Official Title: A PHASE IV, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY OF EMICIZUMAB PROPHYLAXIS IN PATIENTS WITH HEMOPHILIA A *WITH OR WITHOUT* INHIBITORS UNDERGOING MINOR SURGICAL PROCEDURES

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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE IV, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY OF EMICIZUMAB PROPHYLAXIS IN PATIENTS WITH HEMOPHILIA A *WITH OR WITHOUT* INHIBITORS UNDERGOING MINOR SURGICAL PROCEDURES**

PROTOCOL NUMBER: ML39791

STUDY DRUG: Emicizumab (HEMLIBRA®)

VERSION NUMBER: 1.0

IND NUMBER: 122954

EUDRACT NUMBER: Not applicable

Date and Time(UTC)	Reason for Signing	Name
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STATISTICAL ANALYSIS PLAN APPROVAL

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1. BACKGROUND

This study will evaluate the safety and efficacy of emicizumab prophylaxis in patients with hemophilia A (PwHA; with and without inhibitors) that are undergoing minor surgical procedures without additional prophylaxis with bypassing agents (BPA; for patients with inhibitors) or factor VIII (FVIII; for patients without inhibitors). Pharmacokinetics will also be evaluated as exploratory objectives of the study. For the purposes of this protocol, study treatment is not intended to imply that the Sponsor is providing the study drug; rather, emicizumab is required for all patients during the study per the inclusion and exclusion criteria.

2. STUDY DESIGN

This Phase IV, multicenter study will evaluate whether PwHA receiving emicizumab prophylaxis can safely undergo minor surgical procedures without additional prophylaxis with BPAs for patients with inhibitors or FVIII for patients without inhibitors. Current guidelines recommend a pre-operative dose of BPA/*FVIII* as surgical prophylaxis, but in patients on emicizumab prophylaxis in this study, additional pre-operative prophylaxis with BPA/*FVIII* will not be used. The use of BPA/*FVIII* for excessive surgical bleeding will be measured intraoperatively and postoperatively. In addition, surgical complications from bleeding and blood product transfusions will be evaluated. This study will assess emicizumab prophylaxis alone to control surgery-related bleeding in PwHA undergoing minor surgical procedures.

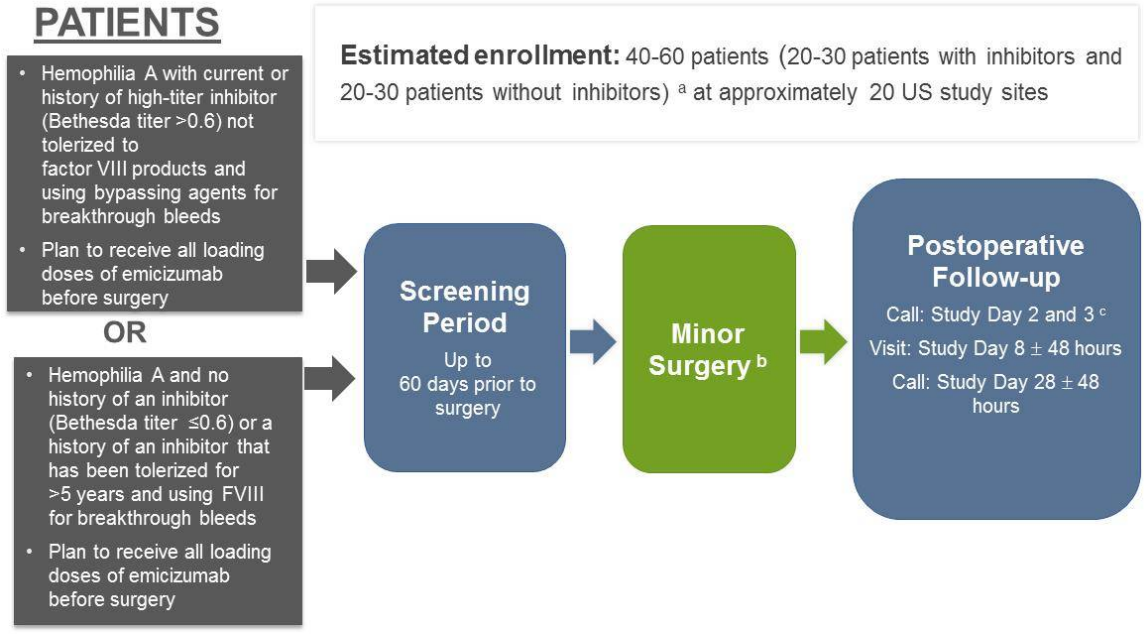
Patients can be screened and enrolled up to 60 days prior to surgery. They must have received a minimum of four loading doses of emicizumab prior to their surgical procedure, been adherent with emicizumab prophylaxis, and must not have received BPA/*FVIII* for at least 24 hours prior to surgery. In addition, they must plan to continue emicizumab prophylaxis for at least 1 month after the surgical procedure. Follow-up will be conducted by phone on Study Days 2 and 3 (approximately 24 and 48 hours post operation) to record any BPA/*FVIII* use and surgical bleeding within the first 48 hours, as well as treatment of any other bleeding unrelated to surgery. BPA/*FVIII* should only be used for treatment of bleeding. Follow-up will be conducted in person on Study Day 8 (± 2 days) to examine the patient for any postsurgical complications and to collect information on treatment of bleeding. Lastly, follow-up will be conducted by phone on Study Day 28 (± 2 days) to record any surgical complications, bleeds, and/or use of BPA/*FVIII* (see Appendix 2).

