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STATISTICAL ANALYSIS PLAN

TITLE: **A SINGLE-ARM, MULTICENTER PHASE IIIB CLINICAL TRIAL TO EVALUATE THE SAFETY AND TOLERABILITY OF PROPHYLACTIC EMICIZUMAB IN HEMOPHILIA A PATIENTS WITH INHIBITORS**

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STATISTICAL ANALYSIS PLAN HISTORY

SAP Version / Date	Description
Version 1.0 / 11 June 2018	Initial version.
Version 2.0 / 6 December 2018	• Revision based on protocol amendment v3.0 dated 09MAR2018: population for patients with surgery on-study added (Section 4.2.5) and analyses on patients with surgeries on-study added (Sections 4.4 and 4.9.4). • Population for efficacy analyses updated to ITT instead of Safety (Section 4.6), for consistency with protocol. • Clarifications added on the study periods (before up-titration, after up-titration, both) to be included in the analyses. • Updates done for consistency with Haven-1 and Haven-4 studies: Definition of efficacy period (Section 4.1); Definition of prior / concomitant medications (Section 4.5). • Addition of analyses done for Haven-1 and Haven-4 studies: Compliance analyses for questionnaires (Section 4.6.1.7); Analysis of the number of days hospitalized (Section 4.6.8). • Updates to the analysis of adverse events (Section 4.9.2): clarification of the reporting period, list of AESIs revised as per protocol. • Details on the PK analysis removed as it will be described in a separate SAP.
Version 3.0 / 5 November 2020	• Definition of treated joint bleeds revised for consistency with Haven-1 and Haven-4 studies: aura criterion removed (Section 2.2.2.7) • Definition of positive ATA patients updated for consistency with Haven-1 and Haven-4 studies (Section 4.8) • Definition of TEAEs clarified (Section 4.9.2) • Section on analysis of surgeries revised (Section 4.9.4) • Section on analysis of biomarkers revised (Section 4.10) • Analyses on impact of COVID-19 added (Section 4.3 and 4.9.2) • Details on the PK analysis added (Section 4.7)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	annualized bleeding rate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATA	anti-therapeutic antibodies
BMI	body mass index
BMQ	Bleed and Medication Questionnaire
BSA	body surface area
BU	Bethesda unit
CI	confidence interval
CSP	clinical study protocol
CVAD	central venous access device
CWA	clot waveform analysis
eCRF	electronic Case Report Form
ELISA	enzyme linked immunosorbent assay
EmiPref	Patient Preference Questionnaire regarding the treatment with Emicizumab
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL Five-Dimension-Five Levels Questionnaire
EQ-VAS	EuroQoL visual analogue scale
FEIBA	*factor eight inhibitor bypassing activity*
FIX	Factor IX
FIXa	activated Factor IX
FIX:Ag	Factor IX antigen
FVIIa	activated Factor VII
FVIII	Factor VIII
FVIII:Ag	Factor VIII antigen
FX	Factor X
FX:Ag	Factor X antigen
Haem-A-QoL	Hemophilia Adult Quality of Life Questionnaire
Haemo-QoL	Hemophilia Quality of Life

Abbreviation	Definition
Haemo-QoL-SF	Hemophilia Quality of Life Short Form
HCP	healthcare provider
HIV	human immunodeficiency virus
HRQoL	Health-Related Quality of Life
iDMC	independent Data Monitoring Committee
IgG	immunoglobulin G
IND	investigational new drug
INR	international normalized ratio
ISR	injection site reactions
ISTH	International Society on Thrombosis and Haemostasis
ITI	immune tolerance induction
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LPLV	last patient, last visit
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
rFVIIa	recombinant activated human Factor VII
rFVIII	recombinant Factor VIII
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SMQ	standardised MedDRA queries
SOC	system-organ class
SSC	scientific and standardization committee
TE	thromboembolic event
TMA	thrombotic microangiopathy
ULN	upper limit of normal
VAS	visual analog scale
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON HEMOPHILIA A WITH INHIBITORS

Hemophilia A is a rare bleeding disorder that is attributable to a congenital absence or hypofunctioning of Factor VIII (FVIII) (Acharya 2013; Witmer and Young 2013). The gene that encodes FVIII is located on the X chromosome. Genetic defects are expressed through X-linked recessive inheritance or *de novo* FVIII mutations, and more than 99% of hemophilia patients are males. The prevalence of hemophilia A is approximately 1 in 5,000 live-born males or 1 out of every 10,000 live births (CDC 2016; Franchini and Mannucci 2013; NIH 2016). No racial differences have been reported, and the numbers of patients registered in 2014 in various regions included 4,870 in Japan, 21,052 in North America, and 11,029 in just two European nations (United Kingdom and France) (World Federation of Hemophilia 2014).

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of hemophilia A is classified in accordance with endogenous FVIII activity in the blood. Patients with FVIII activity of less than 1% have severe disease, those with activity between 1% and 5% have moderate disease, and those with activity greater than 5% and less than 40% have mild disease. Patients who have severe hemophilia who do not initiate and/or comply with rigorous FVIII prophylaxis regimens, or do not have access to FVIII products, experience bleeding episodes several times a month, which is much more frequent than in patients with moderate or mild disease. In addition, patients with severe hemophilia have a high frequency of spontaneous bleeding. Hence, the maintenance of plasma FVIII activity at 1% or higher is important to prevent the onset of recurrent bleeding episodes, reduce comorbidities such as arthropathy, and improve Health Related Quality of Life (HRQoL) in patients with severe hemophilia A (Srivastava et al. 2013).

1.2 BACKGROUND ON EMICIZUMAB

Emicizumab (also known as ACE910, CH5534262, and RO5534262) is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated Factor IX (FIXa) and Factor X (FX), thereby 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. Emicizumab therefore has no potential to induce or enhance the development of direct inhibitors to FVIII or other coagulation factors. In addition, emicizumab offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because of the expected pharmacokinetic (PK) properties of this antibody, markedly extending the dosing interval to once weekly or even more, this compound has the potential to improve the treatment of patients with hemophilia A with and without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

In the Phase I/II study (ACE001JP) 18 Japanese patients with hemophilia A, either with or without inhibitors, were treated with emicizumab at three different dosing regimens (0.3 mg/kg/week, 1 mg/kg/week, or 3 mg/kg/week). During the course of emicizumab administration, the Annualized Bleeding Rate (ABR) significantly decreased in all patients compared with the ABR prior to study enrollment, regardless of whether or not the patient

had inhibitors, with the exception of one patient without inhibitors in the 3 mg/kg/week group (see Section 1.2.2 of the protocol).

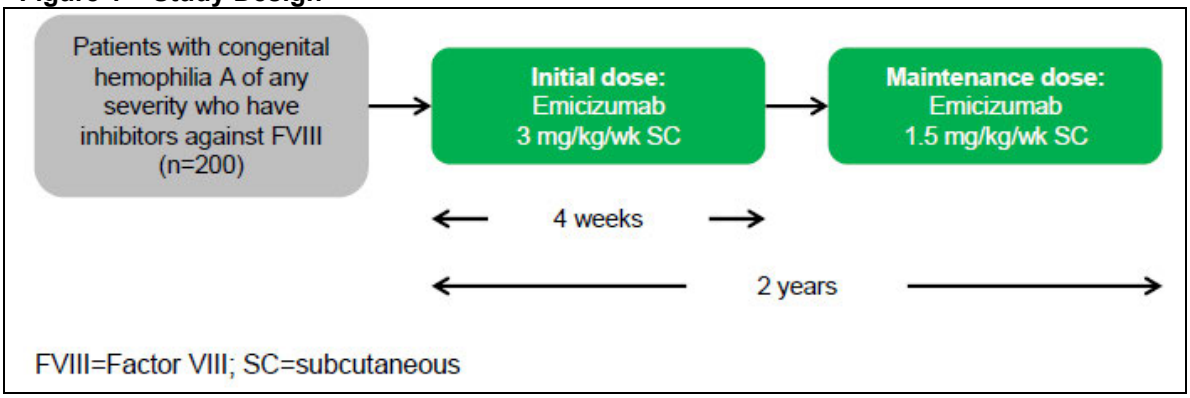
Emicizumab has been well tolerated in patients in the Phase I/II studies (cut-off date 15th February 2016). The majority of adverse events have been mild in intensity, with the most common being injection-site reactions (ISRs). The majority of the adverse events have not been considered to be related to emicizumab. In these studies, no thromboembolic or systemic hypersensitivity adverse events have been observed. However, as of April 2017, three cases of thrombotic microangiopathy (TMA), and three thromboembolic events in two patients, have been observed in the ongoing Phase III Study BH29884 in patients who received emicizumab as well as bypassing agents for the treatment of breakthrough bleeds. Four of these patients have fully recovered and the fifth patient died (death due to serious adverse event of rectal haemorrhage unrelated to emicizumab, with the TMA related to emicizumab and aPCC) (see Sections 5.1.1.2 and 5.1.1.3 of the protocol).

Given the unmet need to develop novel therapeutics for use in hemophilia A patients with inhibitors and the positive risk-benefit assessment observed, a Phase IIIb safety study with emicizumab is warranted in this patient population.

2. STUDY DESIGN

This single-arm, multicenter, open label Phase IIIb clinical study will enroll patients aged 12 years or older with congenital hemophilia A who have persistent inhibitors against FVIII at enrollment. Approximately 200 patients with inhibitors will be enrolled globally. Patients will receive prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period (Figure 1).

Figure 1 – Study Design



The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with congenital hemophilia A who have persistent inhibitors against FVIII at enrollment. In order to achieve this objective, all adverse events, including adverse events of special interest, will be captured on an ongoing basis, as they occur during the study. Physical examinations, vital signs, and laboratory values will be assessed as per the Schedule of Activities (Appendix 2: Schedule of Activities).

The secondary objective of this study is to evaluate the efficacy of prophylactic administration of emicizumab. As part of this objective, the number of bleeds over time will be recorded for all of the enrolled patients.

The final analysis will be conducted when all patients have completed 2 years of treatment or have withdrawn, whichever occurs sooner. Patients, or their legally authorized representative, will be asked to report bleed information on an electronic patient-reported outcome (ePRO) device where possible, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. HRQoL will be assessed and the EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) will be completed prior to the first emicizumab administration (Week 1), at the Month 3, 6, 12, and 18 assessments, and at study completion as outlined in the Schedule of Activities (Appendix 2: Schedule of Activities). Additional secondary endpoints include assessing patient preference for the emicizumab regimen compared with the previous regimen using a questionnaire (EmiPref).

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2: Schedule of Activities.

2.2 OBJECTIVES AND ENDPOINTS

- To evaluate the overall safety and tolerability of prophylactic administration of emicizumab (primary objective): Incidence and severity of all adverse events (AEs), including AEs of special interest, AEs leading to discontinuation and SAEs will be analyzed. Additionally, changes in physical examination findings, vital signs and laboratory parameters will be presented.
- To evaluate the efficacy of prophylactic administration of emicizumab (secondary objective): the number of bleeds over time, the HRQoL of patients according to Haem-A-QoL (≥18 y) or Haemo-QoL-SF (ages 12−17) scores, the health status of patients according to EQ-5D-5L scores over time and the patient preference for the emicizumab regimen compared with the previous regimen used are shown.
- To evaluate the immunogenicity of emicizumab (immunogenicity objective): the occurrence and clinical significance of anti-emicizumab antibodies are assessed.
- Emicizumab PK data (pharmacokinetic objective) at defined time points are analyzed.

2.2.1 Adverse Events of Special Interest

Adverse events of special interest (AESI) for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Protocol Section 5.3.5.7).
- Suspected transmission of an infectious agent by the study drug, as defined below. Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions (see Sampson's Criteria in Protocol Appendix 4).
- Thromboembolic events.
- Microangiopathic hemolytic anemia or TMA (e.g. hemolytic uremic syndrome).

