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

NCT Number: NCT03361137

Document Date: Protocol Version 4: 15-March-2019

PROTOCOL

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®)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 22 June 2017
DATE AMENDED:	Version 2: 16 August 2017 Version 3: 15 June 2018 Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	[redacted]	15-Mar-2019 16:05:27

CONFIDENTIAL

PROTOCOL AMENDMENT, VERSION 4
RATIONALE

Protocol ML39791 has been amended primarily to add an additional cohort of patients with hemophilia A (PwHA) without inhibitors, but has also been modified for clarification. Changes to the protocol and the rationale are summarized below:

- Emicizumab has been approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors. Because of this label change, the following updates have been made:
  - An additional cohort of PwHA without inhibitors has been added, as investigators would like prospectively collected data surrounding minor surgical procedures in this population. The Phase III trials were not designed to determine surgical outcomes from procedures that may have occurred. The study design, including the total length of the study, has been updated to reflect the addition of PwHA without inhibitors (Sections 1.3, 2, 3.1, 3.2, 4.1, 6, 9.4).
  - The inclusion and exclusion criteria have been updated to reflect the additional cohort and label change (4.1.1 and 4.1.2).
  - Background and other general language have been updated to reflect the label change (Section 1.2 and throughout protocol).
- The length of study has been corrected to begin at the time the first patient is enrolled (Section 3.1).
- Contraception requirements have been updated to align with the Phase III HAVEN studies (Section 4.1.1).
- The timing for HIV testing has been updated to within 24 weeks of enrollment (Section 4.1.2).
- The time window for concomitant therapy has been updated to 28 days before enrollment until Study Day 28 (Section 4.4).
- Height is no longer listed as a necessary assessment in Section 4.5.4, as it is not required per protocol.
- It has been clarified that biological samples will be destroyed no later than 5 years after the final study results have been reported (Section 4.5.6).
- The Background and Safety sections of the protocol have been updated with recent clinical data to align with the most recent United States Package Insert (USPI; Sections 1.2, 5.1.1.1, 5.1.1.2, 5.1.1.3).
- A section on immunogenicity has been added to align with the USPI (Section 5.1.1.5).
- For adverse event reporting purposes, it has been clarified that a protocol-mandated intervention may include additional surgical procedures unrelated to the primary surgery (Section 5.2.1).

- It has been clarified that the consent date will be considered the date of enrollment (Appendix 1).
- Timing for standard-of-care tests or examinations performed prior to obtaining informed consent has been clarified (Appendix 1).
- The list of minor surgical procedures that are acceptable for entry into this study has been updated to include lysis of penile adhesions (Appendix 3).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE 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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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the contract research organization (CRO).

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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	annualized bleeding rate
aPCC	activated prothrombin complex concentrate
BPA	bypassing agent
COX-2	cyclooxygenase-2
CVAD	central venous access device
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
FIXa	activated factor IX
FVIII	factor VIII
FVIII	activated factor VIII
FX	factor X
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
IgG4	immunoglobulin G4
IMP	investigational medicinal product
IRB	Institutional Review Board
LPLV	last patient last visit
NOAEL	no observed adverse effect level
PK	pharmacokinetic
PwHA	Patients with Hemophilia A
rFVIII	recombinant FVIII
rFVIIa	recombinant activated factor VII
TE	thrombotic events
TMA	thrombotic microangiopathy
USPI	US Package Insert

1. BACKGROUND

1.1 BACKGROUND ON HEMOPHILIA A WITH *AND WITHOUT* INHIBITORS

Hemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with hemophilia A (PwHA) have a deficiency or defect 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 having one defective copy of the relevant gene on their X chromosome. Because an affected male will transmit a normal Y chromosome to all his sons and an abnormal X chromosome to all his daughters, his sons will not be affected and all of his daughters will be carriers. For female carriers, with each birth there is a 50% chance to transmit the disorder to male infants and a 50% chance for female infants to be a carrier. Women 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 that is less than 35% (Plug and Mauser-Bunschoten 2006). Rarely, women can have more severe bleeding symptoms requiring treatment and may develop FVIII inhibitors. Approximately 30% of PwHA do not have a family history of the disorder; these cases arise from spontaneous FVIII gene mutations.

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of the disease roughly correlates with the residual endogenous level of FVIII activity. Approximately 68% of PwHA have moderate (25%) or severe (43%) hemophilia, characterized by FVIII activity levels of 1%–<5% or <1%, respectively, leading to frequent bleeding events with the sequelae of musculoskeletal complications, such as arthropathy, local functional deficits, hemorrhagic shock, neurocognitive defects, or even death (World Federation of Hemophilia 2013). These disease-related issues can have a significant impact on the health-related quality of life (HRQoL) of both adult and adolescent patients (Brown et al. 2009).

Prophylactic FVIII replacement therapy (i.e., administered on a scheduled basis with the intent to prevent bleeds) has been proven to minimize bleeding events and complications (Manco-Johnson et al. 2007). Since the 1990s, recombinant FVIII concentrates have been standard-of-care treatment options for PwHA (Kingdon and Lundblad 2002). Treatment regimens to achieve optimal prevention of bleeding events vary individually; some patients tolerate nadir FVIII levels of 1%, whereas others require higher nadir FVIII levels to achieve the desired therapeutic outcome (Ahnstrom et al. 2004; Collins et al. 2010). Current standard prophylactic regimens commonly use

infusion therapy administered three times weekly; other regimens can vary from every other day administration to less frequent dosing, depending on the patient's needs and the FVIII product being used (Shapiro 2013; Croteau 2015).

