Investigator Initiated Study

Study Title	Prospective, single-arm, open-label use of Hemlibra (emicizumab) to treat hemophilic pseudotumor
ClinicalTrials.gov #	NCT03921294
Internal tracking #	RO-IIS-2018-10581
Study Phase	4
Product Name	US-labeled Hemlibra (emicizumab-kxwh)
Indication	Hemophilic pseudotumor in hemophilia A patients
Principal Investigator	Amy D. Shapiro, M.D.
Sponsor	The Indiana Hemophilia and Thrombosis Center (IHTC)
Grantor	Genentech

Protocol Version: 3.0

Date of Original Approved Protocol (v1.1): March 28, 2019

Date of Amendment: June 16, 2020

Confidentiality Statement

Part or all the information in this protocol may be unpublished material. Accordingly, this protocol should be treated as confidential information and its use restricted to supplying information to investigators, regulatory authorities, ethics committees, and other personnel involved in this study who need to be aware of the content of the protocol.

Approved by: *See electronic signature and date/timestamp.*

Signature *Date*

Amy D. Shapiro, MD

Printed Name

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HISTORY OF PROTOCOL REVISIONS

Version	Date approved	Comments
1.1	March 28, 2019	Original protocol
2.0	**February 27, 2020**	Amendment #1
3.0	**June 16, 2020**	Amendment #2

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PROTOCOL VERSION 2.0 (AMENDMENT #1)
RATIONALE FOR CHANGES

Changes to the protocol that modify the study design or analyses, along with a rationale for each change are summarized below:

Change	Rationale	Affected protocol sections
Dose escalation from 1.5 mg/kg QW to 3.0 mg/kg QW (maintenance dose)	Subjects may continue to experience suboptimal control of breakthrough bleeding on Hemlibra (emicizumab) prophylaxis. If so, an increase in maintenance dose to 3 mg/kg QW may be appropriate.	5.1.1 5.3.2 5.3.3 7.3
Visit windows row added to the schedule of events	Clarify visit windows on visual schedule of events	Appendix 12

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PROTOCOL VERSION 2.0 (AMENDMENT #1)
SUMMARY OF CHANGES

Protocol Synopsis
The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

Section 5.1.1 Study Drug
The study drug is US-labeled Hemlibra (emicizumab). It will be administered using the FDA approved once-weekly doing regimen for loading dose (3 mg/kg) and prophylactic dose (1.5 mg/kg*, or 3 mg/kg if dose escalation is determined appropriate by the Study Investigator [**Section 5.3.3**]*).

Section 5.3.2 Prophylactic Doses of Hemlibra (emicizumab)
Prophylactic administration of Hemlibra (emicizumab) will continue on a weekly basis (1.5 mg/kg subcutaneous dosing, *or 3 mg/kg kg if dose escalation is determined appropriate by the Study Investigator [**Section 5.3.3**]*) until the subject withdraws from the study, is involuntarily withdrawn from the study, or the study is terminated, whichever occurs first (**Section 7.3**).

5.3.3 Dose escalation of Prophylactic Hemlibra (emicizumab)
All subjects with suboptimal control of bleeding as defined by the protocol will be offered the option to increase their Hemlibra (emicizumab) maintenance dose to 3 mg/kg QW, with approval from the Study Investigator. Suboptimal response is defined as follows:

- *Two qualifying bleeds within 24 weeks while on prophylactic Hemlibra (emicizumab)*

A qualifying bleed is defined as spontaneous, verified by an investigator (eg, by imaging or physical examination or reliable symptoms reported by patient including increased pain with swelling, decreased ability to function etc clearly related to presence/site of pseudotumor), and occurring while on prophylactic Hemlibra (emicizumab) at steady state (after week 5). If the investigator believes that a specific subject warrants dose escalation on the basis of a different reason, he or she may discuss the case with the Study Investigator for consideration and potential approval.

If this 3 mg/kg maintenance dose does not result in increased control of breakthrough bleeding, the subject may return to the standard 1.5 mg/kg maintenance dose upon approval of the Study Investigator, assuming this 1.5 mg/kg dose had resulted in an improvement in breakthrough bleeding compared to their pre-study regimen.

7.3 Prophylactic Administration of Hemlibra (emicizumab)

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Prophylactic administration of Hemlibra (emicizumab) will continue on a weekly basis (1.5 mg/kg subcutaneous dosing*, or 3 mg/kg kg if dose escalation is determined appropriate by the Study Investigator [**Section 5.3.3**]*) until subject withdrawal or study termination, whichever occurs first.

