Official Title: A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Emicizumab in Patients with Mild or Moderate Hemophilia A Without FVIII Inhibitors

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STATISTICAL ANALYSIS PLAN

TITLE: **A MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, EFFICACY, PHARMACOKINETICS, ANDPHARMACODYNAMICS OF EMICIZUMAB IN PATIENTS WITH MILD OR MODERATE HEMOPHILIA A WITHOUT FVIII INHIBITORS**

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STUDY DRUG: Emicizumab (RO5534262)

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STATISTICAL ANALYSIS PLAN APPROVAL

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1. BACKGROUND

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

Hemophilia A is most commonly caused by an inherited FVIII gene mutation within the Xq28 region of the X chromosome. It occurs almost exclusively in males with one defective copy of the relevant gene on their X chromosome. Females who are carriers of hemophilia A may experience bleeding symptoms similar to those seen in men with mild hemophilia A, as approximately 10% of carriers have a FVIII activity less than 35% (Plug et al. 2006). Rarely, women can have more severe bleeding symptoms requiring treatment and may develop FVIII inhibitors. Approximately 30% of patients with hemophilia A do not have a family history of the disorder; these cases arise from spontaneous FVIII gene mutations. The severity of the disease roughly correlates with the residual endogenous level of FVIII activity. However, classifying patients into mild, moderate and severe categories based on the residual FVIII levels alone has been called into question. Recent guidance now recommends classification incorporating treatment strategies (e.g., prescribing prophylaxis vs. on-demand regimens based on bleeding phenotype).

Emicizumab (also known as ACE910, RO5534262, and HEMLIBRA®) is a recombinant, humanized, bispecific, immunoglobulin G4 monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of FVIII. Based on the Phase III program, emicizumab gained approval in many countries, including the United States and the European Union (EU) and is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adults and children with hemophilia A (congenital FVIII deficiency) with or without FVIII inhibitors and can be used in all age groups. In the EU however, the non-inhibitor label is restricted to patients with severe hemophilia A (FVIII level < 1%).

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

2. STUDY DESIGN

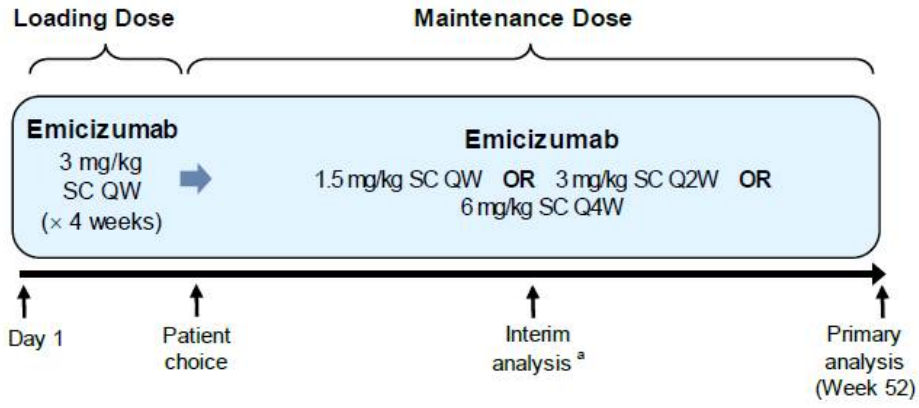
Study BO41423 is a multicenter, open-label, single-arm study designed to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients with mild or moderate hemophilia A without inhibitors against FVIII. Four loading doses of emicizumab 3 mg/kg will be administered subcutaneously once weekly (QW) for

4 weeks followed by patient preference of one of the following maintenance regimens: 1.5 mg/kg QW, 3 mg/kg every 2 weeks (Q2W), or 6 mg/kg every 4 weeks (Q4W). The three maintenance dose regimens have shown equivalent average steady-state exposure, and demonstrated consistent efficacy and safety, and are approved in several countries for the treatment of hemophilia A with or without FVIII inhibitors. As patients with mild or moderate hemophilia A have residual FVIII levels of ≥ 1%, it is of interest to collect safety data over a longer time period.

