and age-related reference ranges of hemostatic tests, at onset of a bleed is crucial to ensure the proper and meaningful interpretation of disease diagnosis for the future management of the affected newborns and infants (Andrew et al. 1992; Monagle et al. 2006, 2010; Ignjatovic et al. 2015).

A comprehensive surveillance study from the Centers for Disease Control and Prevention (CDC) Universal Data Collection (UDC) project analyzed prospective data collected in 580 children with hemophilia from 0 to 2 years of age who were followed in Hemophilia Treatment Centers (HTCs) (Kulkarni et al. 2009, 2017). The study showed that 75% of infants were diagnosed early in the first month of life: Of the 580 children, 64.7% of infants had a family history or mothers who were known carriers, 33% presented with bleed during the first 2 years of life, and more than 80% of children experienced at least one bleed.

Bleeds in newborns commonly result from the mode of delivery (vacuum extraction or forceps) that can potentially lead to an intracranial hemorrhage (ICH). ICH is a life-threatening condition in children with hemophilia A. Several studies were published with a uniform consensus that around 3%–4% of boys with hemophilia born in countries with a good standard of obstetric care have had ICH diagnosed during the neonatal period (Ljung et al. 1994; Klinge et al. 1999; Revel-Vilk et al. 2004). Prenatal

referral of pregnant women who are known or potential carriers to HTCs often results in avoidance of the use of instrument-assisted deliveries so that the newborns are more likely to be delivered by cesarean section (Andersson et al. 2019). Another common bleed in newborns occurs as a result of complications related to circumcision. Subsequently, the other types of bleeds experienced during the first 2 years of life are related to other iatrogenic procedures (heel punctures, venipunctures, intramuscular injections) and are caused by ambulation with frequent falls during the toddler years, resulting in soft tissue/intramuscular hematomas, head trauma, joint hemorrhages, and other oral and nasal bleeds (Kenet et al. 2010).

At birth, routine vitamin K injection is recommended in all newborns for the coagulant activity of factor II (FII), factor VII (FVII), factor IX (FIX) and factor X (FX) and Proteins C and S. In newborns with hemophilia A, the administration of prophylactic vitamin K is important to avoid early- and late-onset vitamin K deficiency bleedings, including ICH (Doneray et al. 2007; Kulkarni et al. 2009). Therapeutic options for the treatment and prevention of bleeds in newborns and infants rely upon proper use of IV replacement therapy with recombinant FVIII or plasma-derived FVIII concentrates administered on demand or prophylactically and repeated hemostatic evaluations of a patient's status, while dealing with underlying etiological causes. Newborns are more likely to receive prophylaxis at birth if they are born to carrier mothers or if they have a family history of hemophilia. In the UDC surveillance study, nearly 10% of newborns with severe hemophilia received factor concentrate within 24 hours of birth; more than one-half of these were given prophylactic administration to prevent bleeds (Kulkarni et al. 2009). In children, the current standard of care is primary prophylaxis with regular FVIII infusions (starting from the first joint bleed onward or earlier), focusing on joint preservation with optimally, no bleeds and the prevention of long-term consequences such as joint damage (Valentino et al. 2012). Because of difficulties in venous access in newborns and infants, replacement therapy often necessitates the placement of central venous access devices (CVADs). However, long-term CVAD use requires considerable commitment from caregivers and parents, and serious complications can occur, including thrombosis, bleeding, mechanical dysfunction, and most commonly, infection (Valentino et al. 2004).

Although the primary indication for routine prophylaxis in hemophilia is to prevent joint damage and to decrease the frequency of joint and other hemorrhages (Manco-Johnson et al. 2007), the high rate of ICH observed in the UDC surveillance study and other cohort studies provides a compelling argument for the initiation of early prophylaxis to prevent a first occurrence of ICH (Kulkarni et al. 2017; Haque et al. 2019). Beyond the neonatal period, infants may present with an ICH as the first manifestation of their bleeding disorder (Kenet et al. 2018). Other life-threatening bleeds include nasopharyngeal and tongue/oral hematomas with airway compression as a result of neck dissection (Hoots 2007; Riley et al. 2012). ICH is one of the most dreaded complications of hemophilia and is associated with a high rate of morbidity and mortality

(Abbondanzo et al. 1988; Yoffe and Buchanan 1988; Nowak-Göttl et al. 2015). Head trauma, as an underlying etiology of ICH, was reported in 38%–67% of cases of hemophilia in all pediatric ages (Witmer et al. 2007). A 10-year French study in 106 patients of all ages, including 32 patients aged less than 24 months, showed 8.1% and 17.9% prevalence of ICH in patients aged 0–1 month and 1–24 months, respectively, among all cases of ICH (Stieltjes et al. 2005). Clinical data showed a high risk of significant and long-term neurological consequences from ICH, including seizure disorder, intellectual and behavioral problems, paralysis, or other motor problems (Kulkarni et al. 2017). The optimal management of ICH depends on immediate recognition and prompt and intensive replacement therapy, for which prophylaxis is highly appropriate, given that these patients are at increased risk of ICH recurrence (Haque et al. 2019).

The administration of prophylactic factor concentrate at birth is recommended because it is highly efficacious to prevent bleeds, but the risks of FVIII inhibitor development from early factor exposure of newborns and infants remain (Buchanan et al. 1999; Rivard et al. 2005; Kulkarni et al. 2006; Chalmers et al. 2007). The development of FVIII inhibitors represents a challenging and costly complication of treatment (Soucie et al. 2010). Clinicians monitor inhibitor development in all newborns and infants with hemophilia who regularly receive factor concentrate because FVIII inhibitors are also associated with increased mortality and morbidity in patients who experience an ICH (Haque et al. 2019).

In summary, this underlines that newborn and infant patients with hemophilia A constitute a vulnerable population with high unmet medical need.

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, IgG4 monoclonal antibody that binds with moderate affinity to activated FIX and 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, the SC administration of emicizumab removes 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; 1.5 mg/kg), every 2 weeks (Q2W; 3.0 mg/kg), or every 4 weeks (Q4W; 6.0 mg/kg).

In vivo pharmacology experiments in cynomolgus monkeys were conducted in a hemophilia A model in which 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 of emicizumab 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 FVII [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) in a 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. In these experiments, normocoagulative monkeys with normal FVIII activity were exposed to repeat doses and showed no prothrombotic effects in any organs or tissues even at supratherapeutic levels of emicizumab. 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 RO5534262 (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 study (ACE002JP) and its extension in patients with hemophilia A; six ongoing Phase III studies in adults and adolescent patients with hemophilia A (with inhibitors BH29884 and MO39129, without inhibitors BH30071 and BO41423 [of note, BO41423 also evaluates pediatric patients less than 12 years old], and with or without inhibitors BO39182 and YP39309); two Phase III studies in pediatric patients less than 12 years of age (with inhibitors BH29992, ongoing; and without inhibitors JO39881, completed).

Based on the Phase III program, emicizumab received approval in many countries, including the United States. Emicizumab is indicated for routine prophylaxis to prevent bleeding or to 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 (E.U.), emicizumab is indicated for routine prophylaxis of bleeding episodes in all ages of patients with hemophilia A treated

with FVIII inhibitors and in the severe phenotype in patients, without FVIII inhibitors. Refer to the emicizumab U.S. Prescribing Information and E.U. Summary of Product Characteristics for full details on approved indications.

Refer to the RO5534262 (Emicizumab) Investigator's Brochure for details on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Emicizumab is approved for use in pediatric patients with hemophilia A, although limited clinical data have been obtained in patients younger than 2 years of age, and particularly in infants. Real-world data on the prophylactic use of emicizumab in infant patients has started to emerge. A recent single-center study prospectively followed children with hemophilia A showed that the emicizumab use was safe and efficacious in young children, including infants (with the youngest patient 2 months of age at the time of initiation of emicizumab treatment) (Barg et al. 2019). Another multicenter observational study enrolled 12 patients with or without FVIII inhibitors who were <2 years of age and the youngest of whom was a non-inhibitor patient 0.16 years of age. Overall, emicizumab was shown to be efficacious and safe in this pediatric population, including in the surgical setting (McCary et al. 2020). However, there remains limited data on the use of emicizumab in newborns and infants in the setting of a controlled clinical trial.

The pediatric study BH29992 demonstrated that emicizumab provided clinically meaningful efficacy and a favorable safety profile in 88 patients with hemophilia A with FVIII inhibitors from 1 to 12 years of age (at the time of enrollment 8 patients were <2 years of age, with the youngest being 14 months of age) receiving QW, Q2W, or Q4W emicizumab regimens; the annualized rate of treated bleeds in the primary cohort was 0.3 (95% CI, 0.17-0.50) with 77% of patients having zero treated bleeds (Young et al. 2019). Of note, the number of patients less than 2 years of age (N=8) was limited in Study BH29992, as the prevalence of patients treated with FVIII inhibitors is rare in this age group. The observed emicizumab PK profiles in patients less than 12 years of age were consistent with those observed in patients more than 12 years of age in Studies BH29884 and BH30071 (Oldenburg et al. 2017; Mahlangu et al. 2018). Recently a small pediatric study (JO39881) of 13 patients from 4 months to 12 years of age (3 of them were <2 years of age) at the time of enrollment with severe hemophilia A without FVIII inhibitors showed that Q2W and Q4W emicizumab exposure was within the variability observed in the preceding adult/adolescent and pediatric studies confirming the appropriateness of the emicizumab use in children with hemophilia A without FVIII inhibitors (Pipe et al. 2019). This study showed substantial efficacy and favourable safety of emicizumab in this pediatric population (Shima et al. 2019).

Given the limited clinical data of emicizumab use in infants, an initial population-PK (pop-PK) model was developed using the data derived from clinical studies conducted with emicizumab, wherein potential baseline covariate effects, including, but not limited to, body size and age, were assessed (Retout et al. 2020). A modified pop-PK model

that also used an explicit age-based maturation function of clearance comparable to the model that predicted the pharmacokinetics of another monoclonal antibody, palivizumab, in infants (Robbie et al. 2012) was also developed (Retout et al. 2019). Using a comprehensive model-based extrapolation approach, including initial and modified pop-PK, physiologically based PK and exposure-response analyses, up to 20-30% lower emicizumab exposure is predicted in patients less than 1 year of age patients compared to the older ones. The efficacy is however expected to be maintained as this exposure level remains at the plateau of the exposure-response relationship, even in newborn patients (Jonsson et al. 2019; Retout et al. 2019). The model showed no evidence of any dependence of the exposure response across the patients enrolled in these studies (i.e., $\geq$1 year of age). Although neonates and young infants have quantitatively lower levels of vitamin K dependent coagulation factors including emicizumab targets (FIX and FX) compared with those in adults, many anticoagulant factors are also reduced at this age, resulting in a hemostatic system that remains balanced (Andrew et al. 1987; Revel-Vilk et al. 2012). Therefore, a similar exposure response relationship was assumed for infants aged less than 1 year of age (as observed with FVIII coagulation factors). Altogether, despite the absence of data in patients less than 1 year of age, PK simulations and pharmacological rationale suggest that a different dose for infant patients less than 1 year of age is not warranted. Using the identical emicizumab dosing strategy as the other pivotal Phase III studies of emicizumab, the objective of Study MO41787 will be to provide clinical evidence of the efficacy, safety, and tolerability of emicizumab in newborn and infant patients $\leq$12 months of age (see Section 5.1 for the safety plan).