Blood samples will also be collected in this study for observational purposes and will not be used to determine eligibility or treatment decisions. Samples will be used to evaluate emicizumab concentration (PK) prior to surgery.

Safety follow-up will be conducted after signing the informed consent form and patients will be monitored for adverse events as noted above to evaluate the safety of emicizumab alone or in combination with BPA/*FVIII*.

Figure 1 shows the study schema.

Figure 1 Study Schema



FVIII = factor VIII; US = United States.

[a] A maximum of 9 patients *in each cohort* will undergo any surgery type

[b] Undergoing minor surgery within 60 days of enrollment. Must have received all loading doses of emicizumab prior to surgery.

[c] ±2 days if Study Day 2 or 3 falls on a weekend.

2.1 PROTOCOL SYNOPSIS

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

2.2 ENDPOINTS

All endpoints will be measured and described separately for the inhibitor and non-inhibitor cohorts. For all endpoints in this section, BPA use is specific for patients with inhibitors and FVIII use is specific for patients without inhibitors.

2.2.1 Primary Efficacy Endpoints

- Percentage of patients without excessive bleeding at surgical sites and did not require BPA/FVIII use for bleeding related to the surgery, from the start of the surgery until the patient is discharged from the surgery. For the purposes of this endpoint, the absence of excessive bleeding and BPA/FVIII use will be measured by a good to excellent rating using the hemostatic efficacy scale (ISTH SSC recommendations, see References) and will be determined upon patient discharge by the healthcare professional performing the procedure.

- Percentage of patients with excessive bleeding at surgical sites and required BPA/*FVIII* use for bleeding related to the surgery, from the start of the surgery until the patient is discharged from the surgery. Bleeding and BPA/*FVIII* use will be assessed using the hemostatic efficacy scale and measured by a rating of fair to poor, and will be determined upon patient discharge by the healthcare professional performing the procedure.
    - Dose and schedule (including number of doses, total dose, and frequency) of BPAs/*FVIII* used per bleed for excessive bleeding at surgical sites will be summarized.

- Percentage of patients who, after being discharged from surgery, experienced bleeds that were either related or unrelated to the surgery and also required BPA/*FVIII* use
    - Dose and schedule (including number of doses, total dose, and frequency) of BPAs/*FVIII* used per bleed will be summarized.