2.2.2 Bleed Assessments

Patients will be trained on how to record their bleeds and hemophilia medication use using an ePRO device. When bleeds occur, patients will need to record the site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. At least once a week, patients will need to record any hemophilia medication use (including emicizumab) and information regarding any bleeding events. Investigator review of patient-reported bleed/medication records with the patient/caregiver will occur for completeness and accuracy throughout the study.

2.2.2.1 Definition of a Bleed

For the purposes of the efficacy analyses, a standardized definition of bleed, adapted from the standard criteria defined by the FVIII and FIX Subcommittee of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), that is similar to the definition used in a recent clinical investigation, will be utilized in this study (Blanchette et al. 2014; Mahlangu et al. 2014):

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

2.2.2.2 Treated bleeds

A bleed is considered to be a "treated bleed" if it is directly followed (i.e., there is not an intervening bleed) by a hemophilia medication reported to be a "Treatment for bleed" (see Haemophilia Medication Record) irrespective of the time between the treatment and the preceding bleed. Note, a bleed occurring at the same time as a treatment, counts as a treated bleed. A bleed and the first treatment thereafter are considered to be pairs (i.e., one treatment belongs to one bleed only), with the following exception: if multiple bleeds occur on the same calendar day, the subsequent treatment is considered to apply for each of these multiple bleeds.

Bleeds due to surgery/procedure will not be included in the primary analysis. In addition, treatments reported as "Treatment for bleed" directly following a bleed due to surgery/procedure are excluded.

2.2.2.3 72-Hour rule

Two bleeds of the same type (e.g., "joint," "muscle," or "other") and the same etiology and at the same anatomical location are considered to be one bleed if the second occurs within 72 hours from the last treatment for the first bleed. Any bleed with a different etiology is considered a separate bleed regardless of time from last injection. The last treatment is defined as the last treatment before a new bleed occurs, either in the same or in a different location. This is in-line with the above definition that bleeds and treatments are considered to be pairs.

If the bleed location is other/other, other/other is used as the bleed location and not the exact location entered on the separate eCRF page.

In case of trauma with multiple different locations of bleed, this will be considered as one bleed for the analyses. However, all data will be collected, including the various locations of the different bleeds.

A listing of all bleeds is produced. The listing includes all bleed and hemophilia medication, except emicizumab, information entered on the Bleed Record, with an indicator which bleeds are included in the primary analysis and which do not count as separate bleeds due to the 72h rule.

2.2.2.4 All bleeds

"All bleeds" comprise both treated and non-treated bleeds. In this definition, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded, as in the primary analysis.

The 72-hour rule will be applied to the “All bleeds” endpoint. For treated bleeds, it will be implemented exactly as defined in Section2.2.2.2. For non-treated bleeds (not followed by any treatments with coagulation factors before the recording of a subsequent bleed), it will be implemented by calculating the interval of 72 hours from the bleed itself. Non-Treated bleeds are bleeds not covered by the definition of treated bleeds for the primary endpoint. To clarify, one bleed can be a composition of treated and non-treated bleeds.

Examples:

RE - 2h – T* – 75h – RE – 2h - T -> 2 bleeds (*72h calculated from last treatment)

RE* - 75h – RE – 2h - T -> 2bleeds (*72h calculated from bleed because there is no treatment)

RE – 70h – RE – 2h - T -> 1 bleed

RE - 50h – RE – 30h – RE -> 1 bleed

RE – 30h – RE - 25h – LE -> 2 bleeds

RE – 2h – T – 3h – T* – 35h – RE– 2h – LE** – 45h – LE- 70h - RE -2h -T -> 3 bleeds (*72h calculated from last treatment, ** calculated from previous bleed due to no treatment)

RE=right elbow bleed, LE=left elbow bleed, T=treatment for bleed

2.2.2.5 Bleed Sites

The bleed sites are defined as follows:

- Joint bleeds, which are defined as having an unusual sensation (“aura”) in the joint in combination with any of the following:
    - Increasing swelling or warmth of the skin over the joint
    - Increasing pain
    - Progressive loss of range of motion or difficulty in using the limb as compared with baseline.
- Muscle bleeds
- Other bleeds.

2.2.2.6 Definitions of Cause/Classification of Bleeds

Bleed assessments will be separated into spontaneous bleeds, traumatic bleeds, and bleeds related to procedures. Both spontaneous bleeds (i.e., the occurrence of hemorrhage where neither the patient nor a caregiver can identify a reason) and traumatic bleeds (i.e., hemorrhage occurring secondary to an event such as trauma, “strenuous” activity, or “overuse”) will be collected. The definitions for the different type of bleeds are as follows:

- **Spontaneous bleeds**. Bleeds will be classified as spontaneous if a patient records a bleed when there is no known contributing factor such as definite trauma, antecedent “strenuous” activity, “overuse”, or procedure/surgery. The determination of what constitutes “strenuous” or “overuse” will be at the discretion of the patient. For example, light jogging may be considered “non-strenuous” while sprinting may be considered “strenuous”; lifting of weights for a short period of time may be considered “moderate use” while repetitive weightlifting may be considered “overuse”.
- **Traumatic bleeds**. Bleeds should be classified as traumatic if a patient records a bleed when there is a known or believed reason for the bleed. For example, if a patient were to exercise “strenuously” and then have a bleed in the absence of any

obvious injury, the bleed would be recorded as a traumatic bleed because, although no injury occurred, there was antecedent "strenuous" activity. Bleeds with preceding injuries would certainly be classified as traumatic. In addition, bleeds related to surgery, such as hematomas resulting from any surgeries, will also be classified as traumatic bleeds. Bleeds related to surgeries will not be associated with any trauma except surgery-induced trauma.

- **Bleeds related to procedures**. This category would include hematomas resulting from any invasive procedure (e.g., tooth extractions, venipuncture, or SC drug administrations) or invasive diagnostic procedures (e.g., lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy, etc.) or surgeries. Any instances of these bleeds would not be counted as bleeds in the context of the study, but the relevant data will be collected. Bleeds related to procedures will not be associated with any trauma except procedure-induced trauma.

2.2.2.7 Treated Joint Bleeds

Joint bleeds are defined as bleeds where the bleed type is "joint" and at least one of the following symptoms has been observed: increased swelling or warmth of the skin over the joint, increased pain in the joint or decreased range of motion, or difficulty moving the joint compared to baseline.

For the analysis, all treated bleeds that fulfill the above joint bleeds definition will be included and then the 72-hour rule will be applied. Bleeds due to procedure/surgery will be excluded.

In case multiple bleeds are counted as one bleed (72h rule), all of these bleeds needs to fulfill the above rule.

Additional analyses will be performed for joint bleeds where the bleed site is "joint", regardless of any accompanying reported symptom.

2.2.2.8 Treated Target Joint Bleeds

Target joints are major joints in which repeated bleeds occur (i.e., $\geq$ 3 bleeds in the same joint over the last 24 weeks prior to study entry). The target joints prior to study entry are identified through the eCRF. The bleeds in target joints during the efficacy period (see Section 4.1) are defined by first selecting the bleeds that fulfill the definition of a treated joint bleed (see Section 2.2.2.7) and then counting how many of these occurred in a target joint prior to study entry. The locations to be taken into account are: shoulder, elbow, wrist, fingers/thumb, hip, knee, ankle, sole/heel, and toes. Left and right side of the same joint type are considered to be separate joints.

2.2.2.9 Treated Spontaneous Bleeds

For the analysis all treated bleeds that fulfil the above spontaneous bleeds definition (section 2.2.2.6) will be included and then the 72-hour rule will be applied.

2.2.3 HRQoL Assessments

The Haem-A-QoL (version AU 3.0; UK English) and the Hemophilia Quality of Life Short Form (Haemo-QoL-SF) (version AU 2.0; UK English) will be completed electronically and

used to measure HRQoL in adults and adolescents, respectively. Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.

The Haem-A-QoL was designed for adult patients with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, feelings, view of yourself, sports and leisure, work and school, dealing with hemophilia, treatment, future, family planning, and partnerships and sexuality) and a scale representing total score. Items are rated according to five response options, although for some items there is also a 'not applicable' option (Mackensen and Gringeri 2010; Wyrwich et al. 2015).

The Haemo-QoL has been developed as a series of age-related questionnaires to measure HRQoL in children and adolescents with hemophilia (Bullinger et al. 2002; Pollak et al. 2006; Von Mackensen and Bullinger 2004). These questionnaires include a 77-item long form, a 35-item short form, and an 8-item index form. Long versions for three different age groups contain 21−77 items and cover 8−12 dimensions of HRQoL. Furthermore, two age-specific short form measures containing 16 and 35 items have been developed. The short version for older children (8−16 years) containing 35 items was selected for this study. This version covers nine dimensions considered relevant for the children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports, dealing with hemophilia, and treatment). Items are rated with respect to five response options: never, rarely, sometimes, often, and all the time.

2.2.4 Health Status Assessments (EQ-5D-5L)

The EQ-5D-5L (version 2; UK English) is a generic, self-report, preference-based health utility measure that consists of six questions that are completed electronically and is used to assess health status and inform pharmacoeconomic evaluations. Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable. The EQ-5D-5L consists of two components. The first part, health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression (Herdman et al. 2011; Janssen et al. 2013). Published weights are available that permit the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The second part is a 0 to 100-point visual analog scale (VAS), which assesses current health status and higher scores are reflective of better health.

2.2.5 Treatment Preference Questionnaire

Patient preference will be assessed through a paper version of the EmiPref questionnaire (see Protocol Appendix 3), which asks patients to specify the treatment they would prefer to continue to receive after receiving treatment with their previous episodic or prophylactic regimen and SC emicizumab. Patients who express a preference are then asked to identify the reasons which may have influenced their decision and indicate the top three reasons for their choice. Patients will complete this questionnaire after 3 months of treatment with emicizumab.

2.3 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 200 patients is planned for this study.

For the purpose of the sample size calculation, the incidence of adverse events was chosen as the safety endpoint of primary interest.

If the observed incidence of adverse events is between 2.5% and 15%, the precision for the estimated incidence rate is presented below according to the 95% Clopper-Pearson confidence intervals (CIs) (Table 1).

Table 1: Clopper-Pearson 95% CIs for the Incidence of AEs (Based on N=200)

Number of AE Events (Observed AE Incidence)	95% Clopper-Pearson CIs
5 (2.5%)	0.8%–5.7%
10 (5.0%)	2.4%–9.0%
20 (10.0%)	6.2%–15.0%
30 (15.0%)	10.4%–20.7%

2.4 ANALYSIS TIMING

The first interim analysis will be performed once approximately 100 patients have received treatment with emicizumab for at least 24 weeks.

A second interim analysis will be performed when approximately 100 patients have received treatment with emicizumab for at least 52 weeks.

The data from these analyses will subsequently be presented to the independent Data Monitoring Committee (iDMC) in order to enable them to effectively monitor the study (see Section 3.3).

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two additional interim efficacy analyses (i.e., beyond what is specified in Section 6.9.1 of the clinical study protocol [CSP]).

The final analysis will be conducted when all patients have completed 2 years of treatment or have withdrawn, whichever occurs sooner.

3. STUDY CONDUCT

The study conduct is described in Section 2.

3.1 RANDOMISATION ISSUES

Not applicable

3.2 INDEPENDENT REVIEW FACILITY

Not applicable

3.3 DATA MONITORING

The iDMC will review safety data on a regular basis until all patients have been enrolled and have completed treatment. All analyses for review by the iDMC will be prepared by the study statistician. Analyses of safety events will be conducted after approximately 100 patients have completed 24 weeks in the study and again after approximately 100 patients have completed 52 weeks in the study. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor according to the emerging safety profile.

Further details are specified in a separate iDMC charter.

4. STATISTICAL METHODS

No formal statistical hypothesis tests will be performed and all analyses are considered descriptive.

Categorical data will be summarized using frequencies and percentages (including a category for missing, if appropriate). Continuous data will be summarized using descriptive statistics (N, mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum). Other analysis methods will be specified (below) where applicable.