Current approaches to prophylaxis initiation are such that infants are likely not on prophylactic therapy until the end of the first year of life or later. This is pragmatic in that spontaneous bleeding is less common, and regular IV access for prophylaxis is challenging (Weyand et al. 2019). Yet, infants remain at risk for significant bleeding with trauma, including ICH. In this context, emicizumab may have a role to play, and if initiated soon after birth, could potentially fill this important treatment gap. Study MO41787 aims to confirm the benefit–risk profile of the efficacy and safety of emicizumab in patients from birth to $\leq$12 months of age observed in the pediatric population enrolled in Studies BH29992 and JO39881. Study MO41787 aims to provide supportive clinical evidence that early initiation of prophylactic treatment with SC emicizumab in newborns and infants with hemophilia A, ideally near birth prior to their first bleed, is beneficial and safe in this high-unmet medical need pediatric population. Importantly, Study MO41787 provides a unique opportunity to describe the natural history of patients with hemophilia A who initiate early prophylaxis soon after birth. As such, Study MO41787 will also contain a long-term follow-up (LTFU) period of 7 years to continue the collection of long-term clinical data (including, but not limited to, safety and joint health outcomes) in patients with hemophilia A from birth to early childhood who are treated with prophylactic emicizumab.

2. OBJECTIVES AND ENDPOINTS

Study MO41787 will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab administered at 3 mg/kg Q2W for a period of 52 weeks in previously untreated patients (PUPs) and minimally treated patients (MTPs) at study enrollment from birth to $\leq$12 months of age with severe hemophilia A (intrinsic FVIII level $<$1%) without FVIII inhibitors. After 1 year of treatment, patients will continue to receive emicizumab (1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W) over a 7-year LTFU period, which will evaluate long-term safety of emicizumab and describe the natural history of these patients, including the preservation of joint health over time. Study MO41787 is a descriptive study with no formal hypothesis testing. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVE

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

- Number of treated bleeds over time (i.e., treated bleed rate)
- Number of all bleeds over time (i.e., all bleed rate)
- Number of treated spontaneous bleeds over time (i.e., treated spontaneous bleed rate)
- Number of treated joint bleeds over time (i.e., treated joint bleed rate)
- Joint health, as assessed through use of the Hemophilia Joint Health Score (HJHS) and magnetic resonance imaging (MRI) score of specific joints at specified timepoints only during the 7-year LTFU period

2.2 SAFETY OBJECTIVE

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

- Incidence and severity of adverse events, with severity determined according to WHO Toxicity Grading Scale (see Appendix 5)
- Incidence of thromboembolic events
- Incidence of thrombotic microangiopathy (TMA)
- Change from baseline in physical examination findings
- Change from baseline in vital signs
- Incidence of laboratory abnormalities
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to study drug discontinuation
- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

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 trough concentrations (C_{trough}) of emicizumab prior to study drug administration at the following timepoints:
  - Q2W during Weeks 1–9
  - Q4W during Weeks 13–53

Additional PK samples will be obtained from patients who require up-titration (only if up-titration occurs during the first year of emicizumab treatment).

Additional PK samples will be obtained in case of clinical suspicion of anti-drug antibody (ADA) development during the 7-year LTFU period.

2.4 BIOMARKER OBJECTIVE

The biomarker objective for this study is to investigate the effect of emicizumab on PD parameters, including aPTT, thrombin generation (TG), and reported FVIII activity, as well as FIX antigen and FX antigen (emicizumab substrates) levels prior to study drug administration at the following timepoints:

- Q2W during Weeks 1–9
- Q4W during Weeks 13–53

Additional biomarker samples will be obtained in patients who require up-titration (only if up-titration occurs during the first year of emicizumab treatment).

Additional biomarker samples will be obtained in case of clinical suspicion of ADA development during the 7-year LTFU period.

Biomarkers related to bone and joint health will be assessed at specified timepoints only during the 7-year LTFU period.

2.5 IMMUNOGENICITY OBJECTIVE

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

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

Additional ADA samples will be obtained from patients who require up-titration (only if up-titration occurs during the first year of emicizumab treatment).

Additional anti-drug antibody (ADA) samples will be obtained in case of clinical suspicion of ADA development during the 7-year LTFU period.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study MO41787 is a Phase IIIb, multicenter, open-label, single-arm study of emicizumab in PUPs and MTPs at study enrollment from birth to ≤12 months of age with severe hemophilia A (intrinsic FVIII level <1%) without FVIII inhibitors. The study is designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab administered at 3 mg/kg Q2W for 52 weeks. After 1 year of treatment, patients will continue to receive emicizumab (1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W) over a 7-year LTFU period under this study frame. Study MO41787 is a descriptive study with no formal hypothesis testing.

Approximately 50 patients from birth to ≤12 months of age and weighing ≥3 kg at time of informed consent will be recruited. A minimum of 20 patients from birth to <3 months of age and a maximum of 30 patients from ≥3 months to ≤12 months of age will be enrolled. Once the 30 patients from ≥3 months to ≤12 months of age have been recruited, no additional patients in this age group will be enrolled. The recruitment of patients from birth to <3 months of age will remain open until 20 patients in this age group are enrolled.

Initially, all patients will receive four loading doses of 3 mg/kg emicizumab SC QW for 4 weeks followed by the maintenance dosing regimen 3 mg/kg SC Q2W for a total of 52 weeks. Starting from Week 17 of treatment with emicizumab, individual patients may have their dose up-titrated to 3 mg/kg SC QW if they experience suboptimal bleeding control (see Section 4.3.2). At the Week 53 clinic visit following consultation with the treating physician, parents/caregivers may elect for their child to continue with the maintenance 3-mg/kg SC Q2W dosing regimen or to switch to the maintenance 1.5-mg/kg SC QW or 6-mg/kg SC Q4W dosing regimen for the subsequent 7-year LTFU period. During the study, patients will be treated with emicizumab until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria specified in the protocol, whichever occurs first. Patients who discontinue study treatment prior to the end of the study (with the exception when the reason for discontinuation is the patient switching to commercial emicizumab product) will return to the clinic for a safety follow-up visit, 24 weeks after the final dose of study drug.

Safety assessments will include physical examinations, vital signs, and safety laboratory assessments (serum chemistry and hematology) performed as specified in the schedule of activities (see Appendix 1 for the details of the respective assessments performed during the first 52 weeks of treatment and the LTFU period). Adverse events will be recorded on an ongoing basis as they occur during the study. All patients in this study will undergo PK assessments. Blood samples will also be collected to assess the PD properties of emicizumab (i.e., aPTT, TG, reported FVIII activity), to assess FIX and FX antigen levels, to assess immunogenicity (i.e., anti-emicizumab antibodies and anti-FVIII antibodies), as well as to assess bone and joint biomarkers (see Appendix 1 for the

details of the respective assessments performed during the first 52 weeks of treatment and the LTFU period).

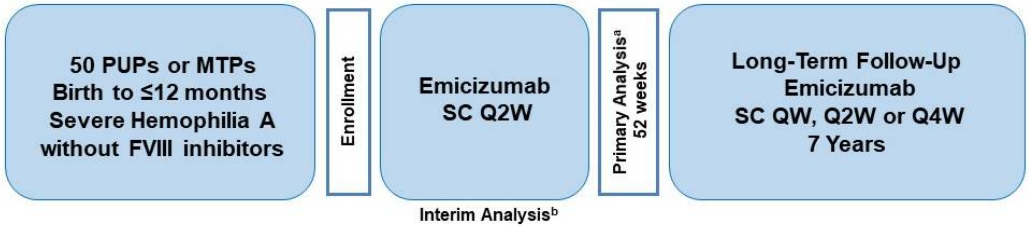
During the study, individual bleeds will be recorded by the parents/caregivers as the bleeds occur using a Bleed and Medication Questionnaire (BMQ). Breakthrough bleeds will be treated with FVIII at the lowest dose expected to achieve hemostasis. When a bleed occurs, parents/caregivers will be required to report bleed information details (e.g., date and time, location, and reason) and medication details including the reason for the use of FVIII (e.g., treatment for bleed, prior to surgery or short-term prophylaxis prior to activity), agent, date, time, and dose on the BMQ. During the *entire study duration,* information on bleeds, hemophilia medications for bleeds, and emicizumab doses will be collected using an electronic BMQ (eBMQ) on an electronic handheld device given to parents/caregivers.

The primary analysis will be performed when the last patient has completed 52 weeks in the study, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first. An interim analysis to review safety, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity data will be performed when the 10th patient from birth to <3 months of age at *the time of informed consent has completed* 24 weeks in the study*, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first*. All patients will be included at the time of the interim analysis irrespective of their age and time in the study. The interim analysis will be performed by the Sponsor's study team. An Internal Monitoring Committee (IMC) and Scientific Overview Committee (SOC) (as needed) will review the interim analysis reports generated by the Sponsor's study team. See Sections 6.9 and 9.5 for details on the IMC/SOC roles and responsibilities.

The 7-year LTFU period will evaluate long-term safety of emicizumab and describe the natural history of this population including the preservation of joint health over time. Joint health will be assessed through the use of MRI of knees, ankles and elbows, the HJHS, bone and joint biomarkers complemented with physical examination of the joints. See Appendix 1 for the details of the assessments performed during the LTFU period.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



FVIII = factor VIII; MTP = minimally treated patient; PUP = previously untreated patient; QW = once a week; Q2W = every 2 weeks; Q4W = every 4 weeks.

Note: Patients who discontinue study treatment prior to end of study (with the exception when the reason for discontinuation is the patient switching to commercial emicizumab product) will return to the clinic for a safety follow-up visit 24 weeks after the final dose of study drug.

[a] The primary analysis will be performed when the last patient has completed 52 weeks in the study, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first.

[b] Interim analysis will be performed when the 10th patient from birth to <3 months of age at *the time of informed consent has completed* 24 weeks in the study*, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first*. The analysis will include all patients enrolled at the time of the interim analysis irrespective of their age and time in the study.

3.2 END OF STUDY AND LENGTH OF STUDY

After 52 weeks in the study, all patients who continue to derive clinical benefit will continue receiving prophylactic emicizumab as part of this study in the 7-year LTFU period or switch to commercial emicizumab product. For an individual patient, the length of the study will be 8 years.

The length of the entire study from screening of the first patient to the last patient completing the LTFU period will be approximately 10 years.

Patients who discontinue study treatment prior to end of study (with the exception where the reason for discontinuation is the patient switching to commercial emicizumab product) will return to the clinic for a safety follow-up visit, 24 weeks after the final dose of study drug.

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., last patient, last visit), as demonstrated by any one of the following:

- Completed the last visit of the LTFU period
- Completed the end of study safety follow-up visit 24 weeks after discontinuing emicizumab
- Switched to commercial emicizumab product
- Withdrew consent
- Was lost to follow-up

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Emicizumab Dose and Schedule

The three maintenance dosing regimens of SC emicizumab QW (1.5 mg/kg), Q2W (3 mg/kg), and Q4W (6 mg/kg) have shown equivalent average steady-state exposure, demonstrated consistent efficacy and safety, and are approved in several countries for the treatment of hemophilia A, with or without FVIII inhibitors, in adult and pediatric patients, including newborn and older children.

Despite the conduct of pivotal Phase III studies in pediatric patients, with and without FVIII inhibitors, receiving the three dosing regimens, limited clinical data have been collected in pediatric patients younger than 2 years of age (see Section 1.3). This study aims to provide clinical evidence of the safety, tolerability and efficacy of emicizumab in the youngest group of patients. In this study, the treatment period until the primary analysis will be 52 weeks, which is similar to the length of treatment in prior pediatric Phase III studies investigating emicizumab. During the first year of treatment, all patients will receive the maintenance dosing regimen of emicizumab 3 mg/kg SC Q2W. Taking into consideration frequency of injection and simplicity of the maintenance dosing regimen (which is the same as the loading doses), the Q2W regimen was selected because the maintenance dose is identical to the loading dose (3 mg/kg). The choice for Q2W dosing regimen is also consensually supported by treating pediatricians who have reported an empirical preference for a lower frequency of injections with limited volume injected with this regimen while treating young patients in their practice (no published data). At the Week 53 clinic visit, following consultation with the treating physician, parents/caregivers may elect to have their child continue treatment with emicizumab Q2W regimen or to switch to QW or Q4W regimen for the 7-year LTFU period.