Bleeding events and self-administered BPA/*FVIII* use in the third endpoint above are self-reported on the Bleeding and Medication Diary CRF page by patients who undergo the surgical procedure in the study. BPA/*FVIII*, whenever administered by the health care provider, will be obtained and reported by the PI on the Concomitant Medication CRF page.

2.2.2 Secondary Efficacy Endpoints

Not applicable.

2.2.3 Exploratory Efficacy Endpoints

- In the original protocol, select efficacy endpoints were to be summarized descriptively by plasma emicizumab concentration levels. Given that this study is being terminated early with limited sample sizes, these will no longer be performed.
- Percentage of patients with zero bleeds (regardless of treated or not) after being discharged from surgery.

2.2.4 Pharmacokinetic Endpoints

- Emicizumab plasma concentrations on the day of the surgery will be summarized descriptively.

2.2.5 Safety Endpoints

- Incidence and severity of all adverse events

  Incidence and severity of serious adverse events

  Incidence and severity of adverse events of special interest

- Percentage of patients with surgical complications requiring hospitalization or return to surgery
- Percentage of patients who need blood/blood product transfusions (i.e., platelets, plasma, etc.) during surgery
- In the original protocol, selected safety endpoints were to be descriptively summarized by plasma emicizumab concentration levels. Given the early termination of this study and limited sample sizes, these will no longer be performed.

2.3 DETERMINATION OF SAMPLE SIZE

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of patients with a planned minor surgery available for participation in this study. Table 5 illustrates the precision of this study for a binary efficacy endpoint assuming a total of approximately 20-30 patients per cohort enrolled into this study, receiving emicizumab, and undergoing a protocol-specified minor surgery.

During the study, a re-assessment of the initially specified sample size was allowed but never needed to be performed.

Table 1 Precision of the Study for a Binary Efficacy Endpoint (Illustrative Purposes)

Sample Size	Count of Events [a]	Estimate of Proportion	Lower Limit of 95% CI [b]	Upper Limit of 95% CI [b]
20	2	0.1	0.012	0.317
20	6	0.3	0.119	0.543
20	10	0.5	0.272	0.728
30	3	0.1	0.021	0.265
30	9	0.3	0.147	0.494
30	15	0.5	0.313	0.687

[a] This is the assumed observed count of events of interest.

[b] Calculated using exact test procedure based on the Clopper-Pearson method (Clopper et al. 1934).

2.4 ANALYSIS TIMING

Only one analysis is planned at the end of the study after the database is cleaned and locked.

3. STUDY CONDUCT

Patients are considered to be enrolled into the study once they sign the informed consent form. Safety follow-up will be conducted after the informed consent form is signed.

3.1 RANDOMIZATION ISSUES

Not applicable.

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

Not applicable.

4. STATISTICAL METHODS

This is an open-label, single-arm, multicenter study. No statistical hypothesis will be tested.

Only descriptive summaries will be presented for data collected in this study and the data will be summarized separately for the inhibitor and non-inhibitor cohorts. Continuous variables will be summarized using means, standard deviations, medians, and ranges; categorical variables will be summarized using proportions, and 95% confidence intervals, where applicable. In the event that sample sizes are too small or data too sparse given the early termination of this study, summaries will be relegated to simple listings.

4.1 ANALYSIS POPULATIONS

4.1.1 All Enrolled Population

All patients who sign informed consent.

4.1.2 Efficacy Analysis Population

All enrolled patients who receive emicizumab and undergo a minor surgery.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients who enroll, discontinue, or complete the study will be analyzed separately for each inhibitor and non-inhibitor cohort and will be summarized overall and by type of surgery for the all enrolled population. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

4.3 ANALYSIS OF DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND MEDICAL HISTORY

Demographic, baseline characteristics, and medical history will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented separately for the inhibitor and non-inhibitor cohorts and will be displayed overall and by type of surgery for the all enrolled population.