4.1 REPORTING PERIODS

The following definitions are used to allocate data to study periods. The same definitions are used for all outputs, e.g. AEs, laboratory data, patient disposition, efficacy and quality of life, unless otherwise specified.

Original Study Day 1:
Original study day 1 is defined as the day of the first emicizumab dose.
For patients who withdrew before week 1 and have neither received emicizumab nor have an entry in the electronic handheld device or site data entry system, original study day 1 is the date of enrollment, defined as week 1 visit, if available, or the date of informed consent.

Up-titration Study Day 1:
Emicizumab is administered at a dose of 3 mg/kg/week for 4 weeks when initiating treatment, followed by 1.5 mg/kg/week for the remainder of treatment period. It is possible to increase the dose to 3 mg/kg/week if protocol defined criteria are met. For all patients whose emicizumab dose was up-titrated to 3 mg/kg/week, up-titration study day 1 is defined as the day of the first higher emicizumab dose (based on eCRF). Up-titration study day 1 is defined for up-titrated patients only.

Study Day:
Study day (original or up-titration respectively) of an event/assessment is defined as the date of the event/assessment minus the date of Study Day 1 (original or up-titration respectively). If the result is a positive number or zero, add one day. In other words, there is no day zero.

Before therapy:
All events/assessments that occur before the original study day 1 are considered to have occurred before therapy and have a negative study day. AEs occurring at the original study

day 1 are assumed to have occurred after therapy started. For handling of laboratory assessment, see definition of baseline.

Baseline:
Baseline assessment is the last valid assessment before or on original study day 1. As defined in the protocol, for all laboratory and immunogenicity assessments at the original study day 1, it is assumed that the assessment was done before the emicizumab intake.
Baseline assessments that are measured only once at screening or week 1 and are not affected by treatment should be considered irrespective of the study day (e.g. gender, height, hemophilia history).
For Haem-A-QoL, Heamo-QoL-SF and EQ-5D-5L, the Week 1 questionnaire is considered to be the baseline irrespective of the collection date/time.

Up-titration Baseline:
For patients who are up-titrated, baseline for this period is defined as the last valid assessment done before or on Up-titration study day 1.

Treatment period:
Treatment period is defined as the time between original study day 1 and last emicizumab injection. For a patient who has not withdrawn from/completed treatment, the end of treatment period is actually defined as the date of the clinical cutoff.

Before up-titration:
The period before up-titration starts on the date of the original study day 1and ends one day before Up-titration study day 1 or, in case of no Up-titration, either the date of study withdrawal or the cut-off date, whichever comes first.

After Up-Titration:
For patients who are up-titrated, the period after up-titration starts on the up-titration study day 1 and ends on the date of study withdrawal or the cut-off date, whichever comes first.

Follow-up:
Follow-up period starts on the day after the end of the treatment period. Follow-up period ends on the day of withdrawal, completion of follow-up, or at the end of the study as defined in the protocol. Only patients who have an assessment during this time period are considered as having entered follow-up.

Observation time:
Observation time is the time between date of enrollment and the day of death or the last actual assessment in the database (=last date known to be alive). At the time of a database cutoff for patients who have not withdrawn from the study, the cutoff date will be used instead of the last assessment date.

Efficacy periods:
The start of the efficacy period for each individual starts on the date of first emicizumab treatment. The end of the efficacy period is defined as the date of the clinical cutoff or the date of withdrawal from/completion of the treatment whichever is earlier.
For patients who withdraw from the study before reaching the Week 1 visit, the duration of efficacy period is set to 1 day, and it starts and ends on the day of enrollment.
For patients whose dose is up-titrated, the efficacy period ends one day prior to the first day on the up-titrated dose (Efficacy period 1).

For patients whose dose is up-titrated, the bleeds occurring during the administration of 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 cutoff or the date of withdrawal from/completion of treatment (Efficacy period 2).

For statistical evaluations (e.g. descriptive summaries) of post-baseline data summarized by visit, only measurements at scheduled visits are considered. If a measurement is repeated at a scheduled visit (or time point), then only the latest retest result will be used in calculation of the statistical summary. All data – including unscheduled measurements – will be included in the listings.

If a time interval was calculated in minutes, hours or days and needs to be converted into months or years the following conversion factors will be used:

1 year = 365.25 days

1 month = 30.4375 days

4.2 ANALYSIS POPULATIONS

4.2.1 Primary Population (Safety Population)

The primary analysis population is all patients who have received at least one dose of study medication (safety population).

4.2.2 Intend-To-Treat Population

The intent-to-treat (ITT) population includes all enrolled patients (enrolled patients are defined as patient who signed the informed consent).

4.2.3 Pharmacokinetic-Evaluable Population (PK Population)

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

4.2.4 Up-Titrated Population

This population includes patients who have received at least one dose up-titrated to 3 mg/kg.

4.2.5 Surgery Population

This population includes patients who received at least one dose of emicizumab and have at least one surgical surgery during study conduct (i.e. while receiving emicizumab).

4.3 ANALYSIS OF STUDY CONDUCT

A clear account of all patients who enrolled in the study and who entered, discontinued, and completed the initial and maintenance phases of the study will be displayed.

The reasons for premature discontinuation from study treatment and the reasons for study withdrawal will be described in listings and summary tables.

In addition, the number of patients who received dose up-titration will also be described.

Enrollment, major protocol deviations and reasons for early discontinuation will be listed and evaluated for their potential effects on the interpretation of study results. The type of

major protocol deviations and the number of patients with at least one major protocol deviation will be summarized in terms of both the safety and ITT populations. Major protocol deviations related to COVID-19 will be summarized and listed.

Patient disposition table describes the flow of patients through the study up to the cutoff. Patients will be tabulated with:

- Number of patients enrolled
- Number of patients who discontinued prematurely prior to Study day 1
- Number of patients with duration of efficacy period <2 years
- Number of patients who completed 24 months in the study (efficacy period)
- Number of patients with at least one dose up-titration (up-titrated population)
- Number of patients who started safety follow-up (for interim analyses only)
- Number of patients who completed safety follow-up
- Number of patients who discontinued treatment
- Number of patients who discontinued from the study
- Number of patients who completed the study

Number of patients included and excluded from each analysis population is listed and summarized. All analysis populations defined for the study are included.
Major protocol deviations are listed and summarized by category and type of deviation.
A listing of investigators is produced with a column indicating the number of patients enrolled. Also enrollment will be summarized by country and investigator number. Observation time, duration of efficacy period and duration of follow-up (as defined in section 4.1) are summarized descriptively (unit weeks) and categorically (cumulative): >0 week, ≥4 weeks, ≥12 weeks, ≥24 weeks, ≥36 weeks, ≥48 weeks, ≥72 weeks, ≥96 weeks.

4.4 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

The following baseline and demographic characteristics will be presented using appropriate descriptive statistics:

For each variable (continuous or categorical), the number of available observations will be reported.

Demographics: demographic information collected at baseline (including age, sex, and self-reported race, ethnicity, height, weight, BSA and BMI). The age will be presented as continuous and categorical (≥12-<18 years, ≥18- <65 and ≥ 65 years) variable. Medical history and Baseline conditions assessment: number and percentage of patients with at least one medical condition and number and percentage of patients by system organ class and preferred term will be presented. Separate summaries will be presented for active and past medical history, where active is defined as ticked on eCRF as ongoing (with or without treatment) and past is defined as ticked as resolved. A listing of all previous and concurrent medical history will also be provided.

Hemophilia history: The following characteristics of the hemophilia history will be presented using appropriate descriptive statistics:

- Hemophilia severity at baseline
- Time from Factor VIII inhibitor diagnosis date (months)
  = (Date of Day 1 - Date of FVIII inhibitor diagnosis)/month
  (continuous and categorical: <24 months, 24-<48 months, 4-<72 months, >=72 months)
- Highest historical inhibitor titer (continuous and categorical: <5 BU, >=5 BU, Unknown)
- Number of patients who already had treatment with ITI
- Time from start of most recent ITI date (years)
  = (Date of Day 1 - Date of Start date of most recent ITI treatment)/year
  (continuous and categorical (< 2 years, 2 – 5 years, >5 years, Unknown))
- Prior episodic treatment in the last 24 weeks
  - Prior prophylactic treatment in the last 24 weeks
  - Reason for not being on prophylactic treatment regimen
- Number of bleeds in last 24 weeks
- Number of target joints prior to study

In addition, the baseline and demographic characteristics will also be summarized on the subset of patients with at least one surgical procedure during study conduct.

Surgery and procedures:

All surgeries and procedures collected on the eCRF page for Surgery and Procedure History Assessment will be listed. In case surgeries are coded, previous surgeries and procedures will in addition be summarized in a frequency table.

4.5 PREVIOUS AND CONCOMITANT MEDICATIONS

Use of prior and concomitant medication will be presented by medication class and standardized medication name. Number and percentage of patients and number of medications will be presented. Summary tables on concomitant medications will include all dates (before and after up-titration).

A medication is considered concomitant if the start date/time is on or after the date/time of Original Study Day 1. Otherwise, a medication is considered prior if the end date/time is not missing and is before the date/time of Original Study Day 1. Otherwise a medication is considered prior-concomitant.

All hemophilia medication (collected on the electronic handheld device or the site data entry system) will be reported separately. The number of doses and the cumulative doses will be summarized by category of hemophilia medication. Summary tables for hemophilia medications will include data up to the up-titration (if any) only. If at least 10 patients are up-titrated then the frequency table will also be produced on the period after up-titration.

Also all prior episodic and prophylactic hemophilia medication collected on the hemophilia history page will be summarized separately.

4.6 EFFICACY ANALYSIS

This is a single arm study and, consequently, no formal treatment group comparisons will be conducted.

The efficacy analyses will be based on the ITT population. Efficacy analyses will be restricted to the period before up-titration, if any, except if stated otherwise.

4.6.1 Efficacy endpoints

The analysis of efficacy endpoints will be based on the efficacy period defined in Section 4.1.

4.6.1.1 Bleeds

The primary analysis will be based on treated bleeds (see definition 2.2.2.2).The number of bleeds over time will be estimated using a negative binomial (NB) regression model, which accounts for different follow-up times. The time that each patient stays in the study (efficacy period) will be included as an offset in the model.

An additional model which adjusts for number of bleeds (< 9 or ≥ 9, according to eCRF) in the last 24 weeks prior to study entry will be used to support the primary analysis.

In the rare case that the negative binomial model does not converge or no bleeds were observed for a given endpoint, the primary analysis will be based on "calculated" annualized bleed rate (ABR).

The ABR is calculated using the following formula (called Calculated ABR on all outputs):

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

The efficacy analyses will include the following endpoints defined in section 2.2.2: treated bleeds, all bleeds, treated joint bleeds, treated target joint bleeds and treated spontaneous bleeds. For each endpoint, the model based ABR will be estimated along with its corresponding 95% CI. In addition, the mean, 95% CI based on Exact Poisson, median, IQR, min and max will be provided for the calculated ABR.

A corresponding listing will be provided which will include for each patient the duration of efficacy period, number of bleeds together with calculated ABR for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds (based on data before up-titration only). A separate listing will also be provided for the up-titrated population, based on data on or after the up-titration.

4.6.1.2 Number of Bleeds/ABR categories

Number of patients with 0, 1-3, 4-10, >10 bleeds as well as number of patients with calculated ABR <1, 1-3.4, 3.5-10, >10 will be summarized. Figures including 95% CI will also be provided. All summaries and figures will be produced for treated bleeds, all bleeds and treated spontaneous bleeds.

4.6.1.3 Cause, type and location of bleed

Cause of bleed (spontaneous, traumatic, procedure/surgery) and location of bleed by bleed type (Joint, Muscle, other) will be summarized. The analysis will be performed separately for treated bleeds (with 72-hour rule) and all bleeds without applying the 72-Hour rule and including bleeds due to surgeries/procedures.