The required adherence to demanding therapeutic regimens that include frequent infusions to achieve adequate hemostatic coverage during periods of highest activity makes these regimens less effective and compromises their cost-benefit ratio (Thornburg 2010). Major issues with current regimens are the need for adequate venous access and patient/family compliance with regular prophylaxis, especially in the very young pediatric population, in whom central venous access devices (CVADs) have been used to overcome technical difficulties. Although CVADs make prophylaxis feasible in young children, CVADs are associated with complications, including mechanical failure, dehiscence of the skin over the reservoir, infection, and thrombosis (Ewenstein et al. 2004). In addition, significant healthcare provider efforts are required to manage optimal treatment solutions and to overcome identified issues (Schrijvers et al. 2013). Thus, both the disease and its treatment have the potential to affect HRQoL, the latter through limitations on daily activities that treatment may impose.

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%–30% of patients with severe hemophilia A and in 3%–13% of those with moderate or mild disease (Franchini and Mannucci 2013). Inhibitors neutralize the activity of endogenous FVIII as well as that of FVIII administered as replacement therapy. For patients with a history of a high-titer (≥5 BU/mL) inhibitor following a re-challenge with FVIII administration (high-responding inhibitor), the only hemostatic options currently available are pro-thrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., "bypassing agents"). Bypassing agents (BPA) include Factor Eight Inhibitor Bypassing Activity (FEIBA), an activated prothrombin complex concentrate (aPCC; FEIBA will be referred to as aPCC throughout this document), and NovoSeven® (recombinant activated human FVIIa [rFVIIa]; NovoSeven® will be referred to as rFVIIa throughout this document) (Srivastava et al. 2013). Both have been used as prophylaxis to prevent bleeding in patients with inhibitors against FVIII ("inhibitor patients"); however, the only available product for this indication in most countries is the aPCC, FEIBA. Of note, treatment of patients with congenital hemophilia A of any severity with high-titer inhibitors is similar, and their severity, as defined at diagnosis based on FVIII activity (mild, moderate, or severe), no longer is prognostic of their clinical phenotype and risk of bleeding. Both rFVIIa and aPCC have indications (Négrier 1997; Shapiro 1998) for use as prophylactic therapy for surgical procedures. Clinical response to BPAs may vary between patients. Surgery is a particular situation requiring effective hemostasis during the procedure and for several days postoperatively to obtain satisfactory wound healing. However, the optimal dose of BPA in different surgical situations has not been clearly established.

The development of effective prophylactic treatment options with decreased immunogenicity and less frequent dosing requirements is a high, unmet medical need in

PwHA. Reducing the time and burden associated with frequent intravenous dosing and the impact of the disease on aspects of physical health and other areas of function, while promoting increased efficacy, may further improve HRQoL. *In patients with inhibitors, d*ata from a study showed that patients receiving prophylactic treatment with FEIBA had improved HRQoL compared to those who received episodic therapy (i.e., administered following bleeds) with FEIBA (Gringeri et al. 2013). Therefore, despite major therapeutic advances in the treatment of hemophilia A, opportunities remain to optimize and transform therapy, in particular for patients with inhibitors.

APCCs may be associated with side effects, such as thromboembolic events, hypersensitivity reactions, and disseminated intravascular coagulation, as well as anemia, diarrhea, hepatitis B surface antibody positive, nausea, and vomiting. RFVIIA side effects may include thrombosis and hypersensitivity, as well as fever, headache, injection site reactions, dizziness, nausea, or vomiting. Both aPCC and rFVIIa are administered intravenously, with aPCC prophylaxis requiring every other day dosing and rFVIIa requiring daily (or more frequent) dosing.

1.2 BACKGROUND ON EMICIZUMAB (HEMLIBRA®)

Emicizumab (HEMLIBRA; ACE910; CH5534262; RO5534262) is a recombinant, humanized, bispecific immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), bridging the factors together to allow for activation of FX by FIXa. Emicizumab is being developed for the treatment of hemophilia A. In the United States, emicizumab is *indicated* for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients *ages newborn and older* with hemophilia A (congenital factor VIII deficiency) with *or without* factor VIII inhibitors.

In PwHA, hemostasis can be restored with emicizumab irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. In addition, emicizumab can be administered via subcutaneous (SC) injection, alleviating the need for venous access. Finally, due to the pharmacokinetic (PK) properties of therapeutic antibodies, markedly extending the dosing interval to once weekly or less frequently is possible with this novel compound and provides an alternate treatment choice for PwHA with and without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

The nonclinical and clinical data with emicizumab support a positive benefit-risk assessment, which has been validated with approval for use by various drug approval agencies. Evaluation of in vivo efficacy under spontaneous or local trauma-induced bleeding conditions in cynomolgus monkeys using a hemophilia A model demonstrated the ability of emicizumab to significantly reduce bleeding tendency under both sets of conditions. In terms of safety, thrombus formation with emicizumab did not markedly exceed thrombus formation observed with FVIIa, aPCC, or FVIII in an in vivo cynomolgus monkey venous stasis model. No toxicologically relevant changes

attributable to SC (at doses up to 30 mg/kg weekly) or IV (at doses up to 100 mg/kg weekly) administration of emicizumab were observed, and the no observed adverse effect level (NOAEL) was the highest tested dose in each toxicity study.

Currently available experience with emicizumab in humans includes data from two completed Phase I studies (ACE001JP and JP29574), and an ongoing Phase I/II extension study (ACE002JP). ACE001JP was a single study conducted in three parts, including 48 healthy male volunteers (Parts A and B) and 18 PwHA (Part C) who received emicizumab. Emicizumab was administered at doses of 0.3, 1, and 3 mg/kg/week. Only PwHA received the 3 mg/kg dose.