3.3.2 Rationale for Patient Population

Hemophilia A is a congenital disease in which the lack of FVIII function since birth results in severe bleeding diathesis throughout patients' lives. Restoring FVIII function and thereby adequate hemostasis is the ultimate goal of management, independent of age. Hemostasis is a dynamic process that starts in utero. Physiologic concentrations of coagulation factors gradually increase with time, with levels lower in premature infants compared with full-term neonates and healthy children (Andrew et al. 1987, 1988, 1992; Monagle at el. 2006, 2010; Ignjatovic et al. 2015; Nowak-Göttl et al. 2017). Neonates display physiologically reduced levels of vitamin K–dependent coagulation factors, including FII, FVII, FIX, and FX that are approximately 50% of adult values, while the levels of FVIII, FV, and FXIII correlate well with adult boundaries (Kenet al. 2010, 2018; Favaloro and Lippi 2017). Coagulation factors in newborns and adults are qualitatively similar in their molecular weights and degree of glycosylation (Hassan et al. 1990). The coagulation cascade is almost mature at birth, with well-balanced hemostasis and thrombosis, and is fully mature at 6 months of age (Andrew et al. 1987; Revel-Vilk et al. 2012). Notably, FVIII activity at birth is equivalent to adult activity level and remains stable from the newborn period onward (Kuhle et al. 2003). Consequently, dosing

strategies are similar for adult and for pediatric patients with hemophilia A, including infants (Mahlangu et al. 2014, Young et al. 2015). Emicizumab mimics FVIII activity and binds to the same qualitatively identical FIX and FX and therefore should be efficacious in newborns and infants with hemophilia A, as in the pediatric population in Studies BH29992 and JO39881. Studying this very young pediatric population with emicizumab early in life in Study MO41787 is designed to provide supportive clinical evidence, that prophylactic emicizumab is safe and efficacious during infancy when the physiologic developmental hemostatic maturation is occurring.

A comprehensive surveillance study from the CDC UDC project of 580 children with hemophilia from 0 to 2 years of age followed in HTCs, showed that 75% of infants were diagnosed in the first month of life; 10% of infants were born prematurely with a range from 28 to 36 weeks of gestation; 64% of all term and preterm infants received vitamin K at birth (Kulkarni et al. 2009, 2017). Thus in Study MO41787, infants from birth to $\leq$12 months of age, including premature babies (gestational age $<$38 weeks; as long as they have reached a body weight of 3 kg at time of informed consent) will be eligible to enroll to benefit from prophylactic treatment with emicizumab as early as possible (i.e., at birth or diagnosis); all patients are expected to have received vitamin K prophylaxis according to local standard practice.

A significant proportion of potentially preventable complications of hemophilia A occur in early childhood, including bleeds, falls, complications of treatment associated with CVAD use, and FVIII inhibitor formation that may have a lifelong impact. While joint disease is a hallmark of hemophilia in the older age groups, bleeds due to circumcision, ICH due to delivery or head trauma, and soft tissue or oral or nasal bleeds, are more likely to occur in early childhood (see Section 1.1). [redacted].

In Study MO41787, the early initiation of prophylaxis with emicizumab between birth and 1 year of age, and before the first exposure of FVIII (PUPs) or a limited number of FVIII doses (MTPs), will likely delay or minimize the early exposure of infants to FVIII, and consequently suspend or limit potential development of FVIII inhibitors.

In Study MO41787, FVIII replacement therapy will remain a treatment option to manage breakthrough bleeds and surgical procedures. Patients will be tested for anti-FVIII antibodies (FVIII inhibitors) when exposed to FVIII (see Section 4.5.7.1). If a patient develops FVIII inhibitors while on study, the patient will be permitted to continue to receive emicizumab on study, as emicizumab is effective irrespective of the presence or absence of FVIII inhibitors. However, the patient will be required to discontinue participation in the study should immune tolerance induction be initiated. While the diagnosis of hemophilia A is being made at an early age, bleeds still predominate as the

diagnostic trigger in newborns (see Section 1.1). Early initiation of prophylactic emicizumab at birth or diagnosis will potentially reduce the occurrence of ICH and associated long-term clinical sequelae. In Study MO41787, newborn and infant patients with evidence of active ICH will not be eligible to enroll.

3.3.3 Rationale for Pharmacokinetic Assessments

PK assessments in this study will help confirm that plasma concentrations in newborns and infants are consistent within the ranges of concentrations predicted by population-PK modeling and are effective and safe as in previous emicizumab Phase III studies. For consistency, the PK sampling in this study will show similarity with the pediatric study BH29992 evaluating emicizumab in patients younger than 12 years of age, with less sampling considering the limits of blood volume drawn in these very young patients. In this study, plasma samples will be collected Q2W until Week 9 and subsequently at less frequent intervals Q4W until Week 53 in order to document the emicizumab exposure in this infant age group, where very limited PK data have been collected yet. 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 ADAs will therefore be collected at regular timepoints during the first 52 weeks of study. Subsequently during the 7-year LTFU, samples for ADAs will be collected only in case of clinical suspicion for ADA development (see Appendix 1). In case of ADA positivity, further investigations will be conducted to assess their neutralizing potential, either through visual inspections of the PK and PD profiles and/or, if available, by means of testing on a neutralizing antibody assay.

De-novo development of anti-FVIII antibodies in patients with emicizumab will be monitored during the study. During screening, one plasma sample for anti-FVIII antibodies will be mandated for MTPs only. Subsequently, all patients will be tested for anti-FVIII antibodies following exposure to FVIII as detailed in Section 4.5.7.1. Non-neutralizing FVIII antibody development may be explored if sample volume permits.

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 (see Appendix 1). These will assess evidence of biologic activity of emicizumab in patients from birth to $\leq$12 months of age at study enrollment with severe hemophilia A (intrinsic FVIII level $<$1%) without FVIII inhibitors. The PD biomarkers include aPTT, TG, and reported FVIII activity. These assays have shown in previous Phase I/II and III studies to exhibit a dose-response

relationship to emicizumab concentration in patients with hemophilia A more than 1 year of age (for more information, refer to the RO5534262 [Emicizumab] Investigator's Brochure).

TG assays will be performed using a FXIa-triggering reagent, which is consistent with what has been used in previous emicizumab clinical studies. Emicizumab PD activity will also be measured using a chromogenic FVIII activity assay containing human coagulation factors.

Plasma concentrations of coagulation factors in the neonate differ from those of adults and older children (Kenet et al. 2019). This includes concentrations of FIX and FX, the binding targets of emicizumab, which are known to be quantitatively lower in neonates versus in adults (Andrew et al. 1987; Attard et al. 2013). FIX and FX concentrations will be monitored over time during emicizumab treatment. Additional coagulation-related biomarkers may be explored if sample volume permits.

During the 7-year LTFU period only and on an annual basis, serum and plasma will be collected for the assessment of bone and joint biomarkers, which may include, but will 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 biomarkers will be collected under fasting conditions if blood volume drawn permits (see Appendix 1).

3.3.6 Rationale for Joint Health Assessments

Prophylaxis replacement therapy prior to the onset of joint bleed is aimed at a reducing or eliminating hemarthrosis and thus joint damage in patients with hemophilia (Fischer et al. 2008). The Joint Outcome Study, evaluating prophylactic versus episodic treatment, has demonstrated improved outcomes with prevention of joint damage and decrease of the frequency of joint bleeds for boys receiving prophylaxis (Manco-Johnson et al. 2007). However, it has also been observed that joint deterioration could be observed in patients despite good bleed management, suggesting that joint abnormalities may be observed in the absence of clinically evident joint bleeds. MRI is considered as the reference standard to assess early joint changes in hemophilia (Foppen et al. 2020). It is an optimal tool for assessment of musculoskeletal outcomes in boys with hemophilia treated with prophylaxis because of its capacity to detect early soft tissue and osteochondral abnormalities in joints into which bleeding has occurred (Kraft et al. 2012; Puetz et al. 2018).

This study provides an opportunity to describe the natural history of a cohort of infants with hemophilia A who initiated prophylaxis early in infancy. Importantly, this study will evaluate the preservation of joint health (pristine joints at birth) over time in patients who initiated emicizumab prophylaxis prior to 1 year of age. The 7-year LTFU will assess health of joints using the MRI score of bilateral knees, ankles and elbows on an annual basis (Lundin et al. 2012), the HJHS (see Appendix 2), and the evaluation of bone and

joint biomarkers complemented with physical examination of the joints. Of note, only patients ≥4 years of age at the time of the assessment will undergo HJHS, and bone and joint biomarker evaluation; only patients ≥5 years of age at the time of the assessment will undergo MRI.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 50 patients from birth to ≤12 months of age and weighing ≥3 kg at time of informed consent will be enrolled with a minimum of 20 patients from birth to <3 months of age and a maximum of 30 patients from ≥3 months to ≤12 months of age. Once the 30 patients from ≥3 months to ≤12 months of age have been recruited, no additional patients in this age group will be enrolled. The recruitment of patients from birth to <3 months of age will remain open until 20 patients in this age group have been enrolled.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Written informed consent obtained from parent or legally authorized representative (latest approved version by Ethics Committee [EC]/Institutional Review Board [IRB]) prior to any study-specific assessments or procedures being performed
- Age from birth to ≤12 months at time of informed consent
- Body weight ≥3 kg at time of informed consent
  - Patients with a lower body weight can be enrolled after they have reached a body weight of 3 kg.
  - Premature babies (gestational age <38 weeks) may be enrolled as long as they have reached a body weight of 3 kg. For premature babies, the corrected gestational age should be reported.
- Mandatory receipt of vitamin K prophylaxis according to local standard practice
- Diagnosis of severe congenital hemophilia A (intrinsic FVIII level <1%)
- A negative test for FVIII inhibitor (i.e., <0.6 Bethesda units [BU]/mL) locally assessed during the 2-week screening period for all patients
- No history of documented FVIII inhibitor (i.e., <0.6 BU/mL), FVIII drug-elimination half-life <6 hours, or FVIII recovery <66%
- PUPs or MTPs (i.e., up to 5 days of exposure with hemophilia-related treatments, such as plasma-derived FVIII, recombinant FVIII, fresh frozen plasma, cryoprecipitate, or whole blood products)
- Documentation of the details of the hemophilia-related treatments received since birth
- Documentation of the details of the bleeding episodes since birth

- For patients from birth to <3 months of age at the time of study entry: no evidence of active ICH, as confirmed by a negative cranial ultrasound at screening irrespective of delivery mode
- Adequate hematologic function, defined as platelet count $\geq 100{,}000/\mu L$ ($\geq 100 \times 10^9$cells/L) and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at screening
- Adequate hepatic function, defined as total bilirubin $\leq 1.5 \times$ the age-specific upper limit of normal (ULN) (excluding patients with Gilbert syndrome *and patients with benign neonatal hyperbilirubinemia because of breastfeeding*) and both AST and ALT$\leq 3 \times$ the age-specific ULN at screening
- Adequate renal function, defined as a serum creatinine $\leq 1.5 \times$ the age-specific ULN

  Note: When the serum creatinine is $\geq 1.5 \times$ ULN, creatinine clearance by Schwartz estimation must be >70 mL/min/1.73 m^2.
- For parents/caregivers: willingness and ability to comply with the study protocol requirements, scheduled visits, treatment plans, laboratory tests, completion of applicable questionnaires, and other study procedures