4.6.1.4 Type of trauma

Type of trauma will be summarized according to the categories on the eCRF. The traumas are analyzed separately for bleed related trauma and non-bleed related trauma including all trauma. Non-bleed related trauma are identified through bleed number=ND on the trauma form.

4.6.1.5 Time of bleed

Time of bleed will be summarized by calculating the difference between start time of bleed and start of efficacy period. The time of bleed will be presented as continuous and categorical (1-4 weeks, >4-12 weeks, >12-24 weeks, >24-36 weeks, >36-52 weeks, >52-88 weeks, >88-104 weeks, > 104 weeks).
The analysis will be conducted separately for treated bleeds and all bleeds without applying the 72-Hour rule and including bleeds due to surgeries/procedures.

4.6.1.6 Use of non-emicizumab hemophilia treatments

The number of treatments to treat a bleed will be summarized. The number of infusions is counted per bleed corresponding to the definition of the primary endpoint, i.e. all treatments that are linked to the same bleed per the 72h rule are considered to belong to the same bleed. If the same treatment/s are associated with multiple bleeds, these are counted multiple times, i.e. linked to both bleeds.

The cumulative dose per kg administered will be summarized by product, e.g. RECOMBINANT FACTOR VIIA [E.G. NOVOSEVEN] or PROTHROMBIN COMPLEX CONCENTRATE [E.G. FEIBA]. The following formulas will be used to annualize the dose and the number of infusions:

$$\frac{\text{Number of Infusions}}{\text{Efficacy Period}} \times 365.25$$

$$\frac{\text{Cumulative dose/kg}}{\text{Efficacy Period}} \times 365.25$$

4.6.1.7 Bleed and Medication Questionnaire Compliance

Patient compliance to the Bleed and Medication Questionnaire (BMQ) will be analyzed. The compliance will be analyzed separately for entries done via the electronic handheld device only, and for all entries (via electronic handheld device or Site data entry system). A patient will be considered to be compliant if he completes the BMQ at least every 8 days (a filled out BMQ makes the patient compliant for the preceding 7 days, i.e. 8 days in total). The compliance rate will be defined as the number of days covered by a BMQ questionnaire divided by the duration in days of the efficacy period. The BMQ compliance will be summarized in a table and listed. The mean of the compliance rate will also be plotted overtime.

4.6.2 HRQoL (Haem-A-QoL and Haemo-QoL-SF)

As different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) will be used for adult and adolescent patients, all calculations and analyses will be conducted separately for each patient population.

The number and percentage of patients who complete the Haem–A–Qol or Haemo-Qol-SF will be summarized at each scheduled time point. The compliance rate will be plotted over time. The compliance rate is based on the total number of patients expected to complete the questionnaire at a particular time point – i.e., those patients who had the opportunity to complete the scale. The number of expected questionnaires is calculated using the time windows of scheduled visits defined in the protocol. The analysis period used will overlap with the corresponding efficacy period, as the start will be the start of the efficacy period and the end will be either then end of the efficacy period or will be extended to the last entry on the device, for the last efficacy period of a subject, if it occurred later.

Total score and domain sub-scales at each visit for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively. The corresponding mean along with its 95%CI plots will be provided.

The change from baseline to 6 months as well as for each of the post-baseline time points in the total score for each questionnaire will be analyzed by the paired t-test.

The proportion of patients who report changes that exceed clinically meaningful thresholds will be reported. A clinically meaningful threshold is defined as a decrease of 7 points in the Haem-A-QoL total score (Wyrwich et al., 2015), 5 points in the Haemo-QoL-SF total score (Santagostino et al., 2014) and 10 points for physical health.

A descriptive summary of each of the scale will be produced, in which the domain score at each visit and the associated change from baseline will be summarized. Paired t-tests will be performed on the change from baseline to 6months for the scales.

Note: before calculation the scale and total score, several items need to be reverse scored. The reverse scoring for those items is as follows: (1=5), (2=4), (3=3), (4=2), and (5=1). Any (0) will be recoded as missing data for the purposes of scale scoring. For details see Appendix 3: HRQoL QUESTIONNAIRES

4.6.3 EQ-5D-5L

The EQ-5D-5L Questionnaire is a health utility measure to assess patients' health status using 5 dimensions. All five dimensions can be combined in a five-digit number which then describes the patient's health state. This descriptive number is converted to a single summary index utility score by using published weights; in this study we use the UK crosswalk value set (as published by the EuroQol Research Foundation at http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d).

Additionally, in the second part of the questionnaire, the current health status is measured by the visual analog scale VAS with values ranging from 0 to 100.

The number and percentage of patients who complete the EQ-5D-5L will be summarized at each scheduled time point. The compliance rate (see section 4.6.2) will be plotted over time. For each of the EQ-5D-5L assessments over time, the number and percentage of patients in each of the five categories for each question will be evaluated. A summary of the EQ-5D-5L index utility score at each visit and the associated change from baseline will

also be provided. The summary statistics presented will include the mean, standard deviation, median, minimum, maximum and interquartile range. Corresponding mean (+95% CI) plots are provided.

In addition, summary statistics including mean, standard deviation, median, minimum, and maximum will be calculated according to the patients' health state using the EuroQoL visual analogue scale (EQ-VAS).

The change from baseline to Post-baseline will be analyzed using the paired t-test. The same outputs will be produced for the EQ-5D-5L VAS score.

The proportion of patients who report changes that exceed the clinically meaningful threshold on the EQ-5D-5L index and the EQ-VAS scores will be reported. A clinically meaningful improvement threshold is defined as a change of +0.07 points in the index utility score and +7 points in the VAS score.

For all completed assessments the five dimensions, the index utility score and VAS score is displayed in a separate listing.

4.6.4 Patient preference

Summary statistics on patient preference for the emicizumab regimen compared with the previous regimen used will be presented.

Preference survey, which is administered to patients at Month 3, consists in main questions:

- the first question is related to the treatment preference with 3 possible responses: (a) older hemophilia IV treatment prior to enrollment in the study; (b) new study drug SC emicizumab treatment; (c) no treatment preference.
- the second question, only asked to patients with a preference (responses a or b at first question), is related to factors influencing treatment preference (14 possible factors). For each factor, the patient should tick whether the factor is important and, if yes, provide an importance rank for the top 3 factors ("1" being the most important, "2" the second most important and "3" the third most important)

The number and percentage of patients who complete the Preference survey will be summarized.

Proportion of patients preferring the older hemophilia treatment, emicizumab, or without treatment preference will be computed along with 95% CIs (using the Pearson−Clopper one sample binomial method).

This defines two sub-populations of the "All patient population":

- The PREFSC population, which includes all the patients that responded: "Prefer the new study treatment (SC)"
- The PREFIV population, which includes all the patients that responded: "Prefer my old hemophilia treatment (IV)"

For patients who have a preference to either emicizumab or the old IV hemophilia treatment, the factors influencing the preference can be treated like ordered categorical variables as follow:

- Category 1 = “Most important”, when factor was ranked first among top factors
- Category 2 = “2nd most important”, when factor was ranked second among top factors
- Category 3 = “3rd most important”, when factor was ranked third among top factors
- Category 4 = “Influenced preference but not most important”, when factor was ticked but not ranked among top factors
- Category 5 = “Did not influence preference”, when factor was not ticked as important

Summaries of these categories will be produced by factor for the PREFSC and the PREFIV populations. Bar charts showing proportions of patient within each preference factors will also be produced for the PREFSC and the PREFIV populations:

4.6.5 Exploratory Efficacy Endpoints

Analysis on 12- and 24-week interval:

Additional analysis of the calculated ABR and the number of patients with zero bleeds will be performed for 12- and 24-week intervals on treated bleeds, all bleeds, treated spontaneous bleed, treated joint bleeds and treated target joint bleeds. The 12/24-week intervals are based on the start and end of the Efficacy Period. A patient has only as many 12/24-week intervals as fully fit into this period. E.g. if the duration of Efficacy Period is 98 days (=14 weeks) he has one full 12-week interval and no full 24-week interval. A bleed is assigned to a certain 12/24-week interval based on the distance between bleed date and start of efficacy period. If a bleed is after the end of the last full interval it is not taken into account.

The calculated ABR for a 12/24-week interval will be derived using the following formula which is based on the general formula:

$$\frac{\text{Number of bleeds during the 12 or 24 – week interval}}{\text{84 or 168 days}} \times 365.25$$

The calculated ABRs will be summarized and a graph for the 12- and 24-week intervals for all subjects will be provided. The table will include the mean with the 95% CI based on Exact Poisson, the median with the IQR and the minimum and maximum.

The number of subjects with zero bleeds within a 12- or 24-week interval will be summarized separately and a graph for all subjects will be provided. The table will include the number and percentage of the subjects with zero bleeds and the 95% CI using the Clopper-Pearson method.

The same analysis as described above may also be performed on 36-, 48-, 60- and 72- and 98-week interval if sufficient number of patients available.

4.6.6 Sensitivity Analyses

The sensitivity analyses will include different methods to define bleeds or eligible bleed data and different statistical models and will be applied to all efficacy endpoints defined in section 4.6.1.1.

Different ways to define bleeds or eligible bleed data:

- Include all bleeds recorded: without the 72-hour rule and “treated bleeds” but excluding bleed due to surgery and procedure
- Include only patients who received at least 12 weeks of emicizumab treatment, i.e. efficacy period ≥12 weeks
- Include only the first 24 weeks of efficacy period in the analysis. The calculated ABR is based on Bleeds that occurred before or on day 168 from efficacy period start. Withdrawals are included for the time they were followed for. The 24 weeks Efficacy Period ends 168 days after efficacy period start, the Cut-off date, the date of withdrawal or the end date of efficacy period 1, whichever comes first.

4.6.7 Subgroup Analyses

Descriptive summaries of both treated bleeds and all bleeds will be produced on the subgroups presented below. The summaries will include subgroup model based ABR (95% CI) and calculated mean ABR (95% CI).

The pre-specified subgroups are:

- Age at baseline: < 18, ≥ 18
- Age at baseline: < 65, ≥ 65
- Race: Asian, Black or African American, White, Other
- Number of bleeds during 24 weeks prior to study entry: <9, ≥ 9
- Number of target joints at baseline: no target joint, any target joint
- Hemophilia severity: mild, moderate, severe
- Previous treatment regimen: prior episodic, prior prophylactic (in case a subject have history of both prior episodic and prior prophylactic treatments, he will be considered as prophylactic)

Additional region- and/or country-specific analyses may be performed to support regulatory submission as needed.

4.6.8 Number of Days Hospitalized

The number of days of hospitalization, during the efficacy period, will be summarized.

4.7 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

PK analyses will be provided by clinical pharmacology.

For all patients, pre-dose (concentration at the end of the dosage interval [C_{trough}]) plasma concentrations of emicizumab will be presented descriptively for each timepoint. Data presented will include arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

4.8 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one pre-dose and one post-dose anti-emicizumab antibody assessment.
Immunogenicity summary tables will be restricted to the period before up-titration, if any, except if stated otherwise.

Patients treated with emicizumab may develop anti-therapeutic antibodies (ATA).

The proportion of all ATA positive patients will be summarized by visit and overall. The by visit summary includes positive/negative status directly from the data. For the overall summary the status is derived as described below.

Overall ATA positivity/negativity to be reported in 4 categories:

- NEGATIVE
  - ✓ patient negative at baseline and negative after treatment start

- NEGATIVE (TREATMENT UNAFFECTED)
  - ✓ patient positive at baseline and negative after treatment start
  - ✓ treatment unaffected (negativity after baseline) defined as a maximum post-baseline titer lower than patient's baseline titer multiplied by 4

- POSITIVE (TREATMENT BOOSTED)
  - ✓ patient positive at baseline and positive after treatment start
  - ✓ treatment boosting (positivity after baseline) defined as a maximum post-baseline titer increase greater or equal to patient's baseline titer multiplied by 4

- POSITIVE (TREATMENT INDUCED)
  - ✓ patient negative at baseline and positive after treatment start

A patient is considered positive if a titer value > 0 is reported. As soon as a patient fulfils the criteria of positivity at one post baseline time point, the patient is counted as positive, i.e., a negative patient has a negative result at all timepoints.