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

Each patient (or their legally authorized representative herein referred to as patient[s]) will choose the preferred emicizumab maintenance regimen (1.5 mg/kg SC QW, 3 mg/kg SC Q2W, or 6 mg/kg SC Q4W) after consultation with his or her treating physician. The chosen regimen needs to be maintained throughout the study until completion of at least 52 weeks. All patients with suboptimal control of bleeding as defined by the protocol will be offered the option to increase their emicizumab maintenance dose to 3 mg/kg QW, with approval from the Medical Monitor.

Figure 1 Study Schema



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

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 27 months depending on the recruitment rate

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1.

2.2 COLLECTION OF PATIENT-REPORTED DATA

2.2.1 Collection of Bleed and Medication Data

Bleed and medication data are collected through an electronic bleed and medication questionnaire (BMQ), which was developed by the Sponsor given that no standard questionnaire for collection of these data exists.

Patients (or their legally authorized representative) will complete a BMQ whenever a bleed occurs or at least on a weekly basis (retrospective reporting for last 7 days) via an electronic, handheld device. For each bleed episode, the patient will provide information regarding bleed start date and time, reason, type, location, and associated symptoms (only collected for muscle and joint bleeds in patients 12 years of age and older). Hemophilia medications and reason for treatment (e.g., bleed, surgery, physical activity) will also be collected through the use of the BMQ. If the electronic, handheld device is not available, a paper questionnaire might be used. Investigators will review the bleed and bleed medication data as per the schedule of activities and will have the option to correct or complete the BMQ in agreement with the patient via a Data Request Form process or via a web-based portal, once implemented. Patients who withdraw from emicizumab treatment will continue to record bleeds and hemophilia medication administration until they complete the safety follow-up visit.

2.2.2 Collection of Health-Related Quality-of-Life Data

At specified visits, patients will complete health-related quality-of-life (HRQoL), health status, and satisfaction/preference questionnaires on a tablet device that will remain at study sites. The instructions for completing the patient-reported outcome (PRO) questionnaires electronically will be provided by the investigator staff during the Week 1 visit at the site. The data will be transmitted automatically after entry to a centralized secure database at the vendor.

Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) is a newly developed, validated instrument to measure the effect of hemophilia and its treatment on pediatric (aged 8−17 years) and adult patients (aged ≥ 18 years), and caregivers of pediatric patients. The adult and pediatric versions of CATCH are composed of seven domains, and the caregiver version of CATCH is composed of two domains. Each domain constitutes a set of specific items and overall items that help to assess the overall impact of the disease on a given domain. The current versions of the CATCH can be administered electronically. The items in the CATCH versions are scored on ordinal scales (3−4 points for pediatric version, 4−5 points for adults and caregiver versions), with an 11-point numeric rating scale for pain. All CATCH raw scores are obtained by calculating the mean of the item scores for all items within the corresponding concept and applying a linear transformation. The transformed scores range from 0 to 100 scale with higher scores indicating higher perceived risk or effect.

2.2.3 Collection of Activity Data

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

Accelerometry data will be collected passively using the study device and uploaded regularly to provide continuous measures of, but not limited to, moderate to vigorous physical activity (MVPA) and daily step count (DSC); in addition, further analyses may be performed.

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

2.3 OBJECTIVES AND ENDPOINTS

2.3.1 Primary Efficacy Objective

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

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

2.3.2 Secondary Efficacy Objective

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

- Number of all bleeds (i.e., those treated and untreated with FVIII) over time
- Number of joint bleeds over time
- Number of target joint bleeds over time (target joints are defined as joints with ≥ 3 bleeds occurring in the same joint during the last 24 weeks)
- Number of spontaneous bleeds over time (spontaneous bleed rate)
- Joint health, as assessed through use of the Hemophilia Joint Health Score (HJHS) at specified timepoints
- Health-related quality of life (HRQoL), as assessed through use of the CATCH Questionnaire over time
- Preference for emicizumab compared with previous FVIII regimen, as assessed through use of the Emicizumab Preference Survey (EmiPref) at Week 17
- Effect of emicizumab prophylaxis treatment on physical activity compared with physical activity at baseline
- Effect of emicizumab prophylaxis treatment on menstruation heaviness and menstruation-related quality of life in female patients of childbearing potential, as assessed through the use of the Menstrual Bleeding Questionnaire (MBQ) and the