4.4 EFFICACY ANALYSIS

Descriptive statistics along with 95% Clopper Pearson confidence intervals will be used to provide point estimates and precision related to efficacy outcomes. All efficacy analyses will be performed on the efficacy analysis population.

4.4.1 Primary Efficacy Endpoint

The first 2 primary endpoints listed under section 2.2.1 are composite endpoints from data points collected on the "On-study Targeted Surgery and Procedure Log" CRF page: "Intraoperative and/or postoperative blood loss increased over expectation for the non-hemophilic patient determined at the time of discharge" and "Did the patient use any BPA/$FVIII$ for the surgery before the discharge?".

Primary endpoint 1 is met when response to "Intraoperative and/or postoperative blood loss increased over expectation for the non-hemophilic patient determined at the time of discharge" is "0 to <10%" or "10% to < 25%" AND response to "Did the patient use any BPA/$FVIII$ for the surgery before the discharge?" is "No".

Primary endpoint 2 is met when response to "Intraoperative and/or postoperative blood loss increased over expectation for the non-hemophilic patient determined at the time of discharge" is "25% to <50%" or ">=50%" AND response to "Did the patient use any BPA/FVIII for the surgery before the discharge?" is "Yes".

For the purposes of summarizing the dose and schedule of BPA use per bleed as it relates to primary endpoint 2, BPAs/$FVIII$ used for excessive bleeding at surgical sites are reported by the investigator and captured in "Concomitant Medications" CRF.

Primary endpoint 3 is also a composite endpoint based on information collected in "Bleed and Medication Diary" and "Concomitant Medications" CRFs.

For primary endpoint 3, bleeding information is self-reported by patients (or patient's legally authorized representative) on the "Bleed and Medication Diary" and transcribed into the "Bleed and Medication Diary" CRF page. BPAs/$FVIII$ used to treat excessive bleeding are also self-reported by patients if they are administered by the patients. BPAs/$FVIII$ administered by the investigators to treat the bleeding will be reported on the "Concomitant Medications" CRF page.

4.4.2 Secondary Efficacy Endpoints

Not applicable.

4.4.3 Exploratory Efficacy Endpoints

As an exploratory efficacy endpoint, the percentage of patients with zero bleeds (regardless of treated or not) after being discharged from surgery will be summarized separately for the inhibitor and non-inhibitor cohorts and will be displayed overall and by surgery type.

4.4.4 Sensitivity Analyses

A descriptive summary of additional post-surgery bleeds requiring BPA/FVIII use beyond the first treated bleed will be presented without any formal statistical testing in order to observe how additional treated bleeds after discharge from the surgery were distributed in the study. Specifically, the percentage of patients with 0 bleeds, 1 bleed, 2 bleeds, 3 bleeds and >3 bleeds will be summarized separately for each of the inhibitor and non-inhibitor cohort and will be displayed overall and by surgery type.

4.4.5 Subgroup Analyses

Not applicable.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Mean and median emicizumab concentrations at the beginning of the surgery will be summarized separately for each of the inhibitor and non-inhibitor cohorts and will be displayed overall and by surgery type.

4.6 SAFETY ANALYSES

Safety will be assessed through descriptive summaries of safety endpoints, adverse events, and vital signs.

4.6.1 Exposure of Study Medication

Information on emicizumab administration after discharge from surgery will be collected on the Bleed and Medication Diary and summarized by presenting the percentage of patients who took their emicizumab as prescribed at each visit as well as the mean/median dose taken. These analyses will be performed separately for the inhibitor and non-inhibitor cohorts and will be displayed overall and by surgery type.

4.6.2 Adverse Events

All adverse events occurring after informed consent is obtained will be coded. Treatment emergent events will be summarized by severity, and tabulated by body system and preferred term for individual events within each system organ class. In addition, serious adverse events, adverse events of special interest (AESIs), and adverse events leading to study discontinuation will be summarized. All serious adverse events and deaths will be listed.