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PROTOCOL VERSION 3.0 (AMENDMENT #2)
RATIONALE FOR CHANGES

Changes to the protocol that modify the study design or analyses, along with a rationale for each change are summarized below:

Change	Rationale	Affected protocol sections
Update for Genentech-required safety language for reporting/collecting of AEs and product complaints	Genentech-required changes	6.11.3.2j

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PROTOCOL VERSION 3.0 (AMENDMENT #2)
SUMMARY OF CHANGES

6.11.3.2j Exchange of single case reports

~~*The IHTC will track all protocol-defined AE and pregnancy reports*~~ *IHTC will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE)* originating from the Study for the Product.

Study Investigators must report all *the above-mentioned single case reports* ~~Adverse Events/ Serious Adverse events (SAEs), AEs of Special Interest (AESIs) pregnancy reports and special situation reports (if applicable)~~ adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed*/emailed* immediately upon completion to Genentech ~~Drug Safety~~ at *the following contacts*:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints with an AE should be sent to:

Fax: 650-238-6067

Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should be called into:

Product Complaint Hotline Phone Number: (800) 334-0290

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met. ~~Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request~~

Serious adverse events (SAEs), pregnancy reports, AEs of special interest (AESIs), ~~and~~ Special Situation Reports *and Product Complaints (with or without an AE)*, where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- **SADRs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

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- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.
- **AESIs**
  AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.
- **Pregnancy reports**
  While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.
- **Special situation reports**
  In addition to all SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
    - Data related to the Product usage during pregnancy or breastfeeding
    - Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
    - Lack of therapeutic efficacy
    - Drug interaction
    - Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)
- ***Product Complaints***
  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

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All other AEs will be reported via CTV reconciliation process (a list of all AEs) on a quarterly basis.

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported

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SYNOPSIS

Study Title

Prospective, Single-Arm, Open-Label use of Hemlibra (Emicizumab) to treat hemophilic pseudotumor

Study Phase

This is a phase 4 study

Name of provided study drug

US-labeled Hemlibra (emicizumab-kxwh)

Study Length

Total study length is 4 years. Enrollment period is 2 years with a minimum of 2 years on study, and a maximum of 4 years on study. No follow-up period is planned.

Overview

This is a single arm, phase 4, prospective, open-label, United States single-center study to assess the hemostatic efficacy and safety of Hemlibra (emicizumab) for hemostatic control of hemophilia A patients (baseline FVIII level <40%) with and without inhibitors with hemophilic pseudotumors; secondary outcomes will assess changes in quality of life and activity level in treated patients.

Study rationale

Hemophilia A is a congenital bleeding disorder caused by deficient or dysfunctional factor VIII (FVIII) which leads to bleeding correlated with level of severity. Management includes replacement of the deficient clotting factor either in reaction to a bleeding event or administered prophylactically to suppress or prevent bleeding. Effective treatment is complicated by the ability to administer standard replacement therapy via intravenous infusion and the development of FVIII neutralizing antibodies, or inhibitors, in approximately ~30% of patients with severe hemophilia A leading to worsened morbidity and mortality and exponentially increasing the cost of care. Inhibitor patients often require the use of bypassing therapy to obtain hemostatic control.

Hemophilic pseudotumor is a complication of hemophilia (1-2% of patients) that consists of a progressive cystic swelling of muscle and/or bone caused by recurrent hemorrhage. It is observed more frequently in geographic areas where hemophilia is diagnosed late, treatment is inconsistently available, prophylaxis is not used due to resource constraints, and in patients who do not recognize that a bleeding event has occurred (eg, moderate or mild deficient patients who experience an injury). FVIII prophylaxis has been used in patients with hemophilia A with

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pseudotumors when surgical intervention is not feasible either due to lack of local expertise or inability to perform the intervention due to extent or site of the pseudotumor. Pseudotumors may be present in patients with hemophilia either with or without an inhibitor and are more common in patients with inhibitors where hemostasis is less well controlled.

It is hypothesized that an agent that confers a consistent FVIII level in the mild deficient range that is not associated with trough levels below 10% will confer a higher degree of hemostasis in patients with pseudotumors; this will result in a decreased rate of breakthrough bleeding requiring intermittent hemostatic therapy, and an associated decrease in uncontrolled bleeding resulting in anemia, transfusion, and hospitalization. If these endpoints are achieved it is also hypothesized that activity and quality of life may increase or improve respectively.