Menstruation Diary (MD) with the Pictorial Blood Assessment Chart (PBAC) over time

2.3.3 Pharmacokinetic Objectives

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

- Plasma concentration of emicizumab at specified timepoints

2.3.4 Safety Objectives

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

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

2.3.5 Immunogencity Objectives

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

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

2.3.6 Biomarker Objective

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

2.3.7 Health Status Utility Objective

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

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

2.4 DETERMINATION OF SAMPLE SIZE

The overall sample size of approximately 70 patients (approximately 50 patients with moderate disease and approximately 20 patients with mild disease) is based primarily on feasibility and clinical considerations, taking into account the limited number of patients with non-severe hemophilia A. This sample size is expected to provide statistically robust point estimates with meaningfully narrow confidence intervals in the overall group of enrolled patients, at the time of the primary analysis or at the time of interim analysis appropriate for regulatory submissions, assuming the same efficacy across dosing regimens.

2.5 ANALYSIS TIMING

An interim analysis and the subsqeuent primary analysis will be performed after all 50 patients with moderate hemophilia A have completed respectively 24 weeks of emicizumab treatment and 52 weeks of emicizumab treatment, or are lost to follow-up, or have withdrawn, whichever occurs first.

The final analysis will occur at the end of the study. Additional updates may be performed between the primary and final analysis as might be requested by Health Authorities or deemed necessary by the Sponsor.

3. STATISTICAL METHODS

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

3.1 ANALYSIS POPULATIONS

3.1.1 All Patients Population

The All patients population includes all patients enrolled in the trial. This population will be used to describe demographic and baseline characteristics.

3.1.2 Treated Population

The Treated population corresponds to all patients who received at least one dose of emicizumab. This population will be the primary population for efficacy and safety analyses.

3.1.3 Pharmacokinetic-Evaluable Population

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

3.1.4 Up-Titrated Population

Should we have any patients whose dose was up-titrated at least once during the study they will be included in this population.

3.1.5 Immunogenicity Population

The immunogenicity population includes patients with at least one postdose ADA assessment.

3.2 ANALYSIS OF STUDY CONDUCT

The flow of patients through the study will be displayed in a 'CONSORT' diagram. A clear account of all patients who were enrolled, who discontinued the study prematurely, who have ongoing treatment with emicizumab and who completed the study will be provided. In addition, reasons for premature discontinuation from study treatment and reasons for withdrawing from study will be described.

Major protocol deviations (MPD) will be captured in the patient data management systems (PDMS) using the MPD guidance. Number of patients with at least one major protocol deviation, total number of major protocol deviations and the reasons for protocol deviations will be provided. Major protocol deviations could be listed based on health authority requests.

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

3.3 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will be based on the Treated population. The efficacy objectives of this study will be investigated without any formal hypothesis testing. All analyses will be of descriptive nature only.

3.3.1 Efficacy Period

Efficacy period for each individual patient is defined as the number of days starting from the day of first emicizumab dose to the day of clinical cut-off or withdrawal from the study, whichever is earlier. For patients whose dose is up-titrated, the efficacy period ends a day prior to the first day on the up-titrated dose.

3.3.2 Efficacy Endpoints

3.3.2.1 Bleed Rate

The efficacy of emicizumab is characterized by the number of bleeds over time. This will be calculated using a negative binomial (NB) regression model, which accounts for different follow-up times, with time that each patient stays in the study (efficacy period) included as an offset in the model. In addition, the number of bleeds will also be annualized for each patient using the following formula:

Annualized bleed rate (ABR) = (Number of bleeds/number of days during the efficacy period) × 365.25.

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

ABR corresponding to treated bleeds, all bleeds, treated joint bleeds, treated target joint bleeds, and treated spontaneous bleeds will be analyzed in a similar manner. These will be summarized for all patients and listed for each patient individually. Several exploratory analyses will be conducted to characterize the type, location, and frequency.

3.3.2.1.1 72-Hour Rule:

Two bleeds of the same type (e.g., “joint”, “muscle”, or “other”) and at the same anatomical location are considered to be one bleed if the second bleed occurs within 72 hours from the last treatment for the first bleed. The last treatment is defined as the last treatment before a new bleed occurs, either in the same or in a different location.