In addition, the clinical program includes Phase III studies in patients with hemophilia A: HAVEN 1 evaluates emicizumab prophylaxis in people 12 years of age or older with hemophilia A and inhibitors to factor VIII who were previously treated with episodic or prophylactic bypassing agents. HAVEN 2 evaluates weekly, every other week, and every 4 weeks dosing in pediatric patients with inhibitors. HAVEN 3 evaluates weekly and every other week dosing in adolescent and adult patients without inhibitors and HAVEN 4 evaluates every 4-week dosing in adolescent and adult patients with and without inhibitors.

The Phase I and I/II studies demonstrated promising results for emicizumab prophylaxis in reducing the annualized bleeding rate (ABR) in Japanese PwHA with and without inhibitors against FVIII. After administration of emicizumab to PwHA, ABRs decreased in all patients compared to the pretreatment period, regardless of whether or not they had FVIII inhibitors, with the exception of 1 patient in the 3 mg/kg/week group who was previously treated with FVIII prophylaxis and had a baseline ABR of 0; in this patient, ABR was maintained at 0 while receiving emicizumab. Among all patients, percentage reduction in ABRs based on initial dose cohort assignment ranged from 22.8% to 100% in the 0.3 mg/kg/week group, from 81.7% to 100% in the 1 mg/kg/week group, and from 92.6% to 100% in the 3 mg/kg/week group.

In the Phase I/II studies, no thromboembolic or systemic hypersensitivity adverse events have been seen to date. The majority of adverse events were of a mild or moderate intensity. The most common related adverse events were mild injection-site reactions. A total of 150 adverse events were observed in the 18 PwHA in Study ACE0001JP. The majority of adverse events were of mild intensity, except for 11 moderate adverse events (upper respiratory tract infection, bipolar disorder, contusion, enteritis infectious, impaired healing, musculoskeletal pain, calculus ureteric, hemophilia [i.e., left hip joint bleeding due to hemophilia], hand fracture, asthma, and headache) and two severe events (appendicitis and mesenteric hematoma), neither of which was deemed related to emicizumab. Local injection site reactions were observed in 7 patients (38.9% of patients).

In the Phase III study in adolescents and adults (HAVEN 1), patients previously treated with episodic BPA were randomized in a 2:1 ratio to receive either prophylactic emicizumab 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC thereafter (Arm A), or to the control arm (Arm B), which consists of no prophylaxis (i.e., only episodic bypassing agent treatment). Patients previously treated with prophylactic BPA were switched immediately to prophylactic emicizumab (Arm C). Episodic treatment of breakthrough bleeds with bypassing agents was allowed per protocol. The primary endpoint of the study is the number of treated bleeds over time with emicizumab prophylaxis (Arm A) versus no prophylaxis (Arm B). The study showed a statistically significant reduction in the number of bleeds over time in people treated with emicizumab prophylaxis compared to those receiving no prophylactic treatment. The study also met all secondary endpoints, including a statistically significant reduction in the number of bleeds over time with emicizumab prophylaxis treatment in an intra-patient comparison in people who had received prior bypassing agent prophylaxis treatment.

Interim results from the Phase III study evaluating emicizumab prophylaxis in children less than 12 years of age with hemophilia A and inhibitors to factor VIII (HAVEN 2) showed a clinically meaningful reduction in the number of bleeds over time after a median of 12 weeks of treatment.

Pooled data from *two randomized trials in adult and adolescent patients (HAVEN 1 and HAVEN 3), one single-arm trial in adult and adolescent patients (HAVEN 4), one single-arm trial in pediatric patients (HAVEN 2), and one dose-finding trial, in which a total of 391 male patients with hemophilia A received at least 1 dose of HEMLIBRA as routine prophylaxis showed that* four patients (*1*%) withdrew from treatment due to adverse reactions, which were thrombotic microangiopathy, skin necrosis and superficial thrombophlebitis, *headache,* and injection site reaction.

Additionally, there were *130* instances of aPCC treatment in *37* patients, of which 13 instances (10%) consisted of on average a cumulative amount of >100 U/kg/24 hours of aPCC for 24 hours or more; 2 of the 13 were associated with thrombotic events and 3 of the 13 were associated with TMA. Both patients with TE and 2 of 3 patients with TMA have fully recovered. One patient with TMA died from rectal hemorrhage (see Section 5.1.1).

Two patients (1 patient with TMA and 1 patient with TE) restarted emicizumab in the HAVEN 1 trial without recurrence of TMA or TE. No TE or TMA events have been observed during the interim analysis of the HAVEN 2 trial.

Results from HAVEN 3 and HAVEN 4 have demonstrated that emicizumab prophylaxis reduced bleeding events requiring treatment in patients without inhibitors on a once weekly or every 2 weeks dosing schedule and in patients with and without

inhibitors on an every 4 weeks dosing schedule (Genentech 2018; Mahlangu et al. 2018; Young et al. 2018).

Note: Investigators are recommended to refer to US-Package Insert (USPI) of HEMLIBRA® (emicizumab) (*2018*) for additional details on results of nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

PwHA with inhibitors routinely require treatment with BPA*,* to control perioperative bleeding*, while PwHA without inhibitors routinely require treatment with FVIII to control perioperative bleeding*. They may receive doses pre-operatively, intra-operatively, and post-operatively depending on the extent of the surgical procedure and likelihood of bleeding. This study will investigate whether or not patients with hemophilia A *with and without* inhibitors who are on emicizumab prophylaxis can undergo minor surgical procedures without the need for additional *prophylaxis with* BPA *or FVIII, respectively, to prevent* excessive surgical bleeding.

