STATISTICAL ANALYSIS PLAN

STUDY 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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PLAN PREPARED BY: [redacted], Ph.D.

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
11-Oct-2021 12:21:23	Company Signatory	[redacted]

SPONSOR: F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS: Grenzacherstrasse 124
4070 Basel, Switzerland

DATE FINAL: See electronic date stamp above

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 2, 26 October 2020.

SAP Version	Approval Date	Based on Protocol MO41787 (Version, Approval Date)
1	See electronic date stamp on title page	Version 3, 8 August 2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ABR	annualized bleeding rate
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
aPTT	activated partial thromboplastin time
BMQ	Bleed and Medication Questionnaire
CDC	Center for Disease Control and Prevention
CSR	Clinical Study Report
CVAD	central venous access device
C_{trough}	trough concentration
eBMQ	electronic Bleed and Medication Questionnaire
FII	factor II (prothrombin)
FIX	factor IX
FVII	factor VII
FVIII	factor VIII
FX	factor X
HCT	Hemophilia Treatment Center
HJHS	Hemophilia Joint Health Score
ICH	intracranial hemorrhage
IMC	Internal Monitoring Committee
IPSG	International Prophylaxis Study Group
IxRS	interactive voice/Web-based response system
LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTP	minimally treated patient
PD	pharmacodynamic
PK	pharmacokinetic
PUP	previously untreated patient
Q2W	every 2 weeks
Q4W	every 4 weeks
QW	once a week
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SOC	Scientific Overview Committee
TG	thrombin generation
WBC	white blood cell

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods that will be used to evaluate the efficacy, safety, pharmacokinetic (PK) and pharmacodynamic (PD) data for Study MO41787 (HAVEN 7). The analyses described in this SAP will supersede those specified in the protocol.

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, Kulkarni et al. 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, Monagle et al. 2010; Ignjatovic et al. 2015).

A comprehensive surveillance study from the Centers for Disease Control and Prevention (CDC) Universal Data Collection 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, Kulkarni et al. 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 bleeding 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.

1.1 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 ≤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.

1.1.1 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.

1.1.2 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 of Protocol v3)
- Incidence of thromboembolic events
- Incidence of thrombotic microangiopathy
- 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.

1.1.3 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.

1.1.4 Biomarker Objective

The biomarker objective for this study is to investigate the effect of emicizumab on pharmacodynamic (PD) parameters, including activated partial thromboplastin time (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.

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

1.2 STUDY DESIGN

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 one 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.

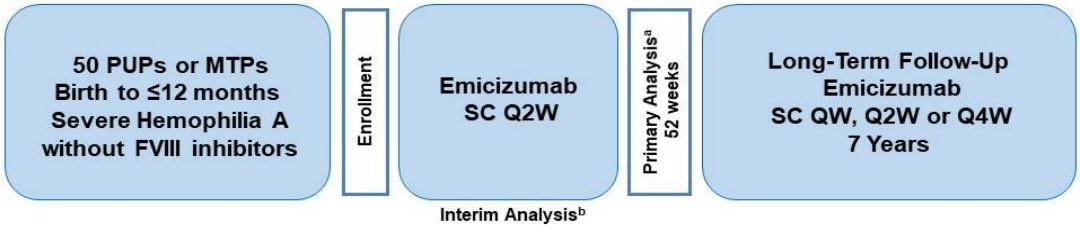
Initially, all patients will receive four loading doses of 3 mg/kg emicizumab subcutaneously (SC) QW for 4 weeks followed by the maintenance dosing regimen 3 mg/kg SC Q2W for a total of 52 weeks. Starting from Week 17, individual patients may have their dose up-titrated if they experience suboptimal 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. The Medical Monitor is available to the investigator for consultation and to answer questions related to up-titration. 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, 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.

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.

Figure 1 Study Schema



FVIII = factor VIII; MTP = minimally treated patient; PUP = previously untreated patient; SC = subcutaneous; 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.