The relationship between ATA (anti-emicizumab antibodies) and safety, efficacy, and/or PK may be analyzed and reported descriptively via subgroup analyses.

Note: The summaries will be provided separately for up-titrated patients and the overall status is defined separately by dose. The baseline is the original baseline and not the baseline just before up-titration.

4.9 SAFETY ANALYSES

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

For all safety analyses, the summary tables will include data up to the up-titration (if any) only, except if specified otherwise.

4.9.1 Exposure of Study Medication

In addition, as part of the safety evaluation, additional assessments will be summarized descriptively as follows:

- Cumulative study medication doses, dose modifications (delays and interruptions), and duration of exposure (continuous and categorized)
- Administration injection site (listed only)
- Patients with up-titrated dose.
- Dose intensity (compliance with respect to emicizumab intake: planned vs. received), for initial and maintenance phases separately

A dose is considered to be missed if there is an interval of >10 days between two doses. A patient who received < 90% or >110% of the planned dose is considered to have received a lower or higher dose than the planned dose, respectively. The planned dose is calculated using the last patient's weight before or at the day of the emicizumab injection and the dose per kilogram according to protocol.

The emicizumab dose is reported by the patient in ml. In order to convert the ml entered by the patient to mg, the following formula should be applied:

$$x\ ml\ \times 150 \frac{mg}{ml} = y\ mg\ of\ emicizumab$$

4.9.1.1 Administration problems

The number and proportion of patients experiencing problems with emicizumab administration at Week 1 will be provided. Details of problems will also be summarized.

4.9.1.2 Exposure to Anti-coagulant factors by bleed

The number of infusions is counted per bleed corresponding to the definition of treated bleed, i.e. all treatments that are linked to the same bleed per the 72h rule are considered to belong to the same bleed. If the same treatment/s are associated with multiple bleeds, these are counted multiple times, i.e. linked to both bleeds.
The treatments are summarized separately for bleeds which were treated with an individual coagulation factors or combinations. In addition the outputs will include a total column which includes all the data for the Prothrombin Complex Concentrate or Recombinant Factor VIIa (only and both combined). That is, the n in this analysis is the number of treated bleeds and not the number of patients. The exposure (dose/kg) by bleed is summarized by using descriptive statistics and categorically: Prothrombin Complex Concentrate (U/kg/bleed: <50, 50-100, 101-150, >150) and Recombinant Factor VIIa (ug/kg/bleed: <90, 90-180, 181-270, >270).The duration of treatment per bleed is summarized: 1, 2, 3, 4, >4. Duration of treatment per bleed is defined as time from the first to the last dose per bleed.

4.9.2 Adverse Events

Definitions of adverse events can be found in the CSP in section 5.2.

The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with congenital hemophilia A who

have persistent inhibitors against FVIII at enrollment. Of primary interest in this study are the incidence and severity of all adverse events, including thromboembolic events, microangiopathic hemolytic anemia or TMA, systemic hypersensitivity, anaphylaxis, and anaphylactoid events.

Overall summaries of adverse events, serious adverse events and local injection site reactions will be presented by the number and percentage of patients having any event, having a related event, having an event leading to modification/interruption of study treatment, having an event leading to discontinuation from study, having an event leading to study treatment withdrawal, having an AESI, having a fatal AE, having grade 3 and above event. The overall number of events will also be presented.
The incidence of AEs, SAEs, AEs grade 3 and above, AEs related to study treatment, SAEs related to study treatment, AEs leading to modification/interruption of study treatment, AEs leading to discontinuation of study, AESIs, local ISRs by injection and by highest grade, fatal AEs, AEs occurring immediately after injection and AEs occurring within 24 hours after injection will be summarized. The incidence of AEs will also be summarized by highest grade.

A patient with more than one occurrence of the same adverse event in a particular System-Organ Class (SOC) or adverse event category will be counted only once in the total of those experiencing adverse events in that particular SOC or adverse event category. Any missing severity, causality, or outcome will not be imputed and classed as unknown.

Patients who died will be listed together with the cause of death.

All other information collected (e.g. action taken) will be listed as appropriate.

Only treatment emergent adverse events (starting on or after exposure to study treatment) starting on or before the end of the reporting period will be included in summaries. To define if an AE is treatment-emergent, only the date of the AE will be used (not the time). The end of the reporting period is defined as the end of the 2-year treatment period, for patients who completed the treatment, and as 24 weeks after the last dose of study treatment or 2 years after the first dose of study treatment, whichever occurs first, for patients who early discontinued from treatment. Non-treatment emergent events and AEs starting after the reporting period will be included in the patient listings and flagged but not included in the above summaries. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

In addition, AEs which start during follow up will be summarized in a separate single table.

Confirmed and suspected COVID-19 AEs will be listed, as well as AEs associated with COVID-19 (i.e. confirmed/suspected COVID-19 AEs and AEs with onset from -7 days to +30 days from the start of a confirmed COVID-19 AE).

Notes:

Tables presented will contain both counts of patients and events (at SOC level only). Patients who have multiple events in the same system organ class and preferred term will be counted only once in the patient counts.

AEs will be coded using MedDRA. The version of the dictionary used will be updated throughout the study.

In addition, a summary of non-serious AEs occurring in 5% or more of patients will be provided (for Disclosure purposes).

Adverse event rate per 100 patient-years

Adverse events per patient years will be calculated for all grade AEs, SAEs, grade ≥3 AEs, TMA, thromboembolic events (TE) and TMA+TE combined. For each category of events, multiple occurrences of the same event (Preferred term) in the same patient will be counted multiple times.

The adverse event rate per 100 patient-years is computed as follows:
AE Rate = (Number of AEs observed/ Total patient-years at risk) * 100

Total patient years is computed as follows:

Total patient-years at risk is the sum over patients of the time intervals (in years) between start of study therapy (study day 1) and the end of follow up or up to the cutoff whichever is earlier. This approach assumes that during an adverse event, patients remain at risk for additional events.

The 95% confidence interval for the event rate is calculated using the following method. Assume that we observe Y events over a total of T person-years at risk.
Exact confidence interval:
If chisq(p,df) is the quantile of the upper tail probability of the $\chi 2$ distribution on df degrees of freedom, then the lower and upper bounds (LB, UB) of the exact $(1 - \alpha/2)$ level interval are given by:
$LB = \text{chisq}(p = \alpha/2, df = 2\,Y)/(2T)$
$UB = \text{chisq}[p = 1 - \alpha/2, df = 2(Y + 1)]/(2T)$

Details on AE reporting

A flag will indicate to which study phase an AE belongs to: before therapy, treatment period (initial treatment 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC) up-titration period, or follow up (general section 4.1).

All treated patients will be analyzed by descriptive summaries of the AEs by SOC mapped term (by descending frequency) and by Preferred Term (PT) (by descending frequency).

Multiple occurrences of the same AE (by PT) per subject are counted only once unless defined otherwise, this also applies for Bleeds which are reported as SAE. For Total number of Events multiple occurrences of the same AE on an individual are counted separately. Symptoms of Injection Site Reactions are summarized separately. For some specific adverse event types, an additional table will display instances where multiple occurrences of the same AE in the same patient are all counted (for Disclosure purposes).

A listing of AEs will be generated for patients with at least one up-titration. If at least 10 patients are up-titrated then a summary table will be produced on the period after up-titration.

A standard summary table is produced for AEs falling into SMQ-hemorrhage (wide).

4.9.2.1 Adverse events of special interest

Adverse Events of Special Interest (AESI) are defined as cases of:

1. Potential drug-induced liver injuries
2. Suspected transmission of an infectious agent by the study drug
3. Systemic hypersensitivity or anaphylactic or anaphylactoid reactions,
4. Thromboembolic events search.
5. TMA events

Notes:
The AESI categories and preferred terms to be summarised will be identified from the project level list which covers the categories defined for this study, if applicable; or based on the investigator's judgement as collected in the eCRF otherwise.

In addition, potential drug-induced liver injuries will have to meet the Hy's Law criteria, based on laboratory results:

- ALT or AST > 3 × baseline

and

- Total bilirubin > 2 × ULN (of which ≥35% is direct bilirubin)

4.9.3 Deaths

Deaths are AEs with fatal outcomes and will be presented separately as described in section 4.9.2.

4.9.4 Surgeries

Surgeries and procedures during study conduct, collected on the eCRF page for "On-study Surgery and Related Hemophilia Medication Log", will be summarized in a frequency table, for the safety population.

In addition, the following analyses will be conducted on the Surgery population, for minor and major surgeries separately, and by surgery category (arthroplasty / CVADs / dental / joint / other).

Surgeries and procedures during study conduct will be summarized by PT.

Surgeries and procedures during study conduct, as well as hemophilia medications related to these surgeries (as collected on the BMQ) and occurrence of post-operative bleeds (treated and untreated), i.e. bleeds caused by a surgery or procedure, will be summarized. The surgery leading to a post-operative bleed will be identified as the last on-study surgery on or prior the start of the post-operative bleed.

The duration of exposure to emicizumab (in days) prior to the start of the surgery will be summarized.
The cumulative dose (dose/kg) of prophylactic hemophilia medications received by surgery, as well as the number of injections by surgery, will be summarized for each hemophilia medication separately. In the same manner, the number of infusions per post-operative bleed, the cumulative dose (dose/kg) by bleed and the duration of treatment (in days) will be summarized, for each hemophilia medication separately.

All on-study surgeries and prophylactic hemophilia medications as collected in the BMQ will be listed together. In addition, all on-study surgeries and prophylactic hemophilia medications as collected on the eCRF page for "Related Hemophilia Medications" will also be listed together.
An additional listing on post-operative bleeds and corresponding treatment for bleed will also be provided.

4.9.5 Laboratory Data

A detailed list of the laboratory parameters can be found in the CSP in section 4.5.6.

Laboratory parameters (hematology and chemistry) will be presented in shift tables of WHO toxicity grade at baseline versus worst grade post-baseline. Low/normal/high categories derived from investigator normal ranges will be listed. The reporting unit of laboratory values are SI units.

Selected laboratory parameters will be summarized in terms of mean, standard deviation, minimum, and maximum.

In calculating change from baseline at any scheduled Visit, only patients with non-missing values at both baseline and that Visit are included. All available data (i.e., scheduled and unscheduled assessments) are, however, used in identifying abnormalities in shift tables.

The laboratory data will be summarized in the following ways:
1) Summary statistics over time
2) Shift tables – this method requires the following;
   a) type of categorization: WHO
   b) time intervals of the shift defined – "shift from baseline" and "shift to worst value during treatment" intervals;
   c) the worst assessment per laboratory parameter is selected per time interval, separately for hypo and hyper. Note, the worst assessment does not have to be unique as the table includes only the grade of the worst assessment.
3) Plots:
   a) Mean Plots of Laboratory Parameters including 95% CI (Hematology and Biochemistry)

   CI interval should be calculated only for time points where there is data for at least 10 patients

Derived parameters
1) Creatinine Clearance

The creatinine clearance will be derived based on the Cockcroft-Gault formula unadjusted and adjusted for body surface area (BSA). Both formulas are given below.

Unadjusted Cockcroft-Gault formula:

$$C_{CR}\ [ml/min] = \frac{(140 - Age\ [years]) \times Weight\ [kg] xF}{0.8143 \times Creatinine\ [umol/l]}$$

where F=1 for male subjects and F=0.85 for female subjects

BSA-adjusted Cockcroft-Gault formula:

$$C_{CR-adj}\ [ml/min] = C_{CR}[ml/min] \times \frac{1.73\ [m^2]}{BSA\ [m^2]}$$

2) Total Neutrophils

Total Neutrophils are derived as the sum of segmented and band Neutrophils. If one of the parameters is missing, it is assumed to be zero. Following this derivation, if there is more than one result per timepoint, the earliest record will be kept. If more than one result is at the same time, the smallest result is kept. In case the total neutrophils are reported together with the segmented and the bands, no calculation will be done and the total neutrophils are used.