All consensus guidelines regarding treatment of bleeding for patients with hemophilia *A with* and *without* inhibitors undergoing surgical procedures recommend treatment with BPA/*FVIII* (Giangrande et al. 2009; Teitel et al. 2009; Shapiro and Cooper 2012*; National Hemophilia Foundation 2017; Collins et al. 2018*). *Treatment with hemostatic agents (BPA/FVIII for patients with and without inhibitors, respectively)* is at the discretion of the physician based on the duration, complexity, and risk of bleeding with the procedure. However, with emicizumab prophylaxis, it is believed that patients will have enough hemostatic ability to forgo the need for additional pre-operative prophylaxis with BPA*/FVIII* when undergoing minor surgical procedures. There has been some experience and case reports of patients who have undergone minor surgical procedures while on emicizumab prophylaxis, though there has not been a uniform approach to these procedures and management was left to the discretion of the treating physician (Kruse-Jarres et al. 2017a; Kruse-Jarres et al. 2017b). In this study, all patients will preoperatively be treated only with emicizumab prophylaxis, and intra-operative or post-operative treatment with BPA*/FVIII* will only be administered for excessive bleeding (or new breakthrough bleeds) at the discretion of the treating physician.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety and efficacy of emicizumab prophylaxis in PwHA *with* and *without* inhibitors undergoing minor surgical procedures. *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 (Sections 4.1.1 and 4.1.2).

Table 1 Objectives and Endpoints

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, see Appendix 2) 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.*

3. STUDY DESIGN

3.1 DESCRIPTION OF THE 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 (for patients with inhibitors) or FVIII (for patients without inhibitors). Note: Throughout the protocol, unless otherwise noted, all references to BPA will be specific for patients with inhibitors and all references to FVIII will be specific for patients without inhibitors.*

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 *and 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 (±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 (±2 days) to record any surgical complications, bleeds, and/or use of BPA*/FVIII* (see Appendix 1).

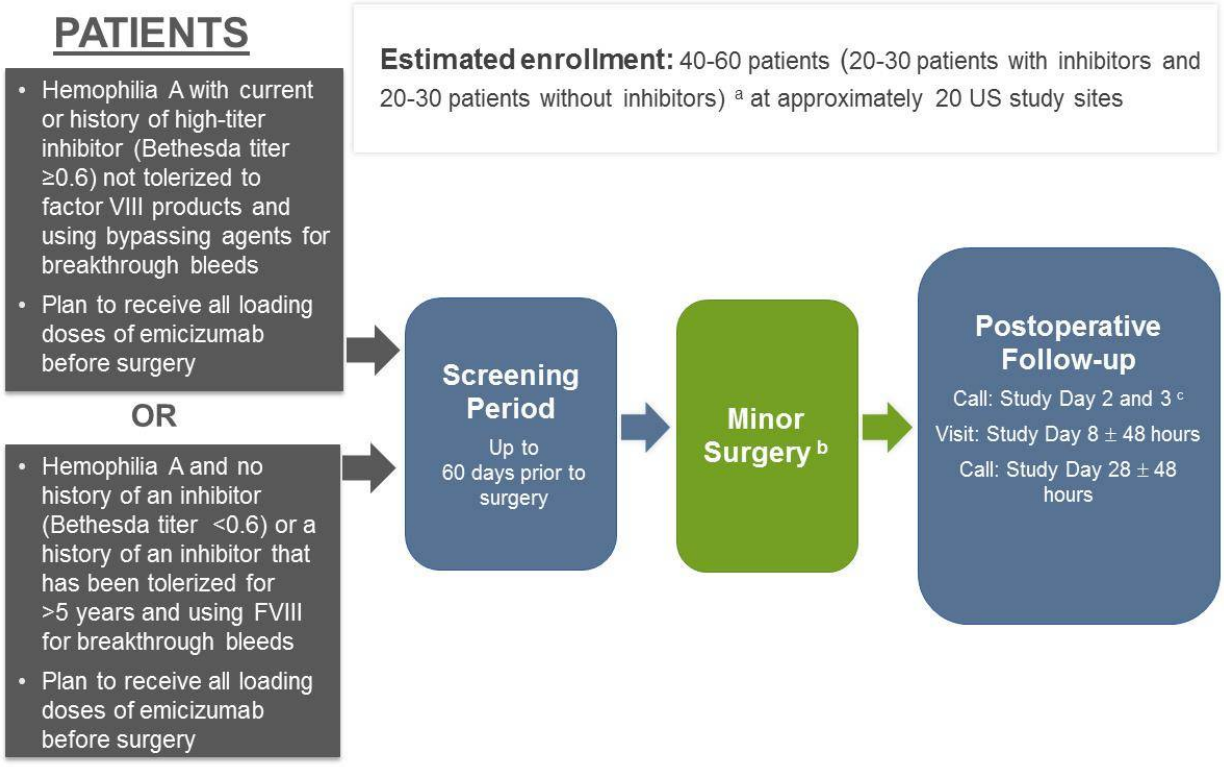
Blood samples will also be collected in this study for observational purposes and will not be used to determine eligibility or treatment decisions. Samples will be used to evaluate emicizumab concentration (PK) prior to surgery.

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.

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.

3.2 END OF STUDY AND LENGTH 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.

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*.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Emicizumab Dose and Schedule

Emicizumab is given at a loading dose of 3 mg/kg SC once weekly for the first 4 weeks followed by 1.5 mg/kg SC once weekly or by any other FDA-approved maintenance regimen.

Note: Investigators are recommended to refer to US-Package Insert (USPI) of HEMLIBRA® (emicizumab) (*2018*) for additional details on emicizumab dose and schedule.

3.3.2 Rationale for Biomarker Assessments

Emicizumab plasma concentration has been shown to vary among patients (data on file) and patients receive similar benefits at various levels. Emicizumab plasma concentration will be collected prior to surgery and assessed in an effort to identify any relationship to efficacy or safety.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately *40–60 PwHA (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. The list of surgery types is provided in Appendix 3.

4.1.1 Inclusion Criteria

- 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 *≥ 0.6* Bethesda units*) and currently using BPA for breakthrough bleed (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 (≥ 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.