Non-treatment-emergent events will be identified through two entries on the “Adverse Events” CRF page: response to “Action taken with emicizumab due to SAE/AE” is “Not applicable” AND response to “Date of most recent dose of Emicizumab prior to AE onset” is missing. These events will not be included in the treatment emergent safety analysis, but will be included in Adverse Event listing with an appropriate flag.

The safety endpoint, “Percentage of patients with surgical complications requiring hospitalization or return to surgery”, is a composite endpoint. Surgical complications are entered as adverse events on the “Adverse Events” CRF page with “Other suspected causes” marked as “Study Surgery or Procedure”. This endpoint is met when response to "It required or prolonged inpatient hospitalization” is checked OR response to response to “Was procedure/surgery performed?” is “Yes”.

4.6.3 Laboratory Data

For clinical laboratory data which are collected from local laboratories, summary statistics will be presented.

4.6.4 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 pressures.

4.7 MISSING DATA

Incomplete dates for AEs, concomitant medication and laboratory data are handled as described in the Roche data analysis standards (GDSR).

Diary cards are used to collect bleeding information post study surgery, either related or unrelated to the study surgery, as well as BPA//FVIII use for any bleeds. Missing information on bleeds are handled as follows:

- 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 cases 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

4.8 INTERIM ANALYSES

Not applicable.

5. REFERENCES

Clopper, C.; Pearson, E. S. "The use of confidence or fiducial limits illustrated in the case of the binomial". Biometrika 1934. 26: 404–413. doi:10.1093/biomet/26.4.404

In-text citation: (Clopper et al. 1934)

Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IV, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY OF EMICIZUMAB PROPHYLAXIS IN PATIENTS WITH HEMOPHILIA A *WITH OR WITHOUT* INHIBITORS UNDERGOING MINOR SURGICAL PROCEDURES**
PROTOCOL NUMBER:	ML39791
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	122954
TEST PRODUCT:	Emicizumab (HEMLIBRA®)
PHASE:	Phase IV
INDICATION:	Hemophilia A with *or without* inhibitors
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the safety and efficacy of emicizumab prophylaxis in patients with hemophilia A (PwHA; *with* or *without* inhibitors) *that are* undergoing minor surgical procedures *without additional prophylaxis with bypassing agents (BPA; for patients with inhibitors) or factor VIII (FVIII; for patients without inhibitors). All endpoints will be measured and described separately for the inhibitor and non-inhibitor cohorts.* Pharmacokinetics will also be evaluated as exploratory objectives of the study. For the purposes of this protocol, study treatment is not intended to imply that the Sponsor is providing the study drug; rather, emicizumab is required for all patients during the study per the inclusion and exclusion criteria.

Note: Throughout the protocol, all references to BPA will be specific for patients with inhibitors and all references to FVIII will be specific for patients without inhibitors, unless otherwise noted.

Primary Objective	Corresponding Endpoints
• To evaluate the efficacy of emicizumab in preventing surgery-related bleeding in PwHA *with* and *without* inhibitors undergoing minor surgical procedures	Efficacy will be measured by: • Percentage of patients without excessive bleeding at surgical sites and did not require BPA/*FVIII* [a] use for bleeding related to the surgery, from the start of the surgery until the patient is discharged from the surgery. For the purposes of this endpoint, the absence of excessive bleeding and BPA/*FVIII* [a] use will be measured by a good to excellent rating using the hemostatic efficacy scale (ISTH SSC recommendations) and will be determined upon patient discharge by the healthcare professional performing the procedure. • Percentage of patients with excessive bleeding at surgical sites and required BPA/*FVIII* [a] use for bleeding related to the surgery, from the start of the surgery until the patient is discharged from the surgery. Bleeding and BPA/*FVIII* [a] use will be assessed using the hemostatic efficacy scale and measured by a rating of fair to poor, and will be determined upon patient discharge by the healthcare professional performing the procedure. – Dose and schedule (including number of doses, total dose, and frequency) of BPAs/*FVIII* [a] used per bleed for excessive bleeding at surgical sites will be summarized. • Percentage of patients who, after being discharged from surgery, experienced bleeds that were either related or unrelated to the surgery and also required BPA/*FVIII* [a] use – Dose and schedule (including number of doses, total dose, and frequency) of BPAs/*FVIII* [a] used per bleed will be summarized
• Safety	• Incidence and severity of all adverse events – Incidence and severity of serious adverse events – Incidence and severity of adverse events of special interest • Percentage of patients with surgical complications requiring hospitalization or return to surgery • Percentage of patients who need blood/blood product transfusions (i.e., platelets, plasma, etc.) during surgery
Exploratory Objective	**Exploratory Endpoints**
• To evaluate potential relationships between drug exposure and the efficacy and safety of emicizumab	• Selected efficacy and safety endpoints will be descriptively summarized by plasma emicizumab concentration levels
• To describe the incidence of spontaneous bleeding in the post-operative period.	• Percentage of patients with zero bleeds (regardless of treated or not) after being discharged from surgery