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 severe hemophilia A
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study
- Receipt of any of the following:
  - *Prior use of emicizumab prophylaxis including investigational or commercial emicizumab*
  - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 drug-elimination half-lives of last drug administration
  - A non–hemophilia-related investigational drug within the last 30 days or 5 drug-elimination half-lives, whichever is shorter
  - An investigational drug concurrently
- Current active severe bleed, such as ICH
- Planned surgery (excluding minor procedures, e.g., circumcision, CVAD placement) during the study
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA, such as thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome) in the investigator's judgment
- Previous or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis in patients for whom anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease

- Any hereditary or acquired maternal condition that may predispose the patient to thrombotic events (e.g., inherited thrombophilias antiphospholipid syndrome)
- Other diseases (e.g., certain autoimmune diseases) that may increase risk of bleeding or thrombosis
- Known infection with HIV, hepatitis B virus, or hepatitis C virus
- Serious infection requiring antibiotics or antiviral treatments within 14 days prior to screening
- Concurrent disease, treatment, abnormality in clinical laboratory tests, vital signs measurements, or physical examination findings that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
- Unwillingness of the parent or caregiver to allow receipt of blood or blood products, or any standard-of-care treatment for a life-threatening condition
- Any other medical, social, or other condition that may prevent adequate compliance with the study protocol in the opinion of the investigator

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a single-arm, open–label study. After initial written informed has been obtained from parent or caregiver, 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). The time between screening and enrollment of eligible patients should be $\leq$2 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 and Packaging

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 according to 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); nominal vial strength 30 mg (30 mg/mL, 1.0 mL). The less-concentrated formulation will enable safe SC weight-based volume dosing of very small children with sufficient precision. The excipient composition and primary packaging are identical for all configurations. For further information on the formulation

of emicizumab, refer to the RO5534262 (Emicizumab) Investigator's Brochure. Details on the devices to be used for withdrawal of study drug from the vial and SC injection are provided in the "Instructions for Use" (IFU) document.

In order to minimize the number of injections for pediatric patients in certain high-weight categories if applicable, the administration per single injection of up to 2 mL of drug product solution may be permitted. This will require combining emicizumab drug product solution from more than one vial of a given concentration (i.e., vial pooling) into a single syringe using a new transfer needle for each vial. The detailed procedure for vial pooling is described in the IFU document. Vials of emicizumab with different concentrations must not be combined.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Patients treated with emicizumab will receive a loading dose of 3 mg/kg SC QW for the first 4 weeks (on Day 1 of each week) followed by a maintenance dose of 3 mg/kg SC Q2W at Week 5 (on Day 1 of each 2-week period). Patients will receive prophylactic emicizumab during their participation in the study for 52 weeks. After the first 52 weeks of treatment with emicizumab, switching to other dosing regimens (1.5 mg/kg SC QW or 6 mg/kg SC Q4W) will be permitted for the 7-year LTFU period. During the study, patients will be treated with emicizumab until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria specified in the protocol, whichever occurs first.

During the first year of treatment, the study drug will be dispensed at the scheduled clinic visits (see Appendix 1 Table 1).

During the 7-year LTFU period, the study drug dispensation will occur every 12 weeks (quarterly) from Week 53 until the end of the 7-year LTFU. Within each year of the 7-year LTFU period, there will be quarterly visits (QV) for drug dispensation (QV1, QV2, QV3 and QV4):

- *At QV1 and QV3 (non-study site visits), the patient's body weight assessed by patient's local general practitioner or local nurse will determine via IxRS the strength and number of vials for the administration of emicizumab for the next 12 weeks. The corresponding vials will then be shipped to patient's home by the site. For convenience, the parents/caregivers may come to the study site for the study drug to be picked-up directly at the study site (see Appendix 1 Table 4). The details for weight assessment are included in Section 4.5.3.*
- *At QV2 and QV4 (study drug dispensation clinic visits), the assessment of the patient's body weight will determine via IxRS the strength and number of vials of study drug to be given to the parents/caregivers for the administration of emicizumab for the next 12 weeks (see Appendix 1 Table 4).*

During the study, individual patients may have their dose up-titrated if they experience suboptimal bleeding control during emicizumab treatment. Patients with more than

2 qualifying bleeds within a 12-week interval may have the opportunity to have their maintenance emicizumab dose increased to 3 mg/kg QW starting at Week 17. *The Medical Monitor is available to the investigator for consultation and to answer questions related to up-titration.* Qualifying bleeds are defined as spontaneous and clinically significant, physician verified (e.g., with diagnostic imaging, clinical examination, photograph), and occurring while on prophylactic emicizumab at steady state on the maintenance dose (after Week 5). Should patients meet protocol-defined criteria for up-titration, the investigator *may* contact the Medical Monitor *regarding advice for* possible up-titration, which will take place as follows (see Appendix 1):

- From Week 17 to Week 41 (included) upon up-titration to the new maintenance dose of 3 mg/kg QW, the patient's schedule of activities will reset to Week 1 where the next five clinic visits must take place at the site and the subsequent clinic visits will follow the reset schedule of activities until one year of treatment (actually after 52 weeks); subsequently the clinic visits will follow the regular schedule of activities of the 7-year LTFU.

  Example of up-titration during Week 40: the first up-titrated dose will be given at Week 41 at 3 mg/kg, the subsequent 3 mg/kg doses will be administered QW. The reset schedule of activities will continue until 53 weeks only; subsequently the clinic visits will follow the schedule of activities of the 7-year LTFU.

- *In case of* up-titration between Week 42 and Week 53, the patient's schedule of activities will reset to Week 1 where the next five clinic visits must take place at the site and the subsequent clinic visits will follow the reset schedule of activities for a duration of 12 weeks only; subsequently the clinic visits will follow the regular schedule of activities of the 7-year LTFU.

  Example of up-titration during Week 52: the first up-titrated dose will be given at Week 53 at 3 mg/kg, the subsequent 3 mg/kg doses will be administered QW. The reset schedule of activities will continue until 65 weeks only; subsequently the clinic visits will follow the schedule of activities of the 7-year LTFU.

- If up-titration takes place after Week 53, the schedule of activities will not be altered. The clinic visits will follow the regular schedule of activities of the 7-year LTFU.

- Once up-titration is initiated, the patient will stay on the maintenance dose of 3 mg/kg QW until the end of the study: *in case the patient missed a scheduled dose (3 mg/kg QW), 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 (3 mg/kg QW).*

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).

If a patient has a systemic hypersensitivity reaction or severe adverse reaction that may be attributable to emicizumab, subsequent doses should be held. The situation *may be* discussed with the Medical Monitor and *advice sought before* dosing is *resumed*. Should unanticipated events occur during the study that require treatment with multiple daily administrations of FVIII concentrates for multiple days, such as non-elective surgery or severe/life-threatening bleeds, the investigator should contact the Medical Monitor immediately to discuss such cases and the management of future emicizumab doses. Any other request for emicizumab dose adjustment *may* require discussion of the clinical case with the Medical Monitor.

Study site healthcare providers (HCPs) will be trained on how to properly prepare the study drug and administer the correct calculated dose subcutaneously as described in the IFU document. Parents/caregivers will in turn be trained by an HCP on study drug preparation and administration at the recommended sites of injection as detailed in the IFU document. The HCP is to inform the parents/caregivers of the volumetric dose to be administered and dosing frequency. Note that during the course of the study, should the patient's body weight change to affect the dose (e.g., ± 10%), the new volumetric dose to be administered must be communicated to the parents/caregivers.

Emicizumab will be administered to patients as an SC injection in the home setting after a period of in-clinic administration and training. The first five study drug administrations must be performed in a monitored setting such as an infusion center, clinic, or hospital, with a 60-minute observation period following each of the first three doses. For patients with a history of a clinically significant hypersensitivity reaction, additional precautions as described in Section 5.1.1.2 should be considered. The fourth and fifth scheduled study drug administrations must also be performed in a monitored setting, and parents/caregivers will be trained and have the opportunity to ask any questions of the HCP before the scheduled start of home administration. Each site will have the discretion to provide additional training if deemed appropriate. If, despite additional training, the investigator determines that the parents/caregivers are unable to inject emicizumab correctly, then arrangements may be made to identify a trained caregiver or HCP to administer the SC injections.

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

Medication administration errors during training will be recorded and competence of the parents/caregivers to administer emicizumab at home will be documented on the electronic Case Report Form (eCRF). If necessary, parents/caregivers 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 an electronic handheld device during the *entire study duration* and by recording collected used and unused vials during each study drug dispensation clinic visit.

Emicizumab should be administered on the scheduled dosing day. On days when trough plasma PK, PD, and ADA samples are to be collected, patients will be dosed after those samples are drawn.

In case the patient missed a scheduled loading dose (3 mg/kg) at Weeks 2 or 3, 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 loading dose should be skipped, and the next loading dose of emicizumab should be taken at the next scheduled time resuming the original dosing schedule (3 mg/kg QW) until Week 4. If the Week 4 loading dose is missed, emicizumab should be administered as soon as possible within a window of 3 days from the scheduled Week 4 dosing date. If more than 3 days have passed, the missed Week 4 loading dose should be skipped, and the next dose of emicizumab should be the Week 5 maintenance dose.

For patients receiving emicizumab 3 mg/kg Q2W from Week 5 (first maintenance dose) during the first 52 weeks of the study and patients receiving emicizumab 3 mg/kg Q2W during the 7-year LTFU period, if parents/caregivers forget or cannot administer study treatment on the scheduled dosing day, study drug should be administered as soon as possible within a window of 7 days from the scheduled dosing date. If more than 7 days have elapsed, the missed dose should be skipped and the parents/caregivers should administer the subsequent dose at the next scheduled time with the study treatment dosing resumed in accordance with the original dosing schedule *(3 mg/kg Q2W).*

For patients receiving emicizumab 1.5 mg/kg QW during the 7-year LTFU period, if parents/caregivers forget or cannot administer study treatment on the scheduled dosing day, study drug should be administered as soon as possible within a window of 3 days from the scheduled dosing date. If more than 3 days have elapsed, the missed dose should be skipped and the parents/caregivers should administer the subsequent dose at the next scheduled time with the study treatment dosing resumed in accordance with the original dosing schedule (1.5 mg/kg QW).

For patients receiving emicizumab 6 mg/kg Q4W during the 7-year LTFU period, if parents/caregivers forget or cannot administer study treatment on the scheduled dosing day, study drug should be administered as soon as possible within a window of 14 days from the scheduled dosing date. If more than 14 days have elapsed, the missed dose should be skipped and the parents/caregivers should administer the subsequent dose at the next scheduled time with the study treatment dosing resumed in accordance with the original dosing schedule (6 mg/kg Q4W).

The parents/caregivers should not administer two doses on the same day to make up for a missed dose.

During the first 52 weeks of study, the emicizumab doses administered to patients will be documented by the parents/caregivers on the handheld electronic observer-reported

outcome (eObsRO) device using the eBMQ, both during patient's clinic visits and when the patient is outside the clinic. *Similarly during* the 7-year LTFU period, the QW, Q2W or Q4W emicizumab doses will be documented by the parents/caregivers on *the hand-held eObsRO device using the eBMQ, both when the patient is outside the clinic and during patient's* clinic visits.

Parents/caregivers will be provided with alert cards, which they will be requested to carry at all times. These will include guidance on how to recognize signs and symptoms of thromboembolic events or allergic, anaphylactic, and anaphylactoid reactions and how to obtain emergency care. In addition, alert cards are designed to notify non-study HCPs that emicizumab will interfere with certain coagulation laboratory tests (see the RO5534262 [Emicizumab] Investigator's Brochure for more information) and the investigator should be contacted for assistance in interpreting the test results.