Bleeding rates and characteristics of bleeding describing location and type will also be provided using the 72-hour rule.

3.3.2.2 Health-Related Quality of Life (HRQoL)

For CATCH questionnaire, descriptive analyses including summaries and 95% confidence intervals of change from baseline for each individual subscale will be performed. Patient compliance with the CATCH will be summarized at each assessed timepoint.

For the EmiPref patient preference questionnaire, the proportion of patients/caregivers preferring either emicizumab after 17 weeks of treatment or previous hemophilia treatment regimen will be presented with 95% CIs. The proportion of patients selecting each reason for their preference and the top three preferred reasons affecting the patient preference will also be summarized. Patient/caregiver compliance with the EmiPref will be summarized for Week 17.

Summary statistics of the number and proportion of days away from school/work and days hospitalized will be presented.

3.3.2.3 Joint Health and Physical Activity

The Hemophilia Joint Health Score (HJHS) measures joint health of the joints most commonly affected by bleeding in hemophilia. The HJHS 2.1 provides joint specific total scores which is added to obtain the sum of joints totals and also a global gait score. These two scores are then added to obtain HJHS total score. For the HJHS, descriptive analyses will be presented by timepoint. All enrolled subjects who contribute to valid activity data will be analyzed for activity.

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

3.3.2.4 Menstruation Heaviness and Menstruation-related Quality of Life

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

3.3.3 Subgroup Analyses

Additional descriptive summaries of both treated bleeds and all bleeds will be computed for various subgroups of the study. The summaries will include subgroup ABR and its 95% CIs. The main pre-specified subgroups are as follows:

- Age: 0 to <2, 2 to <6, 6 to <12, 12 to <18, 18 to <65, ≥65 years
- Race: Asian, Black or African American, White, Other
- Hemophilia severity: mild, moderate
- Number of target joints at study entry: no target joint, any target joint
- Previous treatment regimen: prior episodic, prior prophylactic
- Prior FVIII inhibitor: Yes/No
- Female patient: Yes/No
- Dosing regimens at enrolment: 1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W

Note that due to the likely small sample sizes, subgroup analyses will be highly susceptible to variability and should therefore be interpreted with caution.

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

3.4 PHARMACOKINETIC ANALYSES

The PK endpoint for this study is the exposure (C_{trough}) of emicizumab in patients assessed prior to drug administration on Day 1 and at the following timepoints:

- Every week during Weeks 1-4 on emicizumab
- Every four weeks during Weeks 5-45 on emicizumab
- Every twelve weeks from Week 49 thereafter while continuing on emicizumab until the end of the study

Plasma concentrations of emicizumab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

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

3.5 BIOMARKER ANALYSES

Change over time in the PD parameters: activated partial thromboplastin time (aPTT), prothrombin time (PT)/ international normalized ratio (INR), reported FVIII activity (emicizumab sensitive and insensitive), FVIII protein level, and thrombin generation as well as fibrinogen, D-dimer and PF1+2 levels will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. In addition, individual patient plots will be provided. Bone and joint health will be summarized.

3.6 IMMUNOGENICITY ANALYSES

3.6.1 Anti-Emicizumab Antibodies

The immunogenicity analyses for emicizumab antibodies will be performed on the immunogenicity population.

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized. Patients are considered to be ADA-positive if they are ADA-negative at baseline or have no baseline value but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA-negative if they are ADA-negative at baseline or have no baseline value and all post-baseline samples are negative, or if they are ADA-positive at baseline but do not

have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

3.6.2 Factor VIII Inhibitors

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

3.7 SAFETY ANALYSES

Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology including complete blood count with differential and platelet counts), ECGs, vital signs, ADAs, and de novo FVIII inhibitors. To evaluate the overall safety of emicizumab, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade. For clinical laboratory data, summary statistics will be presented. In addition, shift tables describing changes from baseline will be presented using the WHO Toxicity Grading Scale.

3.7.1 Exposure to Study Medication

Information on study drug administration will be summarized by duration and cumulative dose. In addition, treatment exposure will be summarized including delays and interruptions.