Figure 1 presents an overview of the study design. 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.

1.2.1 Method of Treatment Assignment and Blinding

This is a single-arm, open–label study. After initial written informed consent 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 ≤2 weeks; otherwise, patients must be re-screened to determine if they continue to meet the inclusion and exclusion criteria.

1.2.2 Magnetic Resonance Imaging of Joints

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 Protocol v3). Of note, MRI scan is a mandatory assessment of the study during the LTFU period. The MRI will focus on knees, ankles, and elbows, because these are the most susceptible to hemophilic arthropathy. 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.

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). 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.

1.2.3 Data Monitoring

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, pharmacokinetics, pharmacodynamics, 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 Agreement.

2. STATISTICAL HYPOTHESES

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

3. SAMPLE SIZE DETERMINATION

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 ≤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.

4. ANALYSIS SETS

4.1 ALL PATIENTS POPULATION

The all-patients population includes all patients enrolled in the study.

4.2 SAFETY-EVALUABLE/TREATED POPULATION

The safety-evaluable population includes all enrolled patients who received at least one dose of emicizumab (i.e., “treated population”). This population will be the primary population for efficacy and safety analyses.

4.3 PHARMACOKINETIC-EVALUABLE POPULATION

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

4.4 IMMUNOGENICITY POPULATION

The immunogenicity population includes patients with at least one post-dose ADA assessment.

4.5 UP-TITRATED PATIENTS

This population includes patients who have received at least one dose of the up-titrated maintenance dosing regimen.

5. STATISTICAL ANALYSES

No formal hypothesis testing is planned for the study. All the analyses will be descriptive. No adjustment for multiplicity of endpoints will be considered.

5.1 GENERAL CONSIDERATION

All efficacy analyses will be performed on the safety-evaluable/treated population.
The start of the efficacy period for each individual patient is defined as the day of the first emicizumab dose.

The end of the efficacy period is defined as the date of the clinical cutoff or the date of withdrawal from the study period (i.e., ‘Open Label Treatment’ and ‘Long-term Follow-up’ according to electronic Case Report Form), whichever is earlier.

For patients whose dose is up-titrated, the bleeds on the up-titrated dose are analyzed separately. The efficacy period on the up-titrated dose starts with the first day on this dose and ends on the day of the clinical cut-off, or the date of withdrawal, whichever is earlier.

All safety analyses will be performed in the safety-evaluable population/treated population.

5.2 PARTICIPANT DISPOSITION: SUMMARIES OF CONDUCT OF STUDY

The flow of patients through the study will be displayed in a 'CONSORT' diagram. A clear account of all patients who entered the study, who were enrolled, who dose up-titrated, and who completed each period of the study will be displayed. In addition, reasons for premature 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.

Observation time and duration of follow-up, as well as adherence to planned assessment schedule and compliance with data entry into the electronic handheld device, will also be evaluated.

5.3 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.

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

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 ≤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)
  Note that, only patients ≥24 weeks of age at time of informed consent qualify for the assignment of a target joint bleed.
- **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. All three bleed types are collected on the eBMQ; however, only spontaneous bleeds and traumatic bleeds will be counted for the efficacy analysis.

- **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.

5.3.1 Efficacy Endpoints

5.3.1.1 Bleed-Related Endpoints

Treated bleeds, all bleeds, treated spontaneous bleeds, and treated joint and muscle bleeds will be reported. 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:

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

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.

On the electronic handheld device, it is not possible to leave questions unanswered or to enter partial data in one BMQ. In the site data entry system, it is possible to leave the time (but not the date) of a treatment or a bleed blank because the caregiver might not be able to remember these in a reliable way.

According to the above definition of a bleed; i.e., what is considered the same bleed, it is assumed that the bleeds and treatments with missing time occurred at 12:00 a.m. If at a given day only the treatment time or the bleed time is partial and the other one complete, the partial time is assumed the same as the complete time. In case of multiple events per day, the last complete time is used.