3) Corrected Calcium

Corrected Calcium is derived using the following formula:

$$CA_{corr}\ [mmol/l] = Serum\ Calcium\ [mmol/l] + 0.02 \times (40\ [g/l] - Albumin\ [g/l])$$

4.9.6 Vital Signs

Vital signs will include measurement of body temperature (oral, rectal, axillary, or tympanic), heart and respiratory rates, blood pressure and weight. Height will be only measured at selected visits. Vital signs data together with their change from baseline will be summarized descriptively over time.

4.10 BIOMARKER

Data from pharmacodynamics (PD), safety biomarker, safety coagulation system biomarker will be analyzed descriptively with summaries over time. Summary statistics, will include arithmetic and geometric means (if appropriate), median, range, and standard deviations.

At least the following safety biomarkers, safety coagulation system biomarkers, and PD biomarker will be analyzed:

Table 2: List of analyzed biomarkers

Factor VIII Inhibitor, chromogenic	CBU
Factor VIII Activity, chromogenic	U/dL
Activated Partial Thromboplastin Time	sec
D-Dimer	ug/mL (FEU)
Factor IX,concentration	ug/mL
Factor X,concentration	ug/mL
Prothrombin fragment 1+2	ng/mL
Prothrombin INR	Fraction of 1
Fibrinogen	g/L

All parameters are quantitative

Outputs to be produced for selected biomarkers and FVIII inhibitor titer are as follows (Table 3: List of outputs to be generated for biomarkers and FVIII inhibitor titers). Additional detail for each lab parameter is provided below.

Table 3: List of outputs to be generated for biomarkers and FVIII inhibitor titers

Output	FIX Antigen	FX Antigen	FVIII Inhibi-tor titer	Pro-thrombin INR	D-dimer	aPTT (not diluted)	Reported FVIII Activity	Pro-thrombin fragment	Fibri-nogen
Biomarker Test Results and Change from Baseline by Visit	X	X	X	X	X	X	X	X	X
Plot of Mean and Individual <Biomarker> over Time by Treatment Group	X	X		X		X	X		
Plot of Median and Individual <Biomarker> over Time by Treatment Group			X		X			X	X
Categorical summary over time				X					
Listing	X	X	X	X	X	X	X	X	X

The following specific data handling rules are used in plots and descriptive summaries. Listings will include the original values.

- FVIII activity: for any value reported as <1% use 0.5 (LLOQ/2)
- D-dimer: for any value reported as <0.36 use 0.18 (LLOQ/2)
- aPTT: for any value reported as >255 exclude from analysis and add footnote "If clotting not detected, the sample is excluded from the analysis"

The bone and joint biomarkers may be analyzed later and presented in a separate report.

4.11 MISSING DATA

The following rules will be used to impute missing data:

- In order to implement the 72-hour rule, it is assumed that the bleeds and treatments with missing time occurred at 12:00 (noon).
- If, on a given day, the treatment time is partial and the bleed time complete, the partial time is assumed to be the same as the complete time. In case of multiple events per day, the last complete time is used.
- All bleeds with an anatomical location in a joint are considered joint bleeds
- All bleeds with missing cause are included as spontaneous bleeds
- If a bleed which was entered through the hand held device was edited through a Data Clarification Process (bleed type changed from other/muscle to joint), it is possible to leave the symptoms unanswered. In this case, the bleed should count as a joint bleed.

See also endpoint definitions for specific data handling rules.

4.12 INTERIM ANALYSES

Owing to the long-term nature of this study, two interim analyses will be conducted in order to obtain accurate information on the safety, efficacy, immunogenicity, and PK of prophylactic emicizumab at specific points throughout the study. The first analysis will be performed once approximately 100 patients have received treatment with emicizumab for at least 24 weeks. A second analysis will be performed when approximately 100 patients have received treatment with emicizumab for at least 52 weeks. The data from these analyses will subsequently be presented to the iDMC in order to enable them to effectively monitor the study.

5. REFERENCES

Acharya SS. Rare bleeding disorders in children: identification and primary care management. Pediatrics 2013;132:882–92.

Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost 2014;12:1935–9.

Bullinger M, Von Mackensen S, Fischer K, et al. Pilot testing of the “Haemo-QoL” quality of life questionnaire for haemophiliac children in six European countries. Haemophilia 2002;8 (suppl 2):47–54.

CDC. Centers for Disease Control and Prevention: Hemophilia Data & Statistics. Available from: https://www.cdc.gov/ncbddd/hemophilia/data.html. Last accessed: 17 August 2016

Franchini M, Mannucci PM. Hemophilia A in the third millennium. Blood Rev 2013;27:179–84.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Mackensen SV, Gringeri A. Quality of life in hemophilia. In: Preedy VR, Watson RR, editors. Handbook of disease burdens and quality of life measures. New York: Springer, 2010:1895–920.

Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood 2014;123:317–25.

NIH. National Institutes of Health: National Heart, Lung, and Blood Institute. What Is Hemophilia? Available from: http://www.nhlbi.nih.gov/health/health-topics/topics/hemophilia. Last accessed: 17 August 2016

Pollak E, Mühlan H, Von Mackensen S, Bullinger M. The Haemo-QoL Index: developing a short measure for health-related quality of life assessment in children and adolescents with haemophilia. Haemophilia 2006;12:384–92.

Santagostino E, Morfini M, Auerswald GK-H, et al. Paediatric haemophilia with inhibitors: existing management options, treatment gaps and unmet needs. Haemophilia

Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013;19:e1–47.

Von Mackensen S, Bullinger M. Development and testing of an instrument to assess the quality of life of children with haemophilia in europe (haemo-qol). Haemophilia 2004;10 (suppl 1):17–25.

Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. Ther Adv Hematol 2013;4:59–72.

World Federation of Hemophilia. Annual Global Survey Data 2014. Available from: http://www1.wfh.org/GlobalSurvey/Public_AGS/AGS_Patients_Severity_EN.aspx. Last accessed: 16 August 2016

Wyrwich KW, Krishnan S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. Haemophilia 2015;21:578–84.

APPENDIX 1: PROTOCOL SYNOPSIS

TITLE:	**A SINGLE-ARM, MULTICENTER PHASE IIIB CLINICAL TRIAL TO EVALUATE THE SAFETY AND TOLERABILITY OF PROPHYLACTIC EMICIZUMAB IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	MO39129
VERSION NUMBER:	3
EUDRACT NUMBER:	2016-004366-25
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	IIIb
INDICATION:	Hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety and tolerability of emicizumab in patients with hemophilia A who have persistent inhibitors against Factor VIII (FVIII) at enrolment. Specific objectives and corresponding endpoints for the study are outlined below (Table 1).

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Objective:	
□ To evaluate the overall safety and tolerability of prophylactic administration of emicizumab	□ Incidence and severity of adverse events, including thromboembolic, thrombotic events, microangiopathic hemolytic anemia or microangiopathy (TMA), systemic hypersensitivity, anaphylaxis, and anaphylactoid events □ Changes in physical examination findings, vital signs, and laboratory parameters
Secondary Objective:	
□ To evaluate the efficacy of prophylactic administration of emicizumab	□ To evaluate the efficacy of prophylactic administration of emicizumab on the basis of the number of bleeds over time □ To evaluate the HRQoL of patients according to Haem-A-QoL (≥18 y) or Haemo-QoL-SF (ages 12−17) scores over time □ To evaluate the health status of patients according to EQ-5D-5L scores over time □ To assess patient preference for the emicizumab regimen compared with the previous regimen used
Immunogenicity Objective:	
□ To evaluate the immuno-genicity of emicizumab	□ To assess the incidence and clinical significance of anti-emicizumab antibodies
PK Objective:	

 To obtain emicizumab PK data

 To obtain PK data for emicizumab at defined timepoints

EQ-5D-5L=EuroQoL Five-Dimension-Five Levels Questionnaire; Haem-A-QoL=Hemophilia Adult Quality of Life Questionnaire; Haemo-QoL-SF=Hemophilia Quality of Life Short Form; HRQoL=Health-Related Quality of Life; PK=pharmacokinetic; TMA=thrombotic microangiopathy

Study Design

Description of Study

This single-arm, multicenter, open label, Phase IIIb clinical study will enroll patients aged 12 years or older with congenital hemophilia A who have persistent inhibitors against FVIII at enrollment. Approximately 200 patients with inhibitors will be enrolled globally. Patients will receive prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period.

The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with congenital hemophilia A who have persistent inhibitors against FVIII at enrollment. In order to achieve this objective, all adverse events, including adverse events of special interest, will be captured on an ongoing basis, as they occur during the study. Physical examinations, vital signs, and laboratory values will be assessed as per the schedule of activities (Protocol Appendix 1).

The secondary objective of this study is to evaluate the efficacy of prophylactic administration of emicizumab. As part of this objective, the number of bleeds over time will be recorded for all of the enrolled patients.

The final analysis will be conducted when all patients have completed 2 years of treatment or have withdrawn, whichever occurs sooner. Patients, or their legally authorized representative, will be asked to report bleed information on an electronic patient-reported outcome (ePRO) device where possible, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. Health-Related Quality of Life (HRQoL) will be assessed and the EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) will be completed prior to the first emicizumab administration (Week 1), at the Month 3, 6, 12, and 18 assessments, and at study completion as outlined in the schedule of activities (Protocol Appendix 1). Additional secondary endpoints include assessing patient preference for the emicizumab regimen compared with the previous regimen using a questionnaire (EmiPref).

Immunogenicity will be monitored by incidence and clinical significance of antibodies to emicizumab. In addition, pharmacokinetic (PK) data for emicizumab will be obtained at defined timepoints as per the schedule of activities (Protocol Appendix 1).

Drugs intended to control breakthrough bleeds (e.g. rFVII, FVIII, activated prothrombin complex concentrate [aPCC]) or bleeds during surgeries should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase the patient's coagulation potential, the doses required to achieve hemostasis may be lower than doses used prior to starting emicizumab. Investigators shall discuss at the start of the study with patients recommended doses of any additional coagulation factors used, following the guidance below.

The use of aPCC for breakthrough bleed treatment for patients on emicizumab should be avoided if possible, and recombinant activated human Factor VII (rFVIIa) should be the first option used to treat, starting with no more than 90 µg/kg as an initial dose. If aPCC needs to be used, no more than 50 IU/kg should be administered as an initial dose and doses of > 100 U/kg/24 hours or more should be avoided, as cases of TMA and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours aPCC was administered for 24 hours or more.

Investigators should provide or remind patients of the exact dose and schedule of bypassing agents or FVIII required to treat any bleed.

When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information on an ePRO device where possible, including site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed (e.g., other than emicizumab in case of breakthrough bleeds). The reason for the use of rFVIIa will be documented (e.g., bleeding, preventative dose before activity). Thorough documentation of the treatments for bleeds and/or surgeries will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. Local and central laboratory assessments are required to monitor the risk for thromboembolic events or microangiopathic hemolytic anemia or TMA, as per the schedule of activities (Protocol Appendix 1), if bypassing agents are used to treat a breakthrough bleed.

Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of emicizumab in order to discuss a potential increase in emicizumab dose to 3 mg/kg/week and additional laboratory evaluations (e.g., coagulation tests), as well as to re-evaluate the patient's individual benefit-risk for continuing treatment.

An independent Data Monitoring Committee (iDMC) will be responsible for monitoring safety throughout the duration of the study.

Number of Patients
This global study will enroll approximately 200 patients with congenital hemophilia A who have persistent inhibitors against FVIII at enrollment. The patients are expected to be enrolled at approximately 85 sites globally.