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

3.7.2 Adverse Events

To evaluate the overall safety of prophylactic emicizumab, adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade (WHO Criteria). All AEs will be coded using the current version of Medical Dictionary For Regulatory Activities (MedDRA) at the time of each database closure (interim and primary analysis). For the purpose of summarization, a patient is counted once in a system organ class or preferred term if the patient reported one or more events in that system organ class or preferred term. Percentages will be based on the number of patients overall.

The total number and percentage of patients with at least one adverse event (AE) and total number of AEs will be summarized. Separate AE summaries for serious adverse events (SAEs), adverse evetns of special interests (AESIs), severity, relatedness, and discontinuation/modification will be provided.

An overall summary of adverse events (including SAEs, AESIs, AEs leading to drug discontinuation, and deaths), which tabulates the number and percentage of patients who experienced any or serious adverse events and the number and percentage of patients who died, will be provided.

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

3.7.3 Laboratory Data

For clinical laboratory data, which were collected from local laboratories, summary statistics in SI units will be presented. Laboratory data not collected in SI units will be converted to SI units as applicable. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the impact of immunogenicity (ADAs) on safety, efficacy, and/or clinical pharmacology and pharmacokinetics will be summarized using standard language/terminology (Shankar et al. 2008).

3.7.4 Vital Signs

Vital signs will be summarized using mean change from baseline tables over time. Measurements consist of heart and respiratory rate, temperature, and systolic and diastolic blood pressure.

3.7.5 ECG

ECG results and corresponding changes from baseline will be summarized by visit for QT, RR, HR, QTcB, QTcF, PR and QRS and T- and U-wave morphology.

3.8 MISSING DATA

On the electronic handheld device, it is not possible to leave questions unanswered or to enter partial data in one BMQ.

In the site data entry system, it is possible to leave the time (but not the date) of a treatment or a bleed blank because the caregiver might not be able to remember these in a reliable way.

In order to implement the 72-hour rule, it is assumed that the bleeds and treatments with missing time occurred at 12:00 a.m. If at a given day only the treatment time or the bleed time is partial and the other one complete, the partial time is assumed to be the same as the complete time. In case of multiple events per day, the last complete time is used.

3.9 INTERIM ANALYSES

Interim data review will be performed when 50 moderate hemophilia A patients have completed 24 weeks of emicizumab treatment. The results of the analysis will be documented in an interim Clinical Study Report.

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Appendix 1
Protocol Synopsis

TITLE:	**A MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, EFFICACY, PHARMACOKINETICS. AND PHARMACODYNAMICS OF EMICIZUMAB IN PATIENTS WITH MILD OR MODERATE HEMOPHILIA A WITHOUT FVIII INHIBITORS**
PROTOCOL NUMBER:	BO41423
VERSION NUMBER:	2
EUDRACT NUMBER:	2019-002179-32
IND NUMBER:	122954
NCT NUMBER:	*NCT04158648*
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase III
INDICATION:	Mild or moderate hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

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

Safety Objective

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

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

Efficacy Objectives

Primary Efficacy Objective

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

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

Secondary Efficacy Objectives

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

- Number of all bleeds (i.e., those treated and untreated with FVIII) over time
- Number of joint bleeds over time
- Number of target joint bleeds over time (target joints are defined as joints with ≥ 3 bleeds occurring in the same joint during the last 24 weeks)
- Number of spontaneous bleeds over time (spontaneous bleed rate)
- Joint health, as assessed through use of the Hemophilia Joint Health Score at specified timepoints
- Health-related quality of life (HRQoL), as assessed through use of the Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) Questionnaire over time
- Preference for emicizumab compared with previous FVIII regimen, as assessed through use of the Emicizumab Preference Survey (EmiPref) at Week 17
- Effect of emicizumab prophylaxis treatment on physical activity compared with physical activity at baseline
- *Effect of emicizumab prophylaxis treatment on menstruation heaviness and menstruation-related quality of life in female patients, as assessed through the use of the Menstrual Bleeding Questionnaire (MBQ) and the Menstruation Diary (MD) with the Pictorial Blood Assessment Chart (PBAC)*