5.3.1.2 Hemophilia Joint Health Score

The HJHS measures joint health of the joints most commonly affected by bleeding in hemophilia. The HJHS 2.1 provides joint specific total scores which is added to obtain the sum of joints totals and also a global gait score. These two scores are then added to obtain HJHS total score. In this study, the HJHS 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. Descriptive analyses will be presented by timepoint.

5.3.1.3 Magnetic Resonance Imaging of Joints

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 (around 8 years) of the LTFU. This endpoint will be summarized descriptively by timepoint.

5.3.2 Sensitivity Analyses for Primary Endpoint(s)

Not applicable.

5.4 EXPLORATORY ENDPOINT(S) ANALYSIS

Not applicable.

5.5 SAFETY ANALYSES

Safety will be assessed through descriptive summaries of

- adverse events (AEs),
- laboratory test results (including serum chemistry, hematology, coagulation, and antibodies to emicizumab),
- medical history, including clinically significant diseases, procedures, medical allergies,
- concomitant medications,
- history of prior anaphylaxis or known thrombophilia since birth
- physical examination findings and vital signs.

5.5.1 Exposure to Study Medication

Information on study drug administration will be summarized by duration and cumulative dose. In addition, treatment exposure will be summarized including delays and interruptions. The number of patients whose dose was up-titrated will be summarized.

Patient withdrawals from study treatment will be reported in listings and summary tables.

5.5.2 Adverse Events

To evaluate the overall safety of prophylactic emicizumab, AEs will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade (WHO Criteria). All AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of each database closure (interim and primary analysis). For the purpose of summarization, a patient is counted once in a system organ class or preferred term if the patient reported one or more events in that system organ class or preferred term. Percentages will be based on the number of patients overall.
The numbers for systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the Sampson Criteria include only the patients that experienced indicative symptoms identified by the Sampson's Criteria (Sampson et al. 2006).

The total number and percentage of patients with at least one AE and total number of AEs will be summarized. Separate AE summaries for serious adverse events (SAEs),

adverse event of special interest (AESIs), severity, relatedness, and discontinuation/modification will be provided. An overall summary of AEs (including SAEs, AESIs, AEs leading to drug discontinuation, and deaths), which tabulates the number and percentage of patients who experienced any of these events will be provided.

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

5.5.3 Laboratory Data

For clinical laboratory data, which were collected from local laboratories up to study Week 53 (see Table 1of Appendix 1, Protocol v3), summary statistics in SI units will be presented. Laboratory data not collected in SI units will be converted to SI units as applicable. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

White blood cell (WBC) differentials reported as percentages will be converted in absolute values based on the WBC count. If neutrophils total is not available from the local lab, it will be derived from the neutrophils segmented and bands results.

Unscheduled assessments are not taken into account in summary tables, only in listings. Non-numeric results for aPPT and international normalized ratio, e.g., "$>$X", "$\geq$X", "$<$X", or "$\leq$X", will be analyzed as X. Any non-numeric results (e.g., "$>$X", "$\geq$X", "$<$X" or "$\leq$X") of other parameters like bilirubin, D-dimer, fibrinogen, FVIII activity, FVIII inhibitor will be analyzed using the "halving rule", i.e., lower limit of quantification divided by 2.

5.5.4 Vital Signs and Anthropometric Measurements

Vital signs will be summarized using mean change from baseline tables over time while considering the patient's age. Measurements consist of pulse and respiratory rate, temperature, systolic and diastolic blood pressure, height/length, and weight.

5.6 OTHER ANALYSES

5.6.1 Summaries of Conduct of Study

The flow of patients through the study will be displayed in a 'CONSORT' diagram.
A clear account of all patients who entered the study, who were enrolled, who dose up-titrated, and who completed each period of the study will be displayed. In addition, reasons for premature discontinuation from study treatment and reasons for withdrawing from the study (e.g., during follow-up) will be described.