BPA = bypassing agent; ISTH SSC = International Society on Thrombosis and Haemostasis Scientific and Standardization Committee; *FVIII = factor VIII;* PwHA = patients with Hemophilia A.

[a] *BPA use is specific for patients with inhibitors and FVIII use is specific for patients without inhibitors.*

Study Design

Description of Study

This Phase IV, multicenter study will evaluate whether PwHA (*with* or *without* inhibitors) receiving emicizumab prophylaxis can safely undergo minor surgical procedures without additional prophylaxis *with BPA or FVIII (for patients with or without inhibitors, respectively)*. The use of BPA/*FVIII* for excessive surgical bleeding will then be measured intra-operatively and post-operatively. In addition, surgical complications from bleeding and blood product transfusions will be evaluated. This study will assess emicizumab prophylaxis alone to control surgery-related bleeding in PwHA with *or without* inhibitors undergoing minor surgical procedures. *Each cohort (PwHA with inhibitors and PwHA without inhibitors) will be assessed separately.*

Patients can be screened and enrolled up to 60 days prior to surgery. They must have received a minimum of four loading doses of emicizumab prior to their surgical procedure, been adherent with emicizumab prophylaxis, and must not have received BPA/*FVIII* for at least 24 hours prior to surgery. In addition, they must plan to continue emicizumab prophylaxis for at least 1 month after the surgical procedure. Follow-up will be conducted by phone on Study Days 2 and 3 (approximately 24 and 48 hours post-operation) to record any bypassing agent use *or FVIII use* and surgical bleeding within the first 48 hours, as well as treatment of any other bleeding unrelated to surgery. BPA/*FVIII* should only be used for treatment of bleeding. Follow-up will be conducted in person on Study Day 8 ($\pm$ 2 days) to examine the patient for any post-surgical complications and to collect information on treatment of bleeding. Lastly, follow-up will be conducted by phone on Study Day 28 ($\pm$ 2 days) to record any surgical complications, bleeds, and/or use of BPA/*FVIII*.

Blood samples will also be collected in this study for observational purposes and will not be used to determine eligibility or treatment decisions. Samples will be used to evaluate emicizumab concentration (PK) prior to surgery.

Safety follow-up will be conducted after signing the informed consent form. Patients will be monitored for adverse events to evaluate the safety of emicizumab alone or in combination with BPA/*FVIII*.

Periodic Safety Review

In order to ensure that patients enrolled in this study are safely undergoing minor surgical procedures without additional pre-operative prophylaxis with BPAs/*FVIII*, periodic safety assessments are planned. The study team will perform periodic data review of all available data.