Guidelines for treatment interruption or discontinuation are provided in Section 4.6.1.

4.3.3 Investigational Medicinal Product Handling 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 (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. 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 for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs 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.

Only patients enrolled in the study may receive IMPs, only authorized staff may supply IMPs, and only parents/caregivers and authorized staff may administer IMPs.

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 study drug accountability log.

Refer to the pharmacy manual and/or the emicizumab IB and IFU document for information on IMP handling, including preparation and storage, and accountability.

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 wouldn't 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

Patients may be eligible to receive emicizumab as part of a potential future extension study.

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) administered to the patient in addition to protocol-mandated treatment

from 4 weeks prior to enrollment to the study completion or safety follow-up visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

During treatment with emicizumab, other medicinal products for SC administration should preferably be injected at different anatomical sites than the sites of emicizumab administration.

All hemophilia-related treatments (e.g., FVIII) administered to patients since birth before enrolling in the study should be documented on eCRF. During the study, hemophilia-related treatments administered to patients will have to be reported by parents/caregivers through the eBMQ on the electronic handheld device.

4.4.1 Permitted Therapy

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

- Intermittent doses or short-term FVIII prophylaxis (e.g., around the time of surgery or procedure)

  However, concomitant routine prophylaxis with FVIII (including low-dose FVIII or ITI) is **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.

  The exact dose and schedule of FVIII should be discussed between the investigator and the parents/caregivers at the beginning and throughout the study. Repeat dosing of FVIII should be performed only under medical supervision and consideration should be given to verifying bleeds prior to repeated dosing.
- Antifibrinolytics intended to control bleeds
- Local anesthetic cream for emicizumab SC administration
- Vaccinations should be administered following national immunization schedules. As per the World Federation Hemophilia (WFH) recommendations for vaccinations (WFH 2012), patients with hemophilia should be vaccinated. Thus, vaccinations should be administered according to the WFH recommendations and local HTC practice and ideally during a period when the bleeding status of the child is well controlled and stable. Vaccinations should not be administered on the same day as an emicizumab administration but ideally at a timepoint between two emicizumab administrations (>48 hours after emicizumab administration). Children who receive vaccinations must be carefully followed for any adverse reactions in the subsequent days following vaccine administration.

- Drugs and therapies to treat adverse events and use of topical antiseptic treatments, anesthetic medications, eye drops, and so forth that are not considered to result in systemic exposure
- Drugs to treat an existing medical condition ongoing at study entry that does not violate the eligibility criteria

The use of bypassing agents is unexpected in patients with hemophilia A without inhibitors. In the interest of completeness, Appendix 6 includes dosing and monitoring guidance for the use of bypassing agents for patients in this study, in case such unforeseen circumstances occur. Use of bypassing agents as concomitant prophylactic treatment, including for short-term prophylaxis, is not permitted.

As per Section 4.1.2, patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA) in the investigator's judgment are excluded from participating in the study. Caution should be used when treating patients in the study who are receiving concomitant medication known to be a risk factor for the development of TMA (e.g. ciclosporin, quinine, and tacrolimus).

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 unless otherwise specified:

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

  However, drugs intended to control bleeding episodes or used in the context of surgeries or injuries (e.g., concussion) to prevent deterioration are allowed.
- Elective surgery during the emicizumab loading phase (prior to Week 5) (excluding minor procedures such as CVAD placement or removal as well as emergency surgeries)
- Use of other investigational drugs

If prohibited therapy is administered for any reason, it should be recorded on the eCRF. If prohibited treatment is prescribed or considered medically necessary, the Medical Monitor *may* be consulted *for advice about* any changes in the benefit–risk assessment and whether the patient should continue in the study.

4.5 STUDY ASSESSMENTS

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

4.5.1 Informed Consent Forms and Screening Log

Written informed consent must be obtained from parent or legally authorized representative for participation in the study before performing any study-related

procedures (including screening evaluations). Informed Consent 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, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, procedures, medical allergies, history of prior anaphylaxis, or known thrombophilia since birth will be recorded on the General Medical History and Baseline Conditions eCRF. All bleeds (date and time, type, location, and reason) experienced since birth and before enrolling in the study on Day 1 should be documented on the eCRF at baseline.

Any medication (e.g., vitamin K, prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) administered to patient in addition to protocol-mandated treatment from 4 weeks prior to enrollment through the study completion or safety follow-up visit should be reported on the Concomitant Medications eCRF. *The receipt of vitamin K should be reported on the Concomitant Medications eCRF independently of the date of administration.* All hemophilia-related treatments (e.g., FVIII, including date and time of administration, type of medication, dose, and purpose) administered to patients since birth and before enrolling in the study on Day 1 should be documented on the eCRF at baseline. During the *entire study duration*, hemophilia-related treatments administered to patients will be reported by parents/caregivers only through the eBMQ on the electronic handheld device.

At baseline, information about nutrition received by patient, breast-feeding or formula (name and type) or other, will be documented on eCRF.

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 should include, but not necessarily be limited to, the evaluation of head, eyes, ears, nose, and throat and include the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Additional targeted physical examinations of joints for bleeds, skin for bruises, hematomas, injection-site reactions, and lipodystrophies should be conducted as noted in the schedule of activities (see Appendix 1) and as clinically indicated. Any

abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened abnormalities from screening should be recorded as adverse events.

Height/length and weight should be recorded before study treatment administration. Frequency of these assessments should be performed as noted in the schedule of activities (see Appendix 1) but may also be obtained any time as unscheduled assessments as judged by the investigator.

During the first year of treatment, the patient's body weight should be assessed in the clinic and recorded on the eCRF when emicizumab is dispensed *(See Appendix 1 Table 1). During the 7-year LTFU period, the patient's body weight should be assessed every 12 weeks (quarterly) from Week 53 until the end of the 7-year LTFU. Within each year of the 7-year LTFU period, there will be four QV for drug dispensation (QV1, QV2, QV3 and QV4):*

- *At QV1 and QV3 (non-study site visits) the patient's body weight will be assessed by patient's local General Practitioner or local Nurse. The weight value will be provided by phone to the site personnel who will check its consistency with the patient's previous weight records before recording it on the eCRF. The weight will be used to determine via IxRS the strength and number of vials for the administration of emicizumab for the next 12 weeks. The corresponding vials will then be shipped to patient's home by the site. For convenience, the parents/caregivers may prefer to come to the study site for the study drug to be picked-up directly in the study site, in this case the patient's body weight will be assessed in the clinic (see Appendix 1 Table 4.*
- *At QV2 and QV4 (study drug dispensation clinic visits), a complete physical examination will be performed. The patient's body weight will also be assessed and recorded on the eCRF. The weight will be used to determine via IxRS the strength and number of vials of study drug to be given to the parents/caregivers for the administration of emicizumab for the next 12 weeks (see Appendix 1 Table 4).*

The HJHS (see Appendix 2) will be assessed annually as part of physical examination during the 7-year LTFU period only in patients ≥4 years of age at the time of the assessment (see Appendix 1).

4.5.4 Vital Signs

Vital signs will include measurements of pulse, respiratory rate, temperature (oral, rectal, axillary, *temporal,* or tympanic), systolic and diastolic blood pressure using age-adapted measurements when possible should be recorded before study treatment administration. Frequency of vital sign assessments should be performed as noted in the schedule of activities (see Appendix 1) but may also be obtained any time as unscheduled assessments as judged by the investigator.

4.5.5 Cranial Ultrasound

Patients from birth to <3 months of age must not demonstrate evidence of active ICH at the time of study entry. A cranial ultrasound will be performed at screening and must be negative to fulfil the bleed-related eligibility criteria.

4.5.6 Magnetic Resonance Imaging of Joints

MRI has been shown to be the most preferable imaging technique for joint abnormalities in young patients with hemophilia (Manco-Johnson et al. 2007). The MRI will focus on knees, ankles, and elbows, because these are the most susceptible to hemophilic arthropathy. In this study, bilateral MRI without contrast of knees, ankles and elbows will be performed during the 7-year LTFU period only in patients ≥5 years of age at the time of the assessment with no requirement for sedation; two MRI timepoints, one around 5 years of age and another in the last year of the LTFU (see Appendix 1). Of note, MRI scan is a mandatory assessment of the study during the LTFU period. *If necessary, the use of gadgets (e.g., movie goggles if available in the radiology department) to facilitate the child's cooperation in staying still during the MRI assessment is encouraged. If it remains* necessary, the use of sedation/anesthesia will be at the discretion of the investigator per strict local institutional guidelines and practice in performing MRI in young children. The priority joints for MRI assessment will be the knees and ankles, while every effort should be made to also assess elbows. *Preferably, all six joints will be assessed during the same MRI assessment visit. However if it is not possible, the MRI assessment could be performed over two visits around the scheduled date of the clinic visit on Years 5 and 8, respectively (see Appendix 1).* MRI scans will be centrally reviewed by two independent radiologists where each of the bilateral elbows, ankles and knees will be scored using the additive MRI scale for hemophilic arthropathy of the International Prophylaxis Study Group (IPSG) (Lundin et al. 2012); disagreement in MRI scores between reviewers should be resolved in a consensus meeting. The IPSG MRI scale for hemophilic arthropathy quantifies the presence of soft tissue changes (effusion/hemarthrosis, synovial hypertrophy, and hemosiderin deposition) and osteochondral changes (surface erosions, subchondral cysts, and cartilage degradation). MRI evaluation of joints has been shown to provide relevant information about association of MRI findings with bleeding, development, and progression of arthropathy in a long-term perspective study (Foppen et al. 2020).

Further details about the MRI review process as well as the roles and responsibilities of the independent radiologists will be provided in a separate radiology charter.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Laboratory assessments will be performed as indicated on the schedule of activities (see Appendix 1). On days of study drug administration, laboratory samples should be drawn before the administration of study treatment. Deviations from the schedule of activities of ±2 days are acceptable; however, pre-dose PK and biomarker sample collections and study treatment 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, and LDH

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 biomarker assessments: aPTT, TG, reported FVIII activity, FIX and FX antigens (emicizumab substrates)

  Other coagulation-related biomarkers may also be considered for exploration only when the blood volume drawn permits.
- Plasma samples for immunogenicity assessment (anti-emicizumab antibodies and anti-FVIII antibodies; see Section 4.5.7.1 for details)
- Plasma and serum samples for bone and joint biomarker assessment (only during the 7-year LTFU period)

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 Commission 2008]). Thus, blood sampling timepoints and volumes will follow the EC guideline on *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population* (European Commission 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 biomarker sample. Refer to the laboratory manual for detailed weight-based blood sampling guidelines.

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

Data arising from sample analysis, 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.

4.5.7.1 Testing for Anti-FVIII Antibodies

During screening, one plasma sample for anti-FVIII antibodies (centralized analysis) will be mandated for MTPs only. Subsequently for all patients while during their participation in the study, after any 3 exposure days to FVIII or a block of FVIII exposure days (e.g., a block is defined as a minimum of two consecutive doses of FVIII) administered for treatment of a bleed, a surgical procedure, or other (e.g., preventative doses before activity), one plasma sample for anti-FVIII antibodies (for centralized analysis) will be collected 14 days after the final dose of FVIII administered. If this occurs during the first 52 weeks of treatment, the blood sampling will be timed with the next scheduled clinic visit. During the 7-year LTFU period, the blood sampling will be performed where applicable (see Appendix 1). In case of clinical suspicion for development of anti-FVIII antibodies, a plasma sample will also be collected if blood volume drawn permits.