4.1.2 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
- Patients who have been tolerized to Factor VIII products *(for PwHA with inhibitors)*
- *Tolerized to FVIII products for <5 years (for PwHA without inhibitors)*
- *Using FVIII products to treat breakthrough bleeds (for PwHA with 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*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label, single-arm study in which all enrolled patients are receiving emicizumab.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

4.3.1 Study Treatment

4.3.1.1 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 (see Sections 4.1.1 and 4.1.2).

4.3.2 Study Treatment Dosage, Administration, and Compliance

All eligible patients receive emicizumab via SC injection at a loading dose 3 mg/kg once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, or by any other approved maintenance regimen, as long as they continue to derive sufficient benefit. Patients must have received all loading doses prior to surgery and plan to continue emicizumab for a minimum of 1 month after surgery. Dosing should be adjusted if the patient has a significant change in body weight.

Note: Investigators are recommended to refer to the USPI of HEMLIBRA® (emicizumab) (*2018*) for additional details on emicizumab dose and administration.

4.3.3 Continued Access to Emicizumab

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Sponsor study drug (emicizumab) or any other study treatments or interventions to patients *during the study or to patients who* have completed the study.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 28 days before *enrollment* until Study Day 28. Hemostatic medications to treat or prevent bleeds in the week prior to starting emicizumab will also be collected. All medications, including treatments for bleeds (i.e., BPA*/FVIII* and other medications to treat bleeds) should be reported to the investigator at each contact with their Healthcare Provider and will be captured in the eCRF.

4.4.1 Permitted Therapy

Concomitant use of the following drugs and therapies will be permitted:

- Drugs intended to treat bleeds, including BPA*/FVIII (for PwHA with and without inhibitors, respectively)* as standard-of-care treatment
  - Emicizumab increases coagulation potential. If a bypassing agent is indicated in a patient receiving emicizumab prophylaxis, the bypassing agent dose required may be lower than that used without emicizumab prophylaxis. The dose and duration of treatment with bypassing agents will depend on the location and extent of bleeding and the patient's clinical condition.
  - Avoid use of aPCC unless no other treatment options are available. If aPCC is indicated in a patient receiving emicizumab prophylaxis, the initial dose should not exceed 50 U/kg. If bleeding is not controlled with the initial dose of aPCC up to 50 U/kg, then additional doses of aPCC should be administered under medical guidance or supervision, and the total aPCC dose should not exceed 100 U/kg over 24 hours of treatment. Weigh the risk of TMA and thromboembolism against the risk of bleeding when considering aPCC treatment beyond the initial 100 U/kg over 24 hours. Continue following this bypassing agent dosing guidance for at least 6 months after discontinuation of emicizumab prophylaxis
- Anti-fibrinolytics will be allowed pre-operatively and use can be continued in the peri-operative and post-operative periods
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to result in systemic exposure
- Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Note: Investigators are recommended to refer to the USPI of HEMLIBRA® (emicizumab) (*2018*) for additional details on emicizumab dose and administration.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 4 weeks prior to study start unless otherwise noted:

- Drugs that would affect hemostasis (e.g., aspirin, non-steroidal anti-inflammatory drugs that are not selective or preferential cyclooxygenase-2 [COX-2] inhibitors, or anticoagulants [other than to flush, dwell, or de-clot a CVAD]) but excluding drugs intended to control bleeding episodes or used in the context of minor surgery (e.g., tooth extraction) or injuries (e.g., concussion) to prevent deterioration
- Systemic immunomodulators (e.g., rituximab, interferon) other than antiretroviral therapy from enrollment to last observation
- FVIII or BPA for prophylaxis or for the treatment of a breakthrough bleed within 24 hours prior to surgery
- Other investigational drugs from enrollment to last observation

If prohibited therapy is administered for any reason, it should be recorded on the eCRF. If prohibited treatment is prescribed or considered medically necessary, the medical monitor should be consulted to discuss any changes in the benefit/risk and determine whether the patient should continue on the study.

4.5 STUDY ASSESSMENTS

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

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Children and adolescents (< 18 years of age) will complete an Assent Form when capable and their parents or legally authorized representatives will also complete an Informed Consent Form. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

If the screening period extends beyond the 60-day window allowed by the protocol for any reason, the patient should be re-consented prior to the expiration of the original 60-day screening window. The complete screening evaluations should also be repeated and documented following the re-consent. Only one extension of the screening period with proper re-consent will be allowed for a patient.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history includes hemophilia-related history, clinically significant diseases, procedures, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior immune tolerance induction, anaphylaxis, or known thrombophilia. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to Study Day 1 will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A limited physical examination will include 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.

4.5.4 Vital Signs

Vital sign assessments will include measurements of body temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, and weight, as indicated in the schedule of assessments (see Appendix 1).

4.5.5 Bleed and Medications Diary

Patients (or patient's legally authorized representative) will complete the bleed/medication diary; one diary card per week for 4 weeks after being discharged from surgery. Information obtained will include start date and time, reason, type, location of each bleed, as well as start date and time, reason, type, and dose of each injection, if any, including emicizumab. Diary entries for events should be completed on the cards as soon as events occur.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (complete blood count with differential [i.e., neutrophils, hemoglobin, platelet count])
- Serum chemistries (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)

- Pregnancy test: Women of childbearing potential must have a negative serum pregnancy test result within 7 days before Study Day 1

Samples for the following laboratory tests will be sent to a central laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Serum samples for pharmacokinetic analysis

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

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. Samples collected for study-related analyses will be *destroyed no later than* 5 years after the final study results have been reported.

Data arising from sample analysis including data on germline mutations will be subject to the confidentiality standards described in Section 8.4.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Discontinuation

Patients must permanently discontinue the study if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue the study prematurely will not be replaced.