Number of Patients

Approximately *40–60 PwHA (approximately 20–30 patients with inhibitors and 20–30 patients without inhibitors)* will be enrolled and undergo a minor surgical procedure at approximately *20* sites in the United States. An effort will be made to ensure enrollment between multiple surgery types. A maximum of 9 patients *in each cohort* will be enrolled in any given surgery type.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent/Assent Form
- *Any age (newborn and older)*
- Ability to comply with the study protocol, in the investigator's judgment
- Diagnosis of hemophilia A and current or history of *an* inhibitor (Bethesda titer $\geq$ *0.6* Bethesda units*) and currently using BPA for breakthrough bleeds (for PwHA with inhibitors)*
- *Diagnosis of hemophilia A and no history of an inhibitor (Bethesda titer <0.6 Bethesda units), or a history of an inhibitor that has been tolerized for* >*5 years and using FVIII for breakthrough bleeds (for PwHA without inhibitors)*

- Plan to receive at least 4 loading doses of emicizumab and been adherent to emicizumab prophylaxis by the time of the surgery
- Undergoing minor surgery within 60 days of study enrollment. Other minor surgical procedures could be included upon consultation and approval of Medical Monitor, but examples include (see Appendix 3 for a full list):
  - Central venous catheter insertion/removal/replacement
  - Simple dental extractions
  - Colonoscopy, cystoscopy, or endoscopy with biopsy
  - Excisional skin biopsy
- Must plan to continue emicizumab prophylaxis for at least 1 month after surgery
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the study period
  - A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a postmenopausal state ($\geq$ 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 contraceptive, bilateral tubal ligation, male sterilization, 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 post-ovulation 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:

- Diagnosis of a bleeding disorder other than hemophilia A
- Tolerized to Factor VIII products *(for PwHA with inhibitors)*
- *Using FVIII products to treat breakthrough bleeds(for PwHA with inhibitors)*
- *Tolerized to FVIII products for <5 years (for PwHA without inhibitors)*
- Treatment with bypassing agents *or FVIII* within 24 hours prior to surgical procedure
- Undergoing a major surgical procedure
- Previous (in the past 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 current signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases, including, but not limited to diseases such as systemic lupus erythematosus, inflammatory bowel disease, and antiphospholipid syndrome) that may increase the risk of bleeding or thrombosis
- Patients who are at high risk for thrombotic microangiopathy (TMA; e.g., have a previous medical or family history of TMA), in the investigator's judgment
- Would refuse treatment with blood or blood products, if necessary.
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Pregnant or lactating, or intending to become pregnant during the study
  - Women of childbearing potential must have a negative serum pregnancy test result within 7 days before Study Day 1

- Treatment with any of the following:
  - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration before Study Day 1
  - A non-hemophilia-related investigational drug within the last 30 days or 5 half-lives before Study Day 1, whichever is longer
  - An investigational drug concurrently
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known HIV infection with CD4 count $<$ 200 cells/μL within 24 weeks prior to *enrollment*

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of a patient's participation in the study is expected to occur after Study Day 28.

Length of Study

The total length of the study, from *enrollment* of the first patient to the end of the study (last patient last visit), is expected to be approximately *24–30* months.

Emicizumab

If a patient is prescribed emicizumab for prophylaxis, emicizumab is administered 3 mg/kg/week subcutaneously for the first 4 weeks when initiating treatment (loading doses), followed by 1.5 mg/kg/week subcutaneously or by any other approved maintenance regimen. Patients must have received all loading doses and been adherent to emicizumab prophylaxis prior to surgery and plan to continue emicizumab for a minimum of 1 month after surgery. For the purposes of this protocol, study treatment is not intended to imply that the Sponsor is providing the study drug; rather, emicizumab is required for all patients during the study per the inclusion and exclusion criteria.

Statistical Methods

Analysis

This is an open-label, single-arm, multicenter study to evaluate emicizumab prophylaxis in PwHA *without inhibitors* and *PwHA with* inhibitors, who are undergoing minor surgical procedures. *Each cohort will be evaluated separately*. No statistical hypothesis will be tested. There are three populations that will be included in the analyses, which are defined as follows:

- All Enrolled Population: All patients who sign informed consent.
- Safety Analysis Population: All enrolled patients who receive emicizumab
- Efficacy Analysis Population: All enrolled patients who receive emicizumab and undergo a minor surgery.