The purpose of this study is to prospectively investigate the hemostatic efficacy and safety of weekly prophylactic Hemlibra (emizicumab) in the treatment/control of pseudotumors in children and adults with FVIII deficiency (baseline FVIII level <40%) either with or without an inhibitor; in addition, changes in quality of life and activity level in subjects with hemophilia A and pseudotumor will be assessed.

Study Design

This is a single arm, phase 4, prospective, open-label, United States single-center study to assess the hemostatic efficacy and safety of Hemlibra (emicizumab) for hemostatic control of hemophilia A patients, (baseline FVIII level <40%), children and adults, with and without inhibitors with hemophilic pseudotumors; secondary outcomes will assess changes in quality of life and activity level in treated patients.

Hemlibra (emicizumab) will be administered as primary weekly prophylaxis after the enrollment/screening visit is complete (approximately 7-10 days after screening, if laboratory results are available and eligibility is confirmed). If an activity monitoring device is typically utilized by the patient (eg, a Fitbit) then permission will be requested from the patient at screening to access the data for 1 month prior to screening as a baseline comparator for post-treatment activity. The use of an activity-monitoring device is not required by the study.

The enrollment period is 2 years and the study will last a maximum of 4 years; subjects will receive study medication (Hemlibra, emicizumab) for a minimum of 2 years and a maximum of 4 years based upon time of enrollment. Hemlibra (emicizumab) will be administered using the FDA-approved once-weekly dosing regimen for loading dose and prophylactic dose. Breakthrough bleeding events will be recorded and treated with locally available FVIII (eg, pdFVIII or rFVIII) in non-inhibitor subjects and inhibitor subjects with low titer inhibitors (titer <5 BU). The lowest dose of FVIII expected to achieve hemostasis will be utilized for treatment of breakthrough bleeding events in non-inhibitor and low-titer inhibitor patients. Subjects with high-titer inhibitors (titer ≥5 BU) and those with low titer inhibitors who do not respond to FVIII will be required to utilize rFVIIa as first line therapy; aPCC (<100 U/kg/day for preferably no more than 1 day) may only be used upon approval of the Study Investigator and under the supervision of a physician.

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The proposed study is seeking to address the following knowledge gaps:

- Does weekly prophylactic Hemlibra (emicizumab) reduce the rate of bleeding events in subjects with hemophilia A and pseudotumor, including the rate of hospitalization, anemia and transfusion?
- Does weekly prophylactic Hemlibra (emicizumab) control the progression of hemophilic pseudotumor?
- Does weekly prophylactic Hemlibra (emicizumab) result in an increase in QoL and activity level?

Primary Objective

To determine the hemostatic efficacy[*] of prophylactic weekly injections of Hemlibra (emicizumab) in hemophilia A subjects (baseline FVIII level <40%) with pseudotumor, with or without FVIII inhibitors

Secondary Objectives

To determine the rate of breakthrough bleeding events, either related or unrelated to the pseudotumor, requiring alternate hemostatic therapy.

To evaluate the control of progression, stabilization or regression of the pseudotumor.

To determine the safety of Hemlibra (emicizumab) based on adverse events (AEs) and serious adverse events (SAEs) including lack of efficacy and development of anti-drug antibodies (ADA). Samples for ADA will be banked for analysis and performed in conjunction with Genentech/Roche either yearly, at the end of the study, or as determined by the Study Investigator based upon suspected lack of clinical efficacy.

To evaluate the change in quality of life and activity as measured by the Haem-A-QoL and EQ-5D-5L with Hemlibra (emicizumab) prophylaxis. If an activity monitoring device is standardly utilized by the patient (eg, FitBit) then data from that device will be requested from the patient to assist in activity monitoring as well.

To evaluate the effect of Hemlibra prophylaxis on any surgical procedures, including the use of other hemostatic agents such as FVIII, aPCC or rFVIIa and overall hemostatic efficacy.

Primary endpoints

The number of breakthrough bleeding events over time requiring the use of alternate hemostatic therapy (bleed rate) related to the pseudotumor.

[*] Hemostatic efficacy is defined as the rate of breakthrough bleeding related to the pseudotumor; which is defined as the number of bleeding episodes while on Hemlibra that require alternative hematinic therapy.

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The number of hospital admissions related to the pseudotumor.

The number of incidences of anemia requiring transfusion or intervention related to the pseudotumor.

The control of progression, stabilization or regression of the pseudotumor (ie, changes in size) as measured by yearly assessments including CT or MRI.

Secondary endpoints

The impact of weekly prophylaxis on quality of life and activity level.

Safety including development of AEs, SAEs, and ADA.