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient's inability or unwillingness to comply with protocol requirements
- Non-compliance despite appropriate education measures taken by the clinical site

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the

appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Emicizumab is being developed for the treatment of hemophilia A, and is FDA approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with *or without* factor VIII inhibitors. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below. Refer to the HEMLIBRA® (emicizumab) USPI for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Emicizumab

5.1.1.1 Thromboembolic Events and Thrombotic Microangiopathy

Thrombotic Microangiopathy Associated with Emicizumab and aPCC

Cases of thrombotic microangiopathy (TMA) were reported from clinical trials when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving emicizumab prophylaxis. In clinical trials, thrombotic microangiopathy was reported in 0.8% of patients (3 of 391) and in 9.7% of patients (3 of 3$7$) who received at least one dose of aPCC. Patients presented with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury, without severe deficiencies in a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity.

Evidence of improvement was seen within one week following discontinuation of aPCC. One patient resumed emicizumab following resolution of TMA.

Consider the benefits and risks if aPCC must be used in a patient receiving emicizumab prophylaxis. Monitor for the development of TMA when administering aPCC. Immediately discontinue aPCC and interrupt emicizumab prophylaxis if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Consider the benefits and risks of resuming emicizumab prophylaxis following complete resolution of TMA on a case-by-case basis.

Thromboembolism Associated with Emicizumab and aPCC

Thrombotic events were reported from clinical trials when on average a cumulative amount of >100 U/kg/24 hours of aPCC was administered for 24 hours or more to patients receiving emicizumab prophylaxis. In clinical trials, thrombotic events were reported in 0.5% of patients (2 of 391) and in 5.4% of patients (2 of 3$7$) who received at least one dose of aPCC.

No thrombotic event required anticoagulation therapy. Evidence of improvement or resolution was seen within one month following discontinuation of aPCC. One patient resumed emicizumab following resolution of thrombotic event.

Consider the benefits and risks if aPCC must be used in a patient receiving emicizumab prophylaxis. Monitor for the development of thromboembolism when administering aPCC. Immediately discontinue aPCC and interrupt emicizumab prophylaxis if clinical symptoms, imaging, or laboratory findings consistent with thromboembolism occur, and manage as clinically indicated. Consider the benefits and risks of resuming emicizumab prophylaxis following complete resolution of thrombotic events on a case-by-case basis.

5.1.1.2 Injection-Site Reactions

In total, 85 patients (22%) reported injection site reactions (ISRs). All ISRs observed in emicizumab clinical trials were reported as mild to moderate intensity. Most ISRs (93%)

resolved without treatment. The most commonly reported ISR symptoms were injection site erythema (*11*%), injection site pain (*4*%)*, and injection site pruritus (4%)*.

Note: Investigators are recommended to refer to the USPI of HEMLIBRA® (emicizumab) (*2018*) for additional details on ISRs observed in PwHA while on emicizumab prophylaxis.

5.1.1.3 *Systemic* Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid

Since emicizumab is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions, may occur. As of *October* 201*8*, in completed and ongoing clinical studies of emicizumab, no *serious adverse events consistent with systemic* hypersensitivity*, anaphylactic, or anaphylactoid* reactions have been reported. These events should be reported as serious adverse events or Adverse Events of Special Interest as described in Section 5.2.3.

HCPs should instruct patients how to recognize the signs and symptoms of *systemic* hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an HCP or seek emergency care in case of any such occurrence.

5.1.1.4 Life-Threatening Bleeding Due to Unreliable Standard Coagulation Tests and Inhibitor Assays in the Setting of Emicizumab

Coagulation laboratory tests (including, but not limited to, aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by Bethesda assay) are not reliable and do not accurately reflect the patient's underlying hemostatic status while receiving emicizumab prophylaxis (see Section 5.1.2). Due to the long $t_{1/2}$ of emicizumab, these effects on coagulation assays may persist for up to 6 months after the last dose.

There is a risk of life-threatening bleeding due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab, which may be observed by practitioners, particularly emergency care practitioners.

Emicizumab's mechanism of action and resulting interference was clearly demonstrated in a wide variety of coagulation laboratory tests approved for in vitro diagnostic use. Clinical trials also demonstrated the effects of emicizumab on laboratory tests. However, as of April 2017, no instances of under-treatment of bleeding events due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab were observed.

5.1.1.5 *Immunogenicity*

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons,

comparison of the incidence of antibodies to emicizumab-kxwh in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of emicizumab was evaluated using an enzyme-linked immunosorbent assay (ELISA) or an electrochemiluminescence (ECL) assay. In the dose-finding trial (n = 18), four patients tested positive for anti-emicizumab antibodies. In the pooled HAVEN clinical trials, 3.5% of patients (14/398) tested positive for anti-emicizumab antibodies and <1% of patients (3/398) developed anti-emicizumab antibodies with neutralizing potential (based on declining pharmacokinetics). One patient from HAVEN 2, who developed an anti-emicizumab neutralizing antibody, experienced loss of efficacy after 5 weeks of treatment.

There was no clinically apparent impact of the presence of anti-emicizumab-kxwh antibodies on safety.

5.1.2 Laboratory Coagulation Test Interference

Emicizumab affects intrinsic pathway clotting-based laboratory tests, including activated clotting time (ACT), aPTT, and all assays based on aPTT, such as one-stage FVIII activity (Table 2). Therefore, intrinsic pathway clotting-based laboratory test results in patients treated with emicizumab should not be used to monitor emicizumab activity, determine dosing for factor replacement or anti-coagulation, or measure FVIII inhibitor titers. Laboratory tests affected and unaffected by emicizumab are shown in Table 2.