Only descriptive summaries will be presented for data collected in this study. Continuous variables will be summarized using means, standard deviations, medians, and ranges; categorical variables will be summarized using proportions, and 95% confidence intervals where applicable, as appropriate. Additional details of the analyses will be presented in the statistical analysis plan.

Determination of Sample Size

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of inhibitor patients with a planned minor surgery available for participation in this study. Table 5 illustrates the precision of this study for a binary efficacy endpoint assuming a total of approximately 20–30 patients *per cohort* enrolled into this study, received emicizumab, and underwent a protocol-specified minor surgery.

During the study, a re-assessment of the initially specified sample size may be performed. This may result in an increase in sample size, if necessary, to expand the safety database.

Appendix 2
Schedule of Activities

	Screening [a]	Surgery [b]	Post-Operative Follow-Up Call [c]	Post-Operative Follow-Up Call [d]	Post-Operative Follow-Up Visit [e]	Post-Operative Follow-Up Call/ Study Completion [f]
Study Day (Window)	−60 to −1	1	2	3	8 (±2 days)	28 (±2 days)
Informed consent [g]	x					
Demographic data	x					
Medical history and baseline conditions	x					
Vital signs	x	x			x	
Weight [h]	x	x				
Limited physical examination [i,j]	x	x[k]			x	
Hematology [l]	x					
Chemistry [m]	x					
Serum pregnancy test	x					
Plasma pharmacokinetic sample		x[n]				
Concomitant medications [o]	x	x	x	x	x	x
Adverse events [p]	x	x	x	x	x	x
Bleed and Medication Diary [q]		x	x	x	x	x

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 60 days prior to Study Day 1 may be used and do not need to be repeated for *enrollment*. Patients can be *re-consented* if surgery is delayed or if they lose and regain eligibility.

[b] All assessments should be completed within 24 hours before surgery except adverse event assessment (peri-operative) and bleed/medication diary.

[c] The clinician is to call the patient on Study Day 2, which is post-operative Day 1 (approximately 24 hours post-operation), for follow-up. The call can be made up to 2 days after Study Day 2 if it falls on a weekend or holiday. This assumes that the patient was discharged and did not remain inpatient (e.g., for observation).

[d] The clinician is to call the patient on Study Day 3, which is post-operative Day 2 (approximately 48 hours post-operation), for follow-up. The call can be made up to 2 days after Study Day 3 if it falls on a weekend or holiday. This assumes that the patient was discharged and did not remain inpatient (e.g., for observation).

[e] The patient is to return to the clinic on Study Day 8 (±2 days) for follow-up.

[f] The clinician is to call the patient on Study Day 28 (±2 days) for follow-up. After this call, the patient will have completed the study.

[g] Informed consent must be documented before any study-specific *(non–standard of care)* screening procedure is performed, and may be obtained up to 60 days before enrollment in the study. *Consent date will be considered the date of enrollment.*

[h] Weight is used to calculate emicizumab dose (based on weight).

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, respiratory, gastrointestinal, and dermatologic systems. Focused examination of the musculoskeletal, genitourinary, and neurological systems should be performed as related to the surgical procedure. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Site must document that patient was clinically stable and not actively bleeding prior to discharge.

[l] Hematology includes complete blood count with differential (i.e., neutrophils, hemoglobin, platelet count).

[m] Chemistry panel includes sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, and creatine phosphokinase).

[n] PK sample must be obtained at the study site 24 hours before surgery.

[o] 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 28 days prior to surgery until Study Day 28.

- [p] After informed consent has been obtained, all adverse events will be reported until Study Day 28. After this period, adverse events should be reported per routine reporting requirements. In addition, 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. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.
- [q] Patients (or patient's legally authorized representative) will complete the bleed/medication diary and will include start date and time, reason, type, location of each bleed, as well as start date and time, reason, type, and dose of bypassing agent, if any, excluding emicizumab.