Target Population
Inclusion Criteria
Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. As per the investigator's judgement, a willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the patient-reported outcome (PRO) questionnaires and bleed diaries through the use of an electronic device or paper
3. Aged 12 years or older at the time of informed consent
4. Diagnosis of congenital hemophilia A with persistent inhibitors against FVIII
5. Documented treatment with bypassing agents or FVIII concentrates in the last 6 months (on-demand or prophylaxis). Prophylaxis needs to be discontinued the latest by a day before starting emicizumab
6. Adequate hematologic function, defined as platelet count ≥100,000/μL and hemoglobin ≥8 g/dL (≥4.97 mmol/L) at the time of screening
7. Adequate hepatic function, defined as total bilirubin ≤1.5 × the upper limit of normal (ULN) (excluding Gilbert's syndrome) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 ×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
8. Adequate renal function, defined as serum creatinine ≤2.5 × ULN and creatinine clearance by Cockcroft-Gault formula ≥30 mL/min
9. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method with a failure rate of <1% per year during the treatment period and for at least five elimination half-lives (24 weeks) after the last dose of emicizumab:
    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12

continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)

- Examples of highly effective contraceptive methods with a failure rate of <1% per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of <1% per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

1. Inherited or acquired bleeding disorder other than hemophilia A
2. Ongoing (or plan to receive during the study) immune tolerance induction (ITI) therapy (prophylaxis regimens with FVIII and/or bypassing agents must be discontinued prior to enrollment). Patients receiving ITI therapy will be eligible following the completion of a 72-hour washout period prior to the first emicizumab administration
3. History of illicit drug or alcohol abuse within 12 months prior to screening, as per the investigator's judgment
4. High risk for TMA (e.g., have a previous medical or family history of TMA), as per the investigator's judgment
5. Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or current signs of thromboembolic disease
6. Other conditions (e.g., certain autoimmune diseases) that may increase the risk of bleeding or thrombosis
7. History of a clinically significant hypersensitivity reaction associated with monoclonal antibody therapies or components of the emicizumab injection
8. Known human immunodeficiency virus (HIV) infection with CD4 count <200 cells/µL within 6 months prior to screening
9. Use of systemic immunomodulators (e.g., interferon or rituximab) at enrollment or planned use during the study, with the exception of antiretroviral therapy
10. Concurrent disease, treatment, or abnormality in clinical laboratory tests 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
11. Receipt of:
    - Emicizumab in a prior investigational study
    - An investigational drug to treat or reduce the risk of hemophilic bleeds within five half-lives of last drug administration
    - A non-hemophilia-related investigational drug within last 30 days or five half-lives, whichever is shorter
    - Any concurrent investigational drug.
12. Pregnancy or lactation, or intent to become pregnant during the study

13. Positive serum pregnancy test result within 7 days prior to initiation of emicizumab (females only)

End of Study and Length of Study
The approximate length of the entire study from the first patient enrolled to the last patient, last visit (LPLV; see below) is approximately 3 years. For each individual patient, the study is expected to last approximately 2 years (patients will receive 3 mg/kg/week emicizumab for the first 4 weeks followed by 1.5 mg/kg/week emicizumab for the remainder of the 2-year treatment period). Patients who discontinue emicizumab prior to the completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first.

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., LPLV). The study will end when all patients have been treated with emicizumab for 2 years, or earlier, if one of the following is documented:

Withdrawal of consent
OR
Completed the Safety Follow-up Visit 24 weeks after discontinuing emicizumab
OR
Lost to follow-up
OR
Death.

Investigational Medicinal Products
Test Product (Investigational Drug)
Emicizumab will be administered at a dose of 3 mg/kg/week subcutaneously for 4 weeks when initiating treatment, followed by 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period. There will be an option to increase the dose to 3 mg/kg/week in cases of insufficient control of bleeds on the 1.5 mg/kg/week emicizumab dose. If the investigator believes that a specific patient warrants dose up-titration following the occurrence of, for example, at least two spontaneous bleeds, significant bleeds, or a traumatic bleed out of proportion to the degree of injury, they must discuss the case with the Medical Monitor for consideration and potential approval.

To support home administration of the drug, patients/caregivers will be required to complete in-person, instructional training on how to administer emicizumab as a subcutaneous (SC) injection. Patients/caregivers will be taught to perform the injections utilizing the Instructions for Use document. In addition, the healthcare provider (HCP) is to inform the patient/caregiver of the volumetric dose to be administered and the dosing frequency. The patients/caregivers will observe at least one SC injection performed by a HCP and will need to successfully administer at least one SC injection under an HCP's supervision prior to starting home administration. The patient/caregiver will also have the opportunity to ask any questions to the HCP before starting home administration. The first three weekly treatments will be administered in a monitored setting, such as an infusion center, clinic, or hospital, in conjunction with emicizumab PK and pharmacodynamic (PD) assessments. Patients will be observed for a minimum of 60 minutes after the first three doses. Patients/caregivers will be instructed on how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. Each site will have the discretion to provide additional training or include additional observation (e.g., after the third or fifth doses), if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject emicizumab, a trained and proficient caregiver or HCP should be identified to administer the SC injections. Patients/caregivers will be provided with contact information for the clinic in case they have questions related to self-administration between visits.

Compliance in the home setting is to be monitored at each site by reviewing reported hemophilia medication use and recording collected used and unused vials.

Statistical Methods

Primary Safety Analyses

The primary objective of this study is to evaluate the overall safety and tolerability of prophylactic administration of emicizumab in patients with congenital hemophilia A who have persistent inhibitors against FVIII at enrollment. Of primary interest in this study are the incidence and severity of all adverse events, including thromboembolic events, microangiopathic hemolytic anemia or TMA, systemic hypersensitivity, anaphylaxis, and anaphylactoid events.

All adverse events will be assessed according to the World Health Organization (WHO) toxicity grading scale. The incidence, type, and grade of adverse events will be summarized according to the primary system-organ class (SOC) and, within each SOC, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. For each adverse event, data will be provided on the timing (start and stop date, time of onset in comparison with last dose of emicizumab received, and doses of emicizumab received), severity, relationship to emicizumab, outcome, and effect on therapy. The data may be presented together with two-sided 95% Clopper-Pearson confidence intervals (CIs) if appropriate.

In addition, as part of the safety evaluation, additional assessments will be summarized descriptively as follows:

1. Cumulative emicizumab doses, dose modifications (delays and interruptions), and duration of exposure
2. Compliance with respect to emicizumab intake (planned vs. received)
3. Changes from baseline in physical examination findings
4. Vital signs over time:
    - Vital signs will be analyzed using descriptive statistics for continuous variables and presented graphically over time with associated 95% CIs.
5. Laboratory parameters (hematology and chemistry):
    - These parameters will be presented in shift tables of WHO toxicity grade at baseline versus worst grade during the treatment period. Selected laboratory parameters will be summarized in terms of mean, standard deviation, minimum, and maximum. Laboratory parameters will also be presented graphically over time.

All safety variables will be analyzed for the safety population. For each variable, the number of available observations will be reported. The safety population includes all patients who have received at least one dose of emicizumab.

The primary safety analysis will occur at the end of the study.

The iDMC will evaluate the study data, including the emerging safety results, at periodic reviews and recommend to the Sponsor whether the study should be stopped early. All summaries and analyses will be prepared by the SMT statistician and presented for iDMC review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

A detailed description of the statistical methods that will be used for the primary and secondary analyses will be provided in the Statistical Analysis Plan (SAP).

Determination of Sample Size

A sample size of approximately 200 patients is planned for this study.
For the purpose of the sample size calculation, the incidence of adverse events was chosen as the safety endpoint of primary interest.

If the observed incidence of adverse events is between 2.5% and 15%, the precision for the estimated incidence rate is presented below according to the 95% Clopper-Pearson CIs (Table 2).

Table 2 Clopper-Pearson 95% CIs for the Incidence of AEs (Based on N=200)

Number of AE Events (Observed AE Incidence)	95% Clopper-Pearson CIs
5 (2.5%)	0.8%–5.7%
10 (5.0%)	2.4%–9.0%
20 (10.0%)	6.2%–15.0%
30 (15.0%)	10.4%–20.7%

Interim Analyses

The first analysis will be performed once approximately 100 patients have received treatment with emicizumab for at least 24 weeks. A second analysis will be performed when 100 patients have received treatment with emicizumab for at least 52 weeks. The data from these analyses will subsequently be presented to an iDMC in order to enable them to effectively monitor the study. Details regarding the planned interim analyses will be provided in the SAP and iDMC charter.

APPENDIX 2: SCHEDULE OF ACTIVITIES

	Screening	Treatment												Early Termination / Study Completion	Safety Follow-up Visit [a]
Visits	**Wk -4 to Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**3 m**	**6 m**	**9 m**	**12 m**	**15 m [b]**	**18 m**	**21 m [b]**	**Unscheduled visit**	**2 years**	
Time Window, days			**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**	**± 14**	**± 30**	**± 30**		**± 30**	
Informed consent [c]	x														
Inclusion / exclusion criteria	x														
Medical history and demographics [d]	x														
Physical examination [e]	x	x	x	x	x	x	x	x	x		x		x	x	x
Vital signs [f]	x	x	x	x	x	x	x	x	x		x		x	x	x
Concomitant medications [g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology and blood chemistry [h,r]	x	x	x	x	x	x	x	x	x		x		x	x	x
Pregnancy test [i,r]	x	x			x	x	x	x	x		x		x	x	
HIV and hepatitis serology [j]	x														
Anti-FVIII antibodies [k,r]		x			x	x	x		x		x			x	x

	Screening	Treatment												Early Termination / Study Completion	Safety Follow-up Visit [a]
Visits	**Wk -4 to Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**3 m**	**6 m**	**9 m**	**12 m**	**15 m [b]**	**18 m**	**21 m [b]**	**Unscheduled visit**	**2 years**	
Time Window, days			**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**	**± 14**	**± 30**	**± 30**		**± 30**	
Anti-emicizumab antibodies [l,r]		x			x	x	x		x		x			x	x
ePRO bleed / medication recording [m]		x	x	x	x	x	x	x	x	x	x	x	x	x	
Surgical events [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Management of emicizumab [p]		x	x	x	x	x	x	x	x	x	x	x	x	x	
HRQoL [q]		x				x	x		x		x			x	
Health status (EQ-5D-5L) [q]		x				x	x		x		x			x	
Treatment preference questionnaire (EmiPref) [r]						x									
PK assessment [s,t]		x	x	x	x	x	x		x		x			x	x
Safety biomarkers assessment [s,u]		x			x	x	x		x		x			x	x
Safety coagulation system biomarkers assessment [s,v]		x			x										

	Screening	Treatment												Early Termination / Study Completion	Safety Follow-up Visit [a]
Visits	**Wk -4 to Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 5**	**3 m**	**6 m**	**9 m**	**12 m**	**15 m [b]**	**18 m**	**21 m [b]**	**Unscheduled visit**	**2 years**	
Time Window, days			± 2	± 2	± 2	± 7	± 7	± 7	± 14	± 14	± 30	± 30		± 30	
PD biomarkers assessment [s,w]		x			x	x	x		x		x			x	
Bone and joint biomarker assessment (fasting) [s,x]		x					x				x			x	
Additional laboratory assessments [y]		For breakthrough bleeds treated with bypassing agents													
Emicizumab administration		Weekly subcutaneous injection													

d=day; eCRF=electronic Case Report Form; EQ-5D-5L=EuroQoL Five-Dimension-Five Levels Questionnaire; FVIII=Factor VIII; Haem-A-QoL=Hemophilia Adult Quality of Life Questionnaire; Haemo-QoL-SF=Hemophilia Quality of Life Short Form; HIV=human immunodeficiency virus; HRQoL=Health-Related Quality of Life; m=months (based on calendar months); PD=pharmacodynamic; PK=pharmacokinetic; Wk=week

Notes: the maximum allowable time between Screening and enrollment is 4 weeks; if the elapsed time between Screening and enrollment is more than 4 weeks, Screening must be repeated.