Table 2 Coagulation Test Results Affected and Unaffected by Emicizumab (HEMLIBRA)

Results Affected by Emicizumab	Results Unaffected by Emicizumab
Activated partial thromboplastin time (aPTT)	Thrombin Time (TT)
Activated clotting time (ACT)	One-stage, PT-based, single factor assays
One–stage, aPTT-based, single factor assays	Chromogenic-based single-factor assays other than FVIII*
aPTT-based Activated Protein C Resistance (APC-R)	Immuno-based assays (i.e., ELISA, turbidometric methods)
Bethesda assays(clotting-based) for FVIII inhibiter titers	Bethesda assays (bovine chromogenic) for FVIII inhibitor titers
	Genetic tests of coagulation factors (e.g., Factor V Leiden, Prothrombin 20210)

Effects of Emicizumab on Coagulation Test Results

Emicizumab restores the tenase cofactor activity of activated factor VIII (FVIIIa). Coagulation laboratory tests based on intrinsic clotting (i.e., aPTT) measure the total clotting time including time needed for activation of FVIII to FVIIIa by thrombin. Such intrinsic pathway-based tests will yield overly shortened clotting times with emicizumab, which does not require activation by thrombin. The overly shortened intrinsic clotting time will then disturb all single-factor assays based on aPTT, such as the one-stage

FVIII activity assay. However, single-factor assays utilizing chromogenic or immuno-based methods are not affected by emicizumab and may be used to monitor coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays as described below.

Chromogenic FVIII activity tests may be manufactured with either human or bovine coagulation proteins. Assays containing human coagulation factors are responsive to emicizumab but may overestimate the clinical hemostatic potential of emicizumab. In contrast, assays containing bovine coagulation factors are insensitive to emicizumab (no activity measured) and can be used to monitor endogenous or infused FVIII activity, or to measure anti-FVIII inhibitors.

Emicizumab remains active in the presence of inhibitors against FVIII and so will produce a false-negative result in clotting-based Bethesda assays for functional inhibition of FVIII. Instead, a chromogenic Bethesda assay utilizing a bovine-based FVIII chromogenic test that is insensitive to emicizumab may be used.

Due to the long half-life of emicizumab, these effects on coagulation assays may persist for up to 6 months after the last dose.

Note: Investigators are recommended to refer to the USPI of HEMLIBRA® (emicizumab) (*2018*) for additional details on which tests can be used and how the test results can be interpreted.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study. Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to Study Day 1 (e.g., screening invasive procedures such as biopsies, *or additional surgical procedures unrelated to the primary surgery)*

All bleeds will be recorded on the bleed/medication diary. Bleeds meeting the criteria of serious adverse events (as per Section 5.2.2) should be reported on the appropriate adverse event eCRF page regardless of whether the bleeds are consistent with patients' pre-study disease state. New, non-serious bleeds consistent with patients' pre-study disease state will not be considered adverse events.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). These include either suspected or confirmed cases. Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.
  - A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Anaphylactic, anaphylactoid, and severe systemic hypersensitivity reactions (see Sampson's Criteria in Appendix 5)
- Thromboembolic events
- Thrombotic microangiopathy

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4 – 5.6

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained, all adverse events will be reported until Study Day 28).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The World Health Organization (WHO) toxicity grading scale (see Appendix 4) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Notes: Developed by the Division of Microbiology and Infectious Diseases.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of study drug

- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged by the investigator to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction") on the Adverse Event eCRF. An injection related reaction that is localized should be marked as a “local injection-site reaction.” Associated signs and symptoms (e.g., injection-site erythema or injection-site rash) should be recorded on the dedicated Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same administration of study drug, each reaction should be recorded separately on the Adverse Event eCRF. Only for local injection-site reactions should the dedicated Injection-Site Reaction eCRF be used to capture the individual signs/symptoms.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

For concerns about laboratory findings on coagulation-related tests in patients receiving emicizumab, refer to Section 5.1.2 or contact the Medical Monitor.

5.3.5.6 Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event of special interest the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice in the absence of cholestasis or other cause of hyperbilirubinemia

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.5) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.2.3).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of hemophilia.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should

be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of hemophilia "hemophilia progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Hemophilic Bleeds

Medical occurrences or symptoms of deterioration that are anticipated as part of hemophilia should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity (e.g., increased number of coagulation factor doses required to stop bleeds with emicizumab, in the absence of neutralizing anti-emicizumab antibodies, compared with before study entry) or frequency of bleeds or changed in nature at any time during the study. When recording an unanticipated worsening of hemophilia on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia").

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) outside of observation post-operatively or prolonged hospitalization (defined as hospitalization for additional nights (more than 1 night) post-operatively) should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2, except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)
- Overdoses, medication errors, drug abuse, or drug misuse (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitors: [redacted], M.D.

Telephone Nos.: [redacted] (United States)

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

Serious Adverse Events and Adverse Events of Special Interest should be reported after informed consent has been obtained, until Study Day 28. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. The Adverse Event eCRF should be completed and submitted via the EDC system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur greater than 28 days after surgery are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue emicizumab and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth

defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.4.4 Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm}
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with emicizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong

dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.

- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or 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.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after surgery) if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- US-Package Insert (PI) of HEMLIBRA (emicizumab)® (*2018*)

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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.

6.1 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.

Table 5 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.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized overall and by type of surgery. 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.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by type of surgery.

6.4 EFFICACY ANALYSES

Descriptive statistics along with 95% confidence intervals will be used to provide point estimates and precision related to efficacy outcomes.

6.5 SAFETY ANALYSES

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

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.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean emicizumab concentrations will be tabulated. Additional analyses will be conducted as appropriate.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and

IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately *40-60 patients (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.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

	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.