4.5.7.2 Testing Following the Use of Bypassing Agents

In patients who receive bypassing agents, the following local laboratory tests will be performed within 24 to 48 hours of initial bypassing agent use, if blood volume drawn permits, so the investigator may monitor for potential thromboembolic events and TMA:

- Platelet count
- Serum creatinine
- LDH
- Peripheral blood smear analysis to evaluate for schistocytes

If blood volume drawn permits, a plasma sample should also be provided for local laboratory monitoring of the following:

- Prothrombin fragment 1+2
- Fibrinogen
- D-dimer

If the test for prothrombin fragment 1+2 is not available at the site, the sample should be sent to the local reference laboratory, if available and if the results from the local reference laboratory can be obtained within a reasonable timeframe to allow for decision-making.

For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the final dose of bypassing agents administered to treat a given bleed.

If applicable, laboratory results should be recorded on the Local Lab Following Treatment with Bypassing Agents eCRF.

4.5.8 Clinical Outcome Assessments

Bleed and medication related observer-reported outcome (ObsRO) data will be collected during the *entire study duration* at home or in the clinic on an eBMQ.

Parent/caregivers should be given the following instructions for completing ObsRO instruments at home:

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

During clinic visits, ObsRO 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 parents/caregivers to complete the instruments.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Parents/caregivers 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.
- Parents/caregivers should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.8.1 Electronic Bleed and Medication Questionnaire

During the study, to capture the administration of emicizumab, the bleed experienced by the patient, and the hemophilia related medication administered to patients, parents/caregivers will complete the BMQ on an electronic handheld device that will be provided to them on the first day of study enrollment at the site. The instructions for completing the electronic handheld device will be provided by site personnel. The device will remain with the parents/caregivers until *the end of the 7-year LFTU period.* Parents/caregivers will be asked on a weekly basis to record at home or in the clinic (when applicable) 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 activity) has been given, and when an emicizumab administration was performed

(possible retrospective reporting for last 7 days): bleed information with date and time, type, location, and reason; information on hemophilia-related medication with date and time of administration, type of medication, dose, and purpose; information on emicizumab with the date and time, vial strength, volume injected and number of injections. After the eBMQ entries have been saved on the electronic handheld device, the data will be transmitted automatically from the device to a centralized vendor database. The data will be available for access by appropriate study personnel. Bleed and medication use data entered since a patient's previous clinic visit will be reviewed and discussed for completeness and accuracy by the parents/caregivers and the investigator at subsequent clinic visits according to the schedule of activities. Investigators will have the ability to *review the data, and in agreement with the parents/caregivers, to* correct/delete or complete entries once verified with the parents/caregivers using a Data *Clarification* Request Form process or through the vendor web-based portal respectively. Of note, if the electronic data collection system becomes unavailable, the site may instruct the parents/caregivers to collect *exactly the same* ObsRO data (bleed data, emicizumab use, hemophilia-related medication use) on paper, and once electronic data entry is available, all information will need to be entered and submitted electronically by the site using the vendor web-based portal. The Sponsor will have view- access- only but will perform a review of the bleed and medication use data as per the Medical Data Review Plan.

4.5.8.2 Bleed Definitions

Definition of a Bleed

For the purpose of the efficacy analyses, a standardized definition of bleed, adapted from criteria defined by the Subcommittee on Standards and Criteria, FVIII/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 final 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 administered to treat the bleed $>$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 the 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 ≥3 bleeds into the same joint over the last 24 weeks prior to study entry)
- Joint bleeds: defined as bleeds with bleed type "joint bleed" reported on the eBMQ 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 compared with baseline
- Muscle bleeds (sites per the eBMQ)
- Other (sites per the eBMQ)

Definitions of Bleed Types

The assessment of a bleed will be separated into spontaneous bleeds, traumatic bleeds, and bleeds related to procedure and surgery. Both spontaneous bleeds (i.e., the occurrence of hemorrhage for which the parents/caregivers cannot identify a reason) and traumatic bleeds (i.e., hemorrhage occurring secondary to an event such as trauma, "strenuous" activity, or "overuse") will be recorded.

- Spontaneous bleeds: Bleeds should be classified as spontaneous if the parents/caregivers record 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 parents/caregivers.
- Traumatic bleeds: Bleeds should be classified as traumatic if parents/caregivers record a bleed when there is a known or believed reason for the bleed.
- Bleeds related to procedure and surgery: For example, hematomas resulting from any surgery or invasive procedure (e.g., *tooth extractions,* venipuncture, or SC study drug administrations), or invasive diagnostic procedures (e.g., lumbar puncture, arterial blood gas determination*, or endoscopy with biopsy*) would be *considered a bleed related to procedure/surgery.* Such bleeds are not associated with any trauma except procedure and surgery-induced trauma.

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

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 (with the exception where the reason for discontinuation is the patient switching to commercial emicizumab product) (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from the Study

Patients will return to the clinic for a safety follow-up visit 24 weeks after the final dose of study drug as per the schedule of activities (see Appendix 1).

Parents/caregivers have the right to voluntarily withdraw the patient 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 by parent or legally authorized representative
- Study termination or site closure
- Adverse event
- Unacceptable toxicity with study treatment
- Patient's requirement for immune tolerance induction therapy
- 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 parents/caregivers request the patient 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 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

The safety plan for patients in this study is based on clinical experience with emicizumab in completed and ongoing studies (see Section 1.3). The anticipated important safety risks for emicizumab are outlined below. Refer to the RO5534262 (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 (see Section 4.1.2). 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 or moderate intensity. Further details for observed injection-site reactions are available in the RO5534262 (Emicizumab) Investigator's Brochure. Directions for emicizumab administration should be followed, as outlined in Sections 3.1 and 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 Sections 5.2.2 and 5.2.3.

HCPs administering study drug 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 3 and Appendix 4). HCPs should also instruct parents/caregivers 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 and 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 history of clinically significant hypersensitivity reactions, 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 in clinical studies. 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 by the investigator to be 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 the 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 RO5534262 (Emicizumab) Investigator's Brochure for further details.

Thromboembolic events should be reported as a serious adverse event or adverse event of special interest as described in Sections 5.2.2 and 5.2.3. HCPs should educate parents/caregivers on how 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. Parents/caregivers 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, and so on.

Three cases of TMA were reported in Study BH29884. All cases were assessed by the investigator as being related to study treatment and occurred after recent concomitant aPCC use. All three TMAs occurred when on average a cumulative amount of $>$100 U/kg/24 hr of aPCC for 24 hours or more was administered during a treatment event. This study will be conducted in infant patients without FVIII inhibitors, and therefore aPCC is not expected to be used for the treatment of breakthrough bleeds. For further details on TMAs, refer to the RO5534262 (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 using 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 using 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 RO5534262 (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 elimination half-life of emicizumab, these effects on coagulation assays may persist for up to 6 months after the final dose of the study drug.

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.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

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. Parents/caregivers will be given guidance on reporting injection-site reactions when administering study 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, site personnel 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. The decision to resume emicizumab after an event of TMA *is encouraged to* be discussed with and *advised* 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. The decision to resume emicizumab after a thromboembolic event *is encouraged to* be discussed with and *advised* 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 International Council for Harmonisation 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 Section 5.3.5.9 and Section 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 the WHO Toxicity Grading Scale; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential study 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 3)
- 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 parents/caregivers 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 final 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 has the patient felt since the last clinic visit?"
- "Has the patient had any new or changed health problems since the last clinic visit?"

5.3.3 Assessment of Severity of Adverse Events

The WHO Toxicity Grading Scale (see Appendix 5) 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 eBMQ). 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 eBMQ.

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., 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

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, 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 Observer-Reported Outcome Data

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

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 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

Medical Monitor: [redacted] Ph.D.

Telephone No.: [redacted]

Mobile Telephone No.:

Emergency Medical Contact: [redacted], M.D.

Telephone No.: [redacted]

Mobile Telephone No.:

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to 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 drug are provided in Section 5.6.

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 withdrawal of patient's 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.

5.5.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, 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:

Study Drug	Document
Emicizumab	RO5534262 (Emicizumab) Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

No formal hypothesis testing is planned for the study. All the analyses will be descriptive. No adjustment for multiplicity of endpoints will be considered. Further details will be provided in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size for this study is based on recruitment feasibility and clinical considerations rather than on statistical considerations, taking into account the limited number of pediatric patients from birth to $\leq$12 months of age, especially patients younger than 3 months with hemophilia A without inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in this population.

During the study, a re-assessment of the initially specified sample size based on enrollment consideration may be performed.

6.2 SUMMARIES OF CONDUCT OF STUDY

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

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

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (e.g., age, sex, weight) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by age groups and overall as appropriate.

6.4 EFFICACY ANALYSES

The efficacy analyses are to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate). This will be based on the treated population, which corresponds to all patients who received at least one administration of emicizumab. Efficacy analyses will be performed for each age group separately, and overall, as appropriate.

6.4.1 Efficacy Endpoint

Treated bleeds, all bleeds, treated spontaneous bleeds, and treated joint and muscle bleeds will be reported (Section 4.5.8.2). The analysis of bleed rates will be performed for each age group separately and overall, as appropriate. The number of bleeds, sites, and types of bleeds will be summarized for all patients and listed for each patient individually. The clinical effect of prophylactic emicizumab will be assessed using the annualized bleeding rate (ABR) estimated using a negative binomial regression model, which accounts for different follow-up times, with the number of bleeds experienced by 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 ABR will be calculated for each patient using the following formula:

$$\text{ABR} = \frac{\text{Number of bleeds during the study period}}{\text{Total number of days during the study period}} \times 365.25$$

The mean and median ABRs 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.

Joint health, as assessed through use of the HJHS and MRI score of specific joints at specified timepoints only during the 7-year LTFU period, will be summarized descriptively.

6.5 SAFETY ANALYSES

The safety analyses will be based on treated population, which corresponds to all patients who receive at least one administration of emicizumab, and will be performed for each age group separately, and overall, as appropriate. Descriptive summaries will be prepared for adverse events (all adverse events, serious adverse events, deaths, adverse events of special interest, adverse events leading to study drug discontinuation or withdrawal from the study, and injection-site reactions), safety laboratory test results (serum chemistry and hematology), ADAs, and vital sign abnormalities. 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, including de novo development of FVIII inhibitors, summary statistics will be presented. In addition, shift tables describing changes from baseline will be presented using the WHO Toxicity Grading Scale (WHO 2003).

6.6 PHARMACOKINETIC ANALYSES

For all patients, pre-dose C_{trough} of emicizumab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling may be used to analyze the dose-concentration-time data of emicizumab following SC administration. Data may be pooled with data from previous Phase I/II and Phase III studies. If performed, these modeling analyses will be reported in a dedicated report.

PK analyses will be completed on the PK-evaluable population, defined as all enrolled patients who received at least one dose of study drug and have sufficient PK data for analysis.

6.7 BIOMARKER ANALYSES

PD biomarkers, including but not limited to aPTT, parameters derived from TG, reported FVIII activity, and other exploratory markers (FIX and FX antigens) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. In addition, bone and joint health biomarkers may be explored.

6.8 IMMUNOGENICITY ANALYSES

6.8.1 Anti-Emicizumab Antibodies

The immunogenicity analyses for emicizumab antibodies will include patients with at least one postdose ADA assessment.

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized. Patients are considered to be ADA positive if they are ADA negative at baseline but develop an ADA

response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater 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 may be analyzed and reported descriptively in subgroup analyses.