Pharmacokinetic Objective

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

- Plasma concentration of emicizumab at specified timepoints

Immunogenicity Objective

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

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

Biomarker Objective

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

Health Status Utility Objective

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

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

Study Design

Description of Study

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

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

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

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

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

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

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

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

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

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

Interim data reviews may be performed at various timepoints (e.g., for regulatory submissions), and the primary analysis for all patients will be conducted after all patients with moderate hemophilia A have completed 52 weeks of emicizumab treatment, are lost to follow-up, or have withdrawn, whichever occurs first. The primary analysis will occur at the specified time regardless if no patients with mild hemophilia A are enrolled; however, enrollment *will* be left open for patients with mild hemophilia A in order to enroll approximately *20* such patients. *The total number of patients in the study might slightly exceed 70 patients depending on the number of female patients enrolled. Ideally, at least 5 female patients will be enrolled. If*

these are not recruited within the pool of 70 patients, the enrollment will remain open until they are enrolled or until the cutoff date of primary analysis, whichever occurs sooner. Note that all patients will be included in the primary analysis irrespective of their follow-up time. After the primary analysis, patients will continue to receive emicizumab according to the Roche Policy on post study drug access until emicizumab is approved and accessible to patients commercially.

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

Number of Patients

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

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

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

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

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

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

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

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

Exclusion Criteria

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

- Inherited or acquired bleeding disorder other than mild (FVIII level between $>$ 5% and $<$ 40%) or moderate (FVIII level between $\geq$ 1% and $\leq$ 5%) congenital hemophilia A
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Planned surgery during the emicizumab loading dose phase

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

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

End of Study

The end of this study is defined as the date when the last remaining patient has completed the last visit, as defined by the following criteria: completion of at least 52 weeks of emicizumab

treatment during the study and either transfers to commercially available emicizumab or receives further emicizumab per Roche Global Policy on Continued Access to Investigational Medicinal Products OR completion of the end of study safety follow-up visit 24 weeks after discontinuing emicizumab OR withdrawal of consent OR lost to follow-up.

Length of Study

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

Investigational Medicinal Products

Test Product (Investigational Drug)

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

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

Statistical Methods

Primary Analysis

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

The safety analyses population will be based on all patients who received at least one administration of emicizumab. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology including complete blood count with differential and platelet counts), ECGs, vital signs, ADAs, and de novo FVIII inhibitors. To evaluate the overall safety of emicizumab, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade. For clinical laboratory data, summary statistics will be presented. In addition, shift tables describing changes from baseline will be presented using the WHO Toxicity Grading Scale.

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

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

Determination of Sample Size

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

Optional Interim Analyses Reviews

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

Appendix 2
Schedule of Assessments

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

Appendix 2
Schedule of Assessments (cont.)

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

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

Appendix 2
Schedule of Assessments (cont.)

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

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

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

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

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

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

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

[g] Questionnaire will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment. For patients younger than 18 years of age, the patient's caregiver will also be asked to fill out the EmiPref (caregiver version). For patients <12 years old, only the caregiver will fill out the EmiPref (caregiver version).

[h] HJHS will be performed as part of the physical examination.

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

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

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

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

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

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

Appendix 2
Schedule of Assessments (cont.)

[o] Pre-dose: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and absolute differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width will be performed locally. Laboratory assessments completed at the screening visit do not have to be repeated at Week 1 if the period between screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator.

[p] Pre-dose: sodium, potassium, glucose, BUN, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, albumin, ALP, ALT, AST, LDH and CPK will be performed locally. Laboratory assessments completed at the screening visit do not have to be repeated at Week 1 if the period between screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator.

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

[r] Bleed information *for each bleed* (start date and time, reason, type, location, and associated symptoms *(only collected for muscle and joint bleeds in patients 12 years of age and older))* and medication for bleeds (breakthrough bleeds) should be reported by the patient via an electronic, handheld device when a bleed occurs or at least on a weekly basis (retrospective reporting for last 7 days). If the patient discontinues study treatment, bleed and bleed medication data should be provided by the patient until the safety follow-up visit (24 weeks after final study drug administration). Emicizumab doses should be recorded by the patient in the BMQ starting on Day 1.

[s] Investigator review of bleed information.

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

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

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