Appendix 2
Assessment of Hemostatic Response for Surgical Procedures

Excellent	Intraoperative and postoperative blood loss similar (within 10%) to the non-hemophilic patient with no extra (unplanned) doses of FVIII/FIX/'bypassing agents' needed and blood component transfusions are similar to the non-hemophilic patient
Good	Intraoperative and/or postoperative blood loss slightly increased over expectation for the non-hemophilic patient (between 10 and 25% of expected), but the difference is judged by the involved surgeon/anesthetist/relevant healthcare professional to be clinically insignificant as evidenced by no extra (unplanned) doses of FVIII/FIX/'bypassing agents' needed and blood component transfusions are similar to the non-hemophilic patient
Fair	Intraoperative and/or postoperative blood loss increased over expectation (25–50%) for the non-hemophilic patient and additional treatment is needed such as extra (unplanned) doses of FVIII/FIX/'bypassing agents' or increased blood component use (within two-fold) of the anticipated transfusion requirement
Poor	Significant intraoperative and/or postoperative blood loss that is substantially increased over expectation (> 50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia, unexpected hypotension or unexpected transfer to an Intensive Care Unit due to bleeding or substantially increased blood component use (> 2 fold) of the anticipated transfusion requirement

Source: Blanchette et al. 2014.

Appendix 3
Minor Surgical Procedures

The below procedures meet the definition of minor for the purposes of this study:

- Abdominal hernia repair
- Botulinum toxin injections
- Central venous catheter insertion/removal/replacement
- Circumcision
- Colonoscopy, cystoscopy, or endoscopy with biopsy
- Simple dental extractions (not oral surgery)
- Excision of nevi
- Excisional skin biopsy
- Hardware (e.g. external fixation, pins, etc.) removal
- Intra-articular injections
- *Lysis of penile adhesions*
- Nail removal
- Tendon lengthening
- Wound debridement
- Other (surgeries not listed here may be included after consultation and approval by the Genentech Medical Monitor)

Appendix 4
World Health Organization Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	< 6.5 g/dL
Absolute neutrophil count	1000–1500/mm^3	750–999/mm^3	500–749/mm^3	< 500/mm^3
Platelets	75000–99999/mm^3	50000–74999/mm^3	20000–49999/mm^3	< 20000/mm^3
Prothrombin time (PT)	1.01–1.25 × ULN	1.26–1.5 × ULN	1.51–3.0 × ULN	> 3 × ULN
Activated partial thromboplastin (APTT)	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3 × ULN	> 3 × ULN
Fibrinogen	0.75–0.99 × LLN	0.50–0.74 × LLN	0.25 - 0.49 × LLN	< 0.25 x LLN
Fibrin split product	20–40 mcg/mL	41–50 mcg/mL	51–60 mcg/mL	> 60 mcg/mL
Methemoglobin	5–9.9%	10.0–14.9%	15.0–19.9%	> 20 %
LIVER ENZYMES				
AST (SGOT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
ALT (SGPT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
GGT	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Alkaline phosphatase	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	> 5.0 × ULN
CHEMISTRIES				
Hyponatremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	> 165 mEq/L or mental status changes or seizures
CHEMISTRIES (cont.)				
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required.	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia

Appendix 4
World Health Organization Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	>7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116–160 mg/dL	161–250 mg/dL	251–500 mg/dL	>500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	<6.1 mg/dL or life-threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	>13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4–1.2 mEq/L	1.1–0.9 mEq/L	0.8–0.6 mEq/L	<0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0–2.4 mg/dL	1.5–1.9 mg/dL or replacement Rx required	1.0–1.4 mg/dL intensive Rx or hospitalization required	<1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1–1.5 × ULN	1.6–2.5 × ULN	2.6–5 × ULN	>5 × ULN
BUN	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	>10 × ULN
Creatinine	1.1–1.5 × ULN	1.6–3.0 × ULN	3.1–6 × ULN	>6 × ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or <0.3% or <3g/L or 200 mg–1 g loss/day	2–3+ or 0.3–1.0% or 3–10 g/L 1–2 g loss/day	4+ or >1.0 % or >10 g/L 2–3.5 g loss/day	nephrotic syndrome or >3.5 g loss/day
Hematuria	microscopic only	gross, no clots	gross + clots	obstructive or required transfusion

Appendix 4
World Health Organization Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires treatment
Hypertension	transient, inc. >20 mm; no Rx	recurrent, chronic, >20 mm, Rx required	requires acute Rx; no hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1–2 units transfused	massive blood loss; >3 units transfused
RESPIRATORY				
Cough	transient; no Rx	treatment-associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx <70%–79% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50%–69% (or peak flow)	no normalization with bronchodilator; FEV_1 25%–49% (or peak flow retractions)	cyanosis: FEV_1 <25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some	severe discomfort; no significant intake; activities limited	minimal fluid intake

Appendix 4
World Health Organization Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
		activity limited		
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3–4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or >7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
NEURO AND NEUROMUSCULAR				
Neuro-cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization

Appendix 4
World Health Organization Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
NEURO AND NEUROMUSCULAR (cont.)				
Neuro control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/ agitation; some limitation of ADL; minimal Rx	severe confusion/agitation; needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle strength	subjective weakness no objective symptoms/signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
OTHER PARAMETERS				
Fever: oral, > 12 hours	37.7–38.5 C or 99.9–101.3 F	38.6–39.5 C or 101.4–103.1 F	39.6–40.5 C or 103.2–104.9 F	> 40.5 C or > 104.9 F
Headache	mild, no Rx therapy	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25–50%	normal activity decreased > 50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	Induration ≥ 10 cm or ulceration	necrosis
Mucocutaneous	erythema; pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema multiforme or suspected Stevens-Johnson or necrosis requiring surgery

For coding purposes, the following toxicity grades may be used interchangeably: 1 = mild; 2 = moderate; 3 = severe; 4 = life threatening.

Appendix 5
Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network.[1] Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue/uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

   - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure [2]
   - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

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1 Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117: 391–7.

2 Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.