6.8.2 Anti-Factor VIII Antibodies

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

6.9 INTERIM ANALYSIS

6.9.1 Planned Interim Analysis

An interim data review will occur when the 10th patient *aged* < 3 months *at the time of informed consent has completed* 24 weeks in the study*, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first*, with the aim of having an early look at the totality of the data (particularly safety) in the youngest population. All patients will be included at the time of the interim analysis irrespective of their age and time in the study. The interim analysis will be performed by the Sponsor's study team. The evaluation of the interim data review will be performed on the safety and efficacy endpoints as well as on the pharmacokinetics, pharmacodynamics, and immunogenicity results. The IMC and SOC (as needed) will review the interim analysis reports generated by the Sponsor's study team (see Section 9.5).

Additional interim analyses may be conducted at an intermediate timepoint during the LTFU period between the primary analysis and the end of the study.

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.

$eObsRO$ data will be collected through the use of an electronic device provided by a vendor (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 OBSERVER-REPORTED OUTCOME DATA

An electronic device will be used to capture ObsRO 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, observer-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 ObsRO 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 International Council for Harmonisation 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 International Council for Harmonisation 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 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 the patient’s parent or legally authorized representative the objectives, methods, and potential risks associated with each optional procedure. The parent or legally authorized representative 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 parent or legally authorized representative agreement to participate in

optional procedures. Parent or legally authorized representative who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the parent or legally authorized representative before the patient participates 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 parent or legally authorized representative for the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the parent or legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. 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 parent or 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 parent or legally authorized representative 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 parent or legally authorized representative 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 parent or legally authorized representative, 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 9.7).

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 parent or legally authorized representative, 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 parents or legally authorized representatives 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 9.6).

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 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 9.6).

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.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will

permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 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 50 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarkers, ADA, and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC and SOC will be in place throughout the duration of the study. The IMC will be composed of selected internal Sponsor members (clinical pharmacologist, biomarker specialist, pediatric medical specialist, safety scientist, and statistician). The SOC will be composed of external pediatric experts specialized in neonatology, pediatric pharmacology and pediatric hematology. The SOC members will be selected on the basis that they have no contact with the sites as part of their responsibilities. At the time of the interim analysis, the IMC will involve the SOC as needed in the review of the safety, efficacy, PK, PD, and immunogenicity data. The interim analysis will occur when the 10th patient *aged* <3 months at *the time of informed consent has completed* 24 weeks in the study*, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first*; all patients will be included in the interim analysis irrespective of their age and time in the study. During the study conduct, the SOC may also be consulted by the IMC as needed. The role of the SOC will be to provide objective scientific advice to the IMC, including, but not limited to, expertise in data interpretation in the use of monoclonal antibodies in neonates and infants. Specific operational details, such as IMC/SOC composition, member roles and responsibilities, data review, and meeting organization will be detailed in a separate IMC/SOC Charter.

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

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.

9.7 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

Table 1 Schedule of Activities Up to Week 53

	Screening	Emicizumab SC Q2W Treatment																		Early Discontinuation Safety FU Visit before Week 53
Week	NA	1	2	3	4	5	7	9	13	17	21	25	29	33	37	41	45	49	53	
Day	–14 to –1	1	8	15	22	29	43	57	85	113	141	169	197	225	253	281	309	337	365	
Informed consent [a]	x																			
Demographics [b]	x																			
Medical history and baseline conditions [b]	x																			
Cranial ultrasound [c]	x																			
Vital signs [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height/length and weight [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Complete physical examination [e]	x					x				x			x			x			x	x
Safety laboratory assessments [f, g, i, q]	x				x				x		x		x		x		x		x	x
Plasma PK sample [g, h, i, q]		x [r]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Plasma sample for biomarkers [g, h, i, q]		x [r]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Plasma ADA sample [g, h, i, j, q]		x [r]				x				x			x			x			x	x
Anti-FVIII antibodies assessment [h]	x [k]		As clinically indicated [l]																	
*e*BMQ [m]		At least once a week, when a bleed occurs and/*or* when a hemophilia medication is administered																		
*e*BMQ data review [n]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications and procedures [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug dispensation		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [p]	x	Ongoing																		

Table 1 Schedule of Activities Up to Week 53 (cont.)

ADA = anti-drug antibody; eBMQ = electronic Bleed and Medication Questionnaire; eCRF = electronic Case Report Form; eObsRO = electronic observer-reported outcome FU = follow-up; FVIII = factor VIII; PD = pharmacodynamic; PK = pharmacokinetic; MTP = minimally treated patient; NA = not applicable; Q2W = every 2 weeks, SC = subcutaneous.

Notes: All patients will receive four loading doses of emicizumab 3 mg/kg SC QW for 4 weeks followed by the maintenance dosing regimen 3 mg/kg SC Q2W for a total of 52 weeks. All study visits and assessments should be performed within ±2 days of the scheduled visit, until Week 53. If the patient discontinues emicizumab early at Week 53 or before Week 53, a safety follow-up visit should be performed 24 weeks after the final dose of study drug; deviation of ±7 days is acceptable. Except for the eBMQ, all other patient data will be collected during clinic visits. Individual patients may have their dose up-titrated if they experience suboptimal bleeding control during emicizumab treatment (see Section 4.3.2); please refer to Table 3 for details about the up-titration process during the first year of treatment. On treatment days, all assessments should be performed prior to emicizumab dosing, unless otherwise specified.

[a] Written informed consent must be obtained from parents and legally authorized representative before performing any study-related procedures (including screening evaluations, distribution of the electronic handheld device and collection of any data). An enrollment form will be completed after informed consent form is obtained. If patient fulfills the inclusion and exclusion criteria, the patient should be enrolled in the study on the same day when the first dose of emicizumab is administered (Day 1).

[b] Information will be collected from patient medical records and documented on the eCRF. Medical history, including clinically significant diseases, procedures, medical allergies, history of prior anaphylaxis, or known thrombophilia since birth, will be recorded on the General Medical History and Baseline Conditions eCRF. All bleeds (date and time, type, location and reason) experienced since birth and before enrolling in the study on Day 1 should be documented at baseline on the eCRF.

[c] Patients from birth to <3 months of age are required to show no evidence of active intracranial hemorrhage at the time of study entry. A cranial ultrasound will be performed at screening and must be negative to fulfil the bleed related eligibility criteria.

[d] Vital signs include measurements of pulse, respiratory rate, temperature (oral, rectal, axillary, *temporal* or tympanic), systolic and diastolic blood pressure using age-adapted measurements when possible. Vital signs, height/length, and weight should be recorded on the eCRF. If screening and Week 1 visits occur on the same date, the vital signs, height/length, and weight should be measured only once. If the screening and Week 1 visits occur on different dates, vital signs, height/length, and weight should be repeated for both assessments.

[e] A complete physical examination and targeted physical examination of joints for bleeds and skin for bruises, hematomas, injection-site reactions, and lipodystrophies will be performed at screening and subsequent visits, in addition to other organ systems as clinically indicated and/or report of new or worsening adverse events.

[f] Pre-dose laboratory data (performed locally) includes: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and absolute differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width; sodium, potassium, glucose, BUN, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, albumin, ALP, ALT, AST, and LDH.

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

Table 1 Schedule of Activities Up to Week 53 (cont.)

[h] Samples will be collected only if blood volume drawn permits (based on patient body weight as described in Section 4.5.7). Refer to the laboratory manual for details.

[i] When blood is drawn by means of a catheter or CVAD, a discard tube (containing only few drops) must be used prior to collection of samples for any laboratory assessment, due to the possibility of contamination by saline or anticoagulants used to flush the device, if blood volume drawn permits. Please consult the study laboratory manual for details on sample collection and processing.

[j] ADA samples may also be drawn if hypersensitivity event occurs or at any time (unscheduled) in the investigator's judgment, if blood volume drawn permits.

[k] During screening, a plasma sample for anti-FVIII antibodies will be mandated for MTPs only.

[l] For all patients, after any 3 exposure days to FVIII or a block of FVIII exposure days (e.g., a block is defined as a minimum of two consecutive doses of FVIII) administered for a treatment of a bleed, a surgical procedure or other (e.g., preventative doses before activity), one plasma sample for anti-FVIII antibodies will be collected 14 days after the final dose of FVIII administered. The samples will ideally be timed with the next scheduled clinic visit. In case of clinical suspicion for development of anti-FVIII antibodies, a plasma sample will also be collected, if blood volume drawn permits.

[m] eObsRO information collected through the eBMQ for each bleed (date and time, type, location and reason) and hemophilia medication for bleed (e.g., FVIII, the date and time of administration, type of medication, dose, and purpose) should be reported by the parents/caregivers on an electronic handheld device when a bleed occurs, when a hemophilia medication is administered or at least on a weekly basis (retrospective reporting for last 7 days). If the patient discontinues study treatment early prior to or at Week 53, bleed and bleed medication information should be provided by the parents/caregivers until the early discontinuation safety follow-up visit (24 weeks after the final dose of study drug). Emicizumab doses (date and time, vial strength, volume injected and number of injections) should be recorded by the parents/caregivers in the eBMQ starting on Day 1 until *the end of study*.

[n] Investigator review of bleed, hemophilia-related medication and emicizumab administration information derived from the electronic handheld device.

[o] Medications (e.g., vitamin K, prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) administered to patient in addition to protocol-mandated treatment from 4 weeks prior to enrollment through Week 53 visit should be reported. *The receipt of vitamin K should be reported on the Concomitant Medications eCRF independently of the date of administration.* All hemophilia medication (e.g., FVIII, including the date and time of administration, type of medication, dose and purpose) administered to patients since birth and before enrolling in the study on Day 1 should be documented at baseline. Historical procedures should be recorded on the Surgery and Procedure History eCRF. Procedures occurring on study should be collected on the On-Study Surgery eCRF.

Table 1 Schedule of Activities Up to Week 53 (cont.)

[p] 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 recorded on an ongoing basis throughout the study. Injection-site reactions will be recorded on a separate form from the Adverse Event eCRF. After initiation of study drug, all adverse events will be reported until Week 53 or until the early discontinuation safety follow-up visit (24 weeks after the last study drug administration).

[q] In case of up-titration, if blood volume drawn permits, additional assessments including PK, biomarkers, ADA and safety laboratory samples will be required, with the schedule of activities reset to Week 1.

[r] Samples should be drawn pre-dose on Day 1.

Table 2 Schedule of Activities during *the* 7-Year *Long-Term* Follow-Up *Period* [a]

	Emicizumab SC QW, Q2W or Q4W Treatment during LTFU							Early Discontinuation Safety FU Visit before End of LTFU [c]
Year	2	3	4	5	6	7	8	
Week [b]	105	157	209	261	313	365	417	
Concomitant medications and procedures [d]	x	x	x	x	x	x	x	x
Vital signs, *height/length* [e]	x	x	x	x	x	x	x	x
HJHS [f]			x	x	x	x	x	
Bilateral MRI of knees, ankles, and elbows [g]				x			x	
Plasma and serum sample for bone and joint biomarkers [h, i, j]	x	x	x	x	x	x	x	
eBMQ [k]	*At least once a week, when a bleed occurs and/or when a hemophilia medication is administered*							
Anti-FVIII antibodies assessment [i, j]	As clinically indicated [l]							
Plasma ADA sample	In case of clinical suspicion for ADA development [m, n]							
Adverse events [o]	Ongoing							

ADA = anti-drug antibody; CVAD = central venous access device; eCRF = electronic Case Report Form; FU = follow-up; FVIII = factor VIII; HJHS = Hemophilia Joint Health Score; LTFU = Long-Term Follow-Up; MRI = magnetic resonance imaging; *e*BMQ = *electronic* Bleed and Medication Questionnaire; *e*ObsRO = *electronic* observer-reported outcome; QW = once a week; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

Notes: The QW, Q2W or Q4W emicizumab doses administered during the LTFU period will be collected on *the electronic handheld device eBMQ*. In the event a patient discontinues emicizumab early before the end of the LTFU period, an early discontinuation safety follow-up visit should be performed 24 weeks after discontinuation of emicizumab; deviation of ±7 days is acceptable. All other patient data will be collected during clinic visits. During the LTFU period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab (see Section 4.3.2).