Major protocol deviations will be summarized.

Observation time and duration of follow up, as well as adherence to planned assessment schedule and compliance with data entry into the electronic handheld device, will also be evaluated.

A patient was considered to be compliant with electronic data collection if they completed the BMQ at least every 8 days, covering the 7 preceding days (eBMQ collects data for each bleed, hemophilia related medication and the emicizumab doses 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 in the handheld device possible for the last 7 days).

The compliance rate should be based on the total number of patients/caregivers expected to complete the questionnaire at a particular time point.

5.6.2 Summaries of Demographics 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.

5.6.3 Pharmacokinetic Analyses

For all patients, pre-dose C_{trough} of emicizumab will be presented descriptively at each timepoint, 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.

5.6.4 Immunogenicity Analyses

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

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the Open Label Treatment and LTFU study 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-boosted 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 numbers and proportions of neutralizing ADA-positive patients and neutralizing ADA-negative patients during both the treatment and follow-up periods will be summarized.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

Incidence of de novo development of FVIII inhibitors will be reported in a listing. Patients qualifying for de novo development of FVIII inhibitors have titer $<$0.6 BU/mL at baseline and $\geq$0.6 BU/mL at two consecutive post-baseline visits with $\geq$14 study days in between.

5.6.5 Pharmacodynamic and Biomarker Analyses

Change over time in PD parameters, i.e., 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, individual patient plots by time after first dose of emicizumab (weeks) as well as by patient age at sample collection will be provided.

Biomarkers related to bone and joint health will be assessed at specified timepoints only during the 7-year LTFU period. Hence, the analyses thereof will not be part of the Clinical Study Reports (CSRs) but later explored for scientific publications. Bone and joint biomarkers will be analyzed by change over time and correlations within biomarkers and between biomarker levels and HJHS and other safety and efficacy endpoints may be explored.

5.6.6 Analyses of Subgroups of Interest

Note that due to the small sample size, all subgroup analyses will be highly sensitive to variability caused by individual patients and need to be interpreted with caution. For the Primary CSR, these analyses will be performed for the all patients' population. These subgroup analyses will not be performed at the time of the interim analyses.

5.6.6.1 Efficacy

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

The pre-specified subgroups are:

- Age: 0 to $<$3 months, $\geq$3 to $\leq$12 months
- Race: Asian, Black or African American, White, Other
- ADA: positive, negative
- MTP and PUP

As an exploratory analysis, historical bleed data prior to study enrollment versus bleed rate on study may be analyzed through intra-patient comparisons using the following subgroups: <1 months, 1–≤3 months, and >3 months of age at the time of informed consent.

5.6.6.2 Safety

Safety summary and adverse events may additionally be analyzed by the following subgroups:

- Age: 0 to <3 months, ≥3 to ≤12 months
- MTP and PUP
- Race: Asian, Black or African American, White, Other
- ADA: positive, negative

5.6.6.3 Pharmacokinetics

Exploratory analyses may additionally present plasma concentrations of emicizumab by the following subgroups:

- Age: <1 month, 1–≤3 months, >3 months of age at the time of informed consent
- MTP and PUP

5.7 INTERIM ANALYSES

5.7.1 Planned Interim Analyses

A planned 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 IMC and SOC (as needed) will review the interim analysis reports generated by the Sponsor's study team.

Additionally, for this study, an IMC + SOC meeting will be organized every six months (starting after the first patient in) to review safety patient data until the interim analysis. The need for further meetings will be decided thereafter.

Further details about the IMC and SOC review as well as the roles and responsibilities is provided in a separate IMC + SOC charter agreement.

5.7.2 Optional Interim Analyses

Additional interim analyses may be conducted at intermediate time point(s) during the LTFU period between the primary analysis and the end of the study.

6. SUPPORTING DOCUMENTATION

This section is not applicable as there is no additional supporting document.

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