Except for the bleed/medication records, all other patient data will be collected during clinic visits.

a. Patients who discontinue emicizumab prior to the completion of the 2-year treatment period will undergo a Safety Follow-up Visit 24 weeks after the patient's last emicizumab dose or at 2 years after emicizumab treatment start, whichever occurs first.

b. Optional visits, as per the investigator's discretion.

c. **Written informed consent** must be obtained before any study-specific screening tests or evaluations are performed. For adolescents (i.e., patients who are 12−17 years of age), an Informed Assent Form will be completed instead. Parents or caregivers of adolescents will also complete an Informed Consent Form. The enrollment form will be completed after informed consent and/or assent is obtained. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.

d. **Medical history and demographics** data will be collected from patient medical records and documented in the eCRF. Medical history includes hemophilia-related history, clinically significant diseases, procedures (including prior surgeries), use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior ITI, anaphylaxis, or known thrombophilia. It should also include all medication taken in the 4 weeks prior to screening (including prescription drugs, over-the-counter drugs, and herbal/homeopathic remedies and therapies). Any hemostatic medications (e.g. bypassing agents) and other medications used to treat or prevent bleeds in the 6-month period prior to starting emicizumab treatment will also be collected. Demographic data will include age, sex, and self-reported race and ethnicity.

e. A complete **physical examination** will be performed during Screening and should include, but not necessarily be limited to, an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF. Targeted physical examinations (i.e., joints for bleeds, evidence of arthropathy; skin for bruises, hematomas, and ISRs;), other organ systems as clinically indicated, should be conducted at subsequent visits or as clinically indicated. New or worsened clinically significant abnormalities from screening should be recorded as adverse events, if appropriate, on the Adverse Event eCRF.

f. **Vital signs** include measurement of body temperature (oral, rectal, axillary, or tympanic), heart and respiratory rates, blood pressure and weight. On treatment days, measurement should occur prior to micizumab administration, if applicable. Height will be measured and recorded only during at Screening and 6 and 12 months after starting emicizumab. Additional vital signs assessments may also be taken anytime as unscheduled assessments as judged by the investigator. In addition, vital signs may be taken to help monitor for hypersensitivity reactions during or after injections at the investigator's discretion, although these data but they should not be entered into the eCRF.

g. The definition of **concomitant medications**, as well as permitted and prohibited medications is described in Section 4.4. Concomitant medications used by a patient from 4 weeks prior to initiation of emicizumab to the Study Completion/Early Termination Visit (or to the Safety Follow-up Visit, if applicable) should be reported to the investigator and recorded on the Concomitant Medications eCRF. Treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), will be collected in the bleed records.

h. **Hematology and blood chemistry** assessments will include a complete blood count with differential and serum chemistries (see Section 4.5.6.1). Safety Laboratory assessments completed at during Screening do not have to be repeated at Week 1, if the period between Screening and Week 1 is ≤ 5 days and there has been no change in the patient's health status as assessed by the investigator. Samples will be sent to the central laboratory for analysis.

i. **Pregnancy tests**: Female patients of childbearing potential (including those who have had a tubal ligation) will be required to have a negative serum pregnancy test result during Screening and again within 7 days prior to the first dose of emicizumab. Urine pregnancy tests will be performed throughout the study treatment period. Pregnancy testing will be conducted at the local laboratory.

j. The specific tests utilized for **hepatitis and HIV serology** testing are per local standard of care. As this patient population is at high risk for HIV, hepatitis A, B and C, sites should consider testing for these. While the specific serological tests used is at the discretion of the Investigator, this is with the understanding that the status of that participants' hepatitis or HIV is confidently known at time at enrollment. HIV and hepatitis serology tests will be conducted at the local laboratory.

k. For the assessment of **anti-FVIII antibodies** (inhibitors), functional assays that utilize a clotting readout (classic Bethesda or Nijmegen assay) cannot be used for patients on emicizumab therapy as emicizumab drives clotting even in the presence of FVIII inhibitors, causing a false-

negative test result (see Section 5.1.3). After the first dose, local measurement of FVIII inhibitors, if indicated, requires use of an ELISA-based test or a chromogenic Bethesda assay. At the discretion of the local investigator, any additional urgent request to assess FVIII inhibitors will need to be sent to the central laboratory (see Protocol Appendix 2 for additional information). Plasma samples for anti-FVIII antibodies will be analysed at the central laboratory

l. Plasma samples are required for immunogenicity assessments to detect **anti-emicizumab antibodies**. Additional samples to detect anti-emicizumab antibodies may also be drawn at the time of hypersensitivity events or following suspected loss of efficacy.

m. **ePRO bleed / medication recording:** At the Week 1 visit, patients will be trained on how to record their bleeds and hemophilia medication use on the ePRO device where possible. Data that need to be recorded will include the site of bleed, type of bleed, time of each individual bleed (day, start and stop time), and treatment for bleed. At least once a week, patients will need to record any hemophilia medication use (including emicizumab) and information regarding any bleeding events. Investigator review of patient-reported bleed/medication records with the patient/caregiver will occur for completeness and accuracy at all of the visits during the treatment period, at study completion, at any unscheduled visits (if required), and at the Early Termination Visit (if required).

n. Thorough documentation on **surgical events** will be requested, including type of surgery or procedures, treatments, outcomes, etc.

o. **Adverse events**: After informed consent has been obtained but prior to initiation of emicizumab, only serious adverse events caused by a protocol-mandated intervention should be reported. Injection-site reaction adverse events will be collected on a the injection site reaction form.

p. **Management of emicizumab**: Drug dispensation will not occur at the Study Completion Visit or the Early Termination Visit (if required). Patients will only receive emicizumab during an unscheduled visit if drug dispensation is required at this time.

q. **HRQoL and EQ-5D-5L**: Patients will be requested to complete Haem-A-QoL (adults age: ≥ 18 years) or the Haemo-QoL-SF (adolescents ages: 12−17 years) questionnaire and the EQ-5D-5L questionnaire. Questionnaires will be self-administered electronically before the patient/caregiver receives any information on disease status, prior to the performance of non-PRO assessments, and prior to emicizumab administration (if on a treatment day). Paper versions of the questionnaires are also available in case of ePRO outage or if an ePRO device is otherwise unavailable.

r. **EmiPref**: At the 3-month assessment, patients will be prompted to complete a paper version of the EmiPref questionnaire (Protocol Appendix 3). The questionnaire will be self-administered before the patient/caregiver receives any information on disease status, prior to the performance of non-PRO assessments, and prior to emicizumab administration (if on a treatment day).

s. On treatment days, blood collection should occur within 2 hours prior to emicizumab administration unless otherwise specified. Unless otherwise specified, additional analysis will be performed at a local laboratory, as per the investigator's discretion. Any additional laboratory results which are required as part of the patient's safety assessment should be recorded in the unscheduled visit eCRFs. Central labs are part of the non-eCRF data which will be sent to the Sponsor directly by the central lab vendor.

t. Plasma samples are required for **PK assessments**. On days where samples are to be collected, the emicizumab injection will be performed in the clinical unit. One single pre-dose sample is required on the applicable visits. Samples will be analysed by the central laboratory.

u. Plasma samples for **safety biomarkers** must be citrate plasma. Tests may include, but are not limited to, D-dimer. Samples will be analysed by the central laboratory. See Protocol Appendix 2.

v. Plasma samples for **safety coagulation system biomarker** assessments must be citrate plasma. Tests include FVIII:Ag, FIX:Ag and FX:Ag Samples will be analysed by the central laboratory. See Protocol Appendix 2.

w. Plasma samples for **PD biomarker assessments** must be citrate plasma. Tests will include, but are not limited to, FVIII activity and modified aPTT (one stage). will beTime windows for sample collection are specified in Protocol Appendix 2. Additional plasma samples will be collected for future exploratory research, which may include tests such as clot waveform analysis (CWA) and others (see Protocol Appendix 2). Samples will be analysed by the central laboratory.

x. Serum and plasma EDTA samples for **bone and joint biomarkers** must be collected after fasting (no food or drink other than water for at least 8 hours prior to the blood draw). Ideally these samples should be collected in the morning (before noon), in order to control for diurnal variation. Please consult the Central Laboratory Services Manual for details. The selection of exploratory bone and joint biomarkers to be tested will build on findings from biomarker analyses in other emicizumab trials and may include CTX-1, OPG, P1NP, and soluble RANK-L (see Protocol Appendix 2). Samples will be analysed by the central laboratory.

y. **Additional laboratory assessments**: In the event of a breakthrough bleed that is treated with bypassing agents, it is recommended that the following laboratory tests will be performed within 24−48 hours of initial bypassing agent use (these tests will be conducted so that the investigator can monitor the patient for potential thromboembolic events and microangiopathic hemolytic anemia or TMA). These tests include platelet count, serum creatinine, LDH and schistocytes. A plasma sample should also be provided for central laboratory monitoring of prothrombin fragment F1+2, fibrinogen and D-dimer. Samples for these tests should ideally be analysed at the central laboratory. Exceptionally in urgent situations where results are required quickly, local laboratory testing can be used, with results recorded in the eCRF. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24−48 hours until 24−48 hours after the last dose of bypassing agents is administered to treat a specific bleed. If applicable, laboratory results should be recorded in the unscheduled visit eCRFs.

APPENDIX 3: HRQOL QUESTIONNAIRES

Recoding and Scales

Before calculating the scale and total scores several items need to be reverse scored (Table_App3.01, Table_App3.02). The reverse scoring for those items is as follows: (1=5), (2=4), (3=3), (4=2), and (5=1). Any (0) will be recoded as missing data for the purposes of scale scoring. In listings of frequencies, the number of patients reporting 'Not applicable' can also be displayed.

After the recoding the 3 scores can be calculated as follows:

1. **Raw Scale Score**: Derived as the sum of all items in a scale. , e.g. the raw score for physical health is the sum of the 5 items from this scale. A Total score is calculated by summing up all of the raw and reverse coded items in the available scales.
2. **Standardized Scale Score:** The raw scale score is divided by the number of items in the scale. That way a comparison of scores across scales per patient is possible.
3. **Transformed Scale Score**: The scores for each scale can be standardized onto a 100 point scale. This is done with the following formula:

$$TSC = 100 \times \frac{(raw\ scale\ score - minimal\ possible\ raw\ score)}{possible\ range\ of\ raw\ scale\ scores}$$

$$= 100 \times \frac{(standardized\ scale\ score - 1)}{4}$$

The transformed Scale Score will be used for all analyses and referred as domain score or total score on the outputs.

Table_App3.01: The questions from Haem-A-QoL whose items need recoding are:

Category	Question
View of yourself	I felt comfortable with my body
	I was able not to think all the time about my hemophilia
Dealing with hemophilia	I tried to recognize early on when a bleed developed
	I was able to tell whether or not I was bleeding
	I was able to control my bleeds
Treatment	I was satisfied with the hemophilia center
Future	I have been expecting that things will get better in the future
Sports and leisure	I played sports just as much as others

Work and school	I was able to go to work/school regularly in spite of my hemophilia
	I was able to work/study like healthy colleagues

Table_App3.02: The questions from Haemo-QoL-SF whose items need recoding are:

Category	Question
View of yourself	I felt as well as other boys my age
	I felt contented about my body
Friends	My best friend cared about how I was feeling
	There was a best friend that I felt very close to
	My friends took care of me when I felt bad
Sports and school	I did as much sports as any other kid
Dealing with hemophilia	I was in control of my complaints due to haemophilia
	Haemophilia was a normal part of my life
	I felt healthy in spite of my haemophilia
	I accepted having haemophilia
Treatment	The treatment I got was okay

Missing items

Scales can be calculated if > 50% of the items have been answered. As the questionnaire is being administered electronically and patients are not able to skip items, there should not be any missing items. However, as patients can answer "Not applicable" to questions in the sports and leisure, work and school, and family planning scales, items could be treated as missing. In this case, the minimum number of items that needs to be completed and not responded to as "Not applicable" is:

- Sports and leisure: 3
- Work and school: 2
- Family planning: 2