Table 2 Schedule of Activities during *the* 7-year *Long-Term* Follow-up *Period* (cont.)

[a] *See Appendix 1 Table 4 for* the *details of* the study drug dispensation visits *during* the *7-year LTFU period*.

[b] The clinic visit with all the expected assessments of the visit should be performed within ± 12 weeks (84 days) of the scheduled date.

[c] A complete physical examination and targeted physical examination of joints for bleeds and skin for bruises, hematomas, injection-site reactions, and lipodystrophies will be performed, in addition to other organ systems as clinically indicated and/or report of new or worsening adverse events.

[d] Medications (except coagulation factors) administered to patient should be reported on the Concomitant Medications eCRF. Procedures should be collected on the On-Study Surgery eCRF.

[e] Vital signs include measurements of pulse, respiratory rate, temperature (oral, rectal, axillary, *temporal* or tympanic), systolic and diastolic blood pressure using age-adapted measurements when possible. Vital signs *and* height/*length should* be assessed in the clinic and recorded on the eCRF. *Please refer to Table 4 for the assessment of patient's body weight.*

[f] Only in children ≥ 4 years of age at the time of the assessment. HJHS should be collected on the eCRF.

[g] MRI without contrast, only in children ≥ 5 years of age at the time of the assessment with no requirement for sedation. If necessary, the use of *gadgets (e.g., movie goggles if available in the radiology department) to facilitate the child's cooperation in staying still during the MRI assessment is encouraged. I*f necessary, the use of *sedation/*anesthe*sia* will be at the discretion of the investigator per strict local institutional guidelines and practice in performing MRI in young children. *The priority joints will be the knees and ankles, while every effort should be made to also assess elbows. Preferably, all six joints will be assessed during the same MRI assessment visit. However if it is not possible, the MRI assessment could be performed over two visits around the scheduled date of the clinic visit on Years 5 and 8, respectively.* Of note, MRI during the LTFU is a mandatory assessment of the study.

[h] Samples to be collected after fasting overnight. Samples should be drawn pre-dose if applicable and blood volume drawn permits.

[i] Samples will only be collected if blood volume drawn permits (based on patient body weight as described in Section 4.5.7). Refer to the laboratory manual for details.

[j] When blood is drawn by means of a catheter or CVAD, a discard tube (containing only few drops) must be used prior to collection of samples for any laboratory assessment, due to the possibility of contamination by saline or anticoagulants used to flush the device, if blood volume drawn permits. Please consult the study laboratory manual for details on sample collection and processing.

[k] *eObsRO* information collected *at least once a week on the electronic handheld device* through the *eBMQ* for each bleed (date and time, type, location and reason), hemophilia related medication (e.g., FVIII; date and time of administration, type of medication, dose, and purpose) and the emicizumab doses (date and time, vial strength, volume injected and number of injections) administered Q2W, QW or Q4W will be reviewed with the Investigator during the *clinic* visits of the LTFU period, when parents/caregivers visit the site for the supply of study drug or intermittently at earlier timepoints if the patient, parents/caregivers have clinic visits. .

[l] In case of clinical suspicion for development of anti-FVIII antibodies, a plasma sample will be collected within 14 days after the final dose of FVIII administered, if blood volume drawn permits.

Table 2 Schedule of Activities during *the* 7-year *Long-Term* Follow-up *Period* (cont.)

[m] PK and biomarkers samples should also be drawn, if blood volume drawn permits.

[n] ADA samples may also be drawn if hypersensitivity event occurs or at any time (unscheduled) in the investigator's judgment, provided the blood volume drawn permits.

[o] Adverse events will be collected on an ongoing basis until the end of the LTFU period or until early discontinuation safety follow-up visit (24 weeks after last study drug administration). 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 study drug treatment (see Section 5.6).

Table 3 Schedule of Activities in Case Up-Titration between Week 42 and Week 53

	Emicizumab SC 3 mg/kg QW Treatment							
Week X =week of initiation of up-titration, weeks	X	X+1	X+2	X+3	X+4	X+6	X+8	X+12
Vital signs [a]	x	x	x	x	x	x	x	x
Height/length and weight [a]	x	x	x	x	x	x	x	x
Complete physical examination [b]					x			
Safety laboratory assessments [c, d, f]				x				x
Plasma PK sample [d, e, f]	x		x		x	x	x	x
Plasma sample for biomarkers [d, e, f]	x		x		x	x	x	x
Plasma ADA sample [d, e, f, g]	x				x			
Anti-FVIII antibodies assessment [h, e]	As clinically indicated [j]							
Concomitant medications and procedures [i]	x	x	x	x	x	x	x	x
Adverse events [k]	Ongoing							

ADA =anti-drug antibody; eCRF =electronic Case Report Form; eObsRO =electronic observer-reported outcome; FVIII =factor VIII; PD =pharmacodynamic; PK =pharmacokinetic; QW =once a week, SC =subcutaneous.

Notes: Study visits and assessments of Table 3 should be performed within ±2 days of the scheduled visit, until 12 weeks after the week of initiation of up-titration. If the patient discontinues emicizumab early at 12 weeks after the week of initiation of up-titration or before 12 weeks after the week of initiation of up-titration, a safety follow-up visit should be performed 24 weeks after the final dose of study drug; deviation of ±7 days is acceptable. On treatment days, all assessments should be performed prior to emicizumab dosing, unless otherwise specified. eObsRO information collected through the eBMQ for each bleed (date and time, type, location and reason), hemophilia related medication (e.g., FVIII, the date and time of administration, type of medication, dose, and purpose) *and the emicizumab doses (date and time, vial strength, volume injected and number of injections)* should be reported for *the entire study duration* by the parents/caregivers on an electronic handheld device when a bleed occurs, when a hemophilia medication is administered*, when emicizumab is administered* or at least *once* a *week* (retrospective reporting for last 7 days). .

[a] Vital signs include measurements of pulse, respiratory rate, temperature (oral, rectal, axillary, *temporal* or tympanic), systolic and diastolic blood pressure using age-adapted measurements when possible. Vital signs, height/length, and weight should be recorded on the eCRF.

[b] A complete physical examination and targeted physical examination of joints for bleeds and skin for bruises, hematomas, injection-site reactions, and lipodystrophies will be performed, in addition to other organ systems as clinically indicated and/or report of new or worsening adverse events.

Table 3 Schedule of Activities in Case Up-Titration between Week 42 and Week 53 (cont.)

[c] Pre-dose laboratory data (performed locally) includes: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and absolute differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width; sodium, potassium, glucose, BUN, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, albumin, ALP, ALT, AST, and LDH.

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

[e] Samples will be collected only if blood volume drawn permits (based on patient body weight as described in Section 4.5.7). Refer to the laboratory manual for details.

[f] When blood is drawn by means of a catheter or CVAD, a discard tube (containing only few drops) must be used prior to collection of samples for any laboratory assessment, due to the possibility of contamination by saline or anticoagulants used to flush the device, if blood volume drawn permits. Please consult the study laboratory manual for details on sample collection and processing.

[g] ADA samples may also be drawn if hypersensitivity event occurs or at any time (unscheduled) in the investigator's judgment, if blood volume drawn permits.

[h] For all patients, after any 3 exposure days to FVIII or a block of FVIII exposure days (e.g., a block is defined as a minimum of two consecutive doses of FVIII) administered for a treatment of a bleed, a surgical procedure or other (e.g., preventative doses before activity), one plasma sample for anti-FVIII antibodies will be collected 14 days after the final dose of FVIII administered. The samples will ideally be timed with the next scheduled clinic visit. In case of clinical suspicion for development of anti-FVIII antibodies, a plasma sample will also be collected, if blood volume drawn permits.

[i] Medications (e.g., vitamin K, prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) administered to patient should be reported. Procedures occurring on study should be collected on the On-Study Surgery eCRF.

[j] In case of clinical suspicion for development of anti-FVIII antibodies, a plasma sample will be collected within 14 days after the final dose of FVIII administered, if blood volume drawn permits.

[k] Adverse events will be recorded on an ongoing basis throughout the study. Injection-site reactions will be recorded on a separate form from the Adverse Event eCRF.

Table 4 Study Drug Dispensation during the 7-Year Long-Term Follow-Up Period

	Study Drug Dispensation during each Year of LTFU			
Quarterly visit (QV) for study drug dispensation	*QV1*	*QV2*	*QV3*	*QV4* [a]
Study drug dispensation in the clinic [c]		*x*		*x*
Study drug shipped to patient's home [b]	*x*		*x*	
Locally: weight assessed by general practitioner or nurse [b]	*x*		*x*	
In clinic: weight and complete physical examination [c]		*x*		*x*

QV =Quarterly visit; LTFU =Long-Term Follow-Up.

Notes: From Week 53 until the end of the LTFU, the study drug dispensation will occur every 12 weeks (quarterly). The quarterly study drug dispensation visits (QV1, QV2, QV3, and QV4 should be performed within ±1 week of the scheduled date.

[a] *The QV4 study drug dispensation clinic visit should coincide with the clinic visit where the assessments are to be performed (see Appendix 1, Table 2).*

[b] *During the study drug dispensation visits QV1 and QV3, the patient's weight will be assessed by local general practitioner or local nurse. The weight value will be provided by phone to the site personnel who will check its consistency with the patient's previous weight records before entering it on the eCRF. The weight will determine via IxRS the strength and number of vials for the administration of emicizumab for the next 12 weeks. The corresponding vials will then be shipped to patient's home by the site. For convenience, the parents/caregivers may prefer to come to the study site for the study drug to be picked-up directly in the study site; in this case, the patient's body weight will be assessed in the clinic.*

[c] *A complete physical examination will be performed during the study drug dispensation clinic visits at QV2 and QV4, where the patient's body weight will also be assessed and recorded on the eCRF. The weight will be used to determine via IxRS the strength and number of vials of study drug to be given to the parents/caregivers for the administration of emicizumab for the next 12 weeks.*

Appendix 2
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 3
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]

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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 of age, less than (70 mmHg + [2 × age]) from 1 to 10 years of age, and less than 90 mmHg from 11 to 17 years of age.

Appendix 4
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, the following procedures should be performed:

1. Stop the study treatment.
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 5
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

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
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
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
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
OTHER PARAMETERS (cont.)				
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

ADL = activities of daily living; FEV_1 = forced expiratory volume in 1 second; GGT = gamma-glutamyl transferase; ULN = upper limit of normal.

Appendix 6
Guidelines for Dosing and Monitoring Bypassing Agents for Patients Treated with Emicizumab

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

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

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

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

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

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

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

MONITORING

In the event of a bleed treated with bypassing agents, the following local laboratory tests will be performed within 24–48 hours of initial bypassing agent use so the investigator

may monitor for potential thromboembolic events and thrombotic microangiopathy: platelet count, serum creatinine, LDH, and peripheral blood smear analysis to evaluate for schistocytes. A plasma sample should also be provided for local laboratory monitoring of prothrombin fragment 1+2, fibrinogen, and D-dimer. If the test for prothrombin fragment 1+2 is not available at the site, the sample should be sent to the local reference laboratory, if available and if the results from the local reference laboratory can be obtained within a reasonable timeframe to allow for decision making. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the final dose of bypassing agents administered to treat a given bleed. If applicable, laboratory results should be recorded on the Unscheduled Visit electronic Case Report Forms.