The dose(s) and number of infusions of alternate hemostatic therapy (FVIII, rFVIIa or aPCC) required to treat a breakthrough bleeding event either unrelated or related to the pseudotumor.

The number of breakthrough bleeding events over time requiring the use of alternate hemostatic therapy (bleed rate) unrelated to the pseudotumor.

The use of alternate hemostatic therapies (eg, FVIII, rFVIIa or aPCC) during surgeries and the hemostatic efficacy.

Inclusion criteria

Patients must meet the following criteria for study entry:

- Signed informed consent form from the subject, parent or guardian
- Diagnosis of congenital hemophilia A (baseline FVIII level <40%) with or without FVIII inhibitor, either high or low responding, regardless of titer
- Diagnosis of a hemophilic pseudotumor confirmed by radiologic assessment such as CT or MRI
- Any weight or BMI
- Medical documentation of prophylactic or episodic treatment (FVIII or bypassing agent) and the number of bleeding episodes for at least 16 weeks, and up to 6 months if available, prior to entry into the study
- Medical documentation of any need for PRBC transfusion or hospitalization for 6 months prior to entry into the study
- Subjects with a history of an inhibitor should provide documentation of the inhibitor history including date of initial diagnosis of inhibitor, peak titer, and agent utilized for hemostatic control

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- Subjects with high titer inhibitors or those with low titer inhibitors who do not respond to FVIII must be willing to use rFVIIa as first line therapy for the treatment of breakthrough bleeding events
- Medical documentation of ITI therapy for subjects with a history of a FVIII inhibitor and ITI, including current FVIII inhibitor titer
- Willingness to discontinue any current prophylactic hemostatic regimen (FVIII or bypassing agent) and/or FVIII ITI therapy for the duration of the study
    - Subjects receiving FVIII prophylaxis must be willing to discontinue their FVIII prophylactic regimen immediately prior to their second loading dose of Hemlibra (emicizumab)
    - Subjects receiving bypassing agent prophylaxis must be willing to discontinue their prophylactic regimen at least 24 hours prior to their first loading dose of Hemlibra (emicizumab)
    - Subjects receiving FVIII ITI therapy must be willing to discontinue ITI immediately prior to their first loading dose of Hemlibra (emicizumab)
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the health-related questionnaires, activity tracking, and bleed diaries, using systems provided during the study
- Adequate hepatic function, defined as total bilirubin ≤1.5 × age-adapted upper limit of normal (ULN) (excluding Gilbert's syndrome) and both AST and ALT ≤3 × age-adapted ULN at the time of screening, and no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Subjects must be willing to be vaccinated against HAV and/or HBV if not previously vaccinated, exposed or immune to HAV and/or HBV
- Adequate hematologic function, defined as a platelet count ≥100,000/μL and a PT≤1.5 times the ULN at the time of screening
- Adequate renal function, defined as serum creatinine ≤2.5 × age-adapted ULN and creatinine clearance ≥30 mL/min by Cockcroft-Gault formula
- For women with hemophilia of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

Exclusion Criteria

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

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- Inherited or acquired bleeding disorder other than congenital hemophilia A
- Baseline FVIII level ≥40%
- Lack of a documented diagnosis of hemophilic pseudotumor
- Patients who are at high risk for TMA (eg, have a previous medical or family history of TMA), in the judgement of the Study Investigator
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the Study Investigator's judgment
- Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (eg, certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the Hemlibra (emicizumab) injection
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Known HIV infection with CD4 counts <200 cells/μL. HIV infection with CD4 counts ≥200 cells/μL permitted
- Use of systemic immunomodulators (eg, interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- Concomitant disease, condition, significant abnormality on screening evaluations or laboratory tests, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the Study Investigator, pose an additional unacceptable risk in administering study drug to the patient
- Receipt of any of the following:
    - Hemlibra (emicizumab) in a prior investigational study
    - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration
    - A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
    - Any other investigational drug currently being administered or planned to be administered
- Inability to comply with the study protocol in the opinion of the Study Investigator

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- Pregnancy or lactation or intention to become pregnant during the study
- Women with a positive serum pregnancy test result within 10 days prior to initiation of study drug

Randomization & Stratification

This is a single arm prospective study without randomization.

Hemlibra (emicizumab) will be provided at no cost to participants. The choice of FVIII preparation such as pdFVIII or rFVIII, to treat breakthrough-bleeding events in non-inhibitor subjects and subjects with low titer inhibitors (titer <5 BU) who respond to FVIII will be at the discretion of the local treating physician throughout the study period and the lowest expected dose to achieve hemostasis will be utilized. Patients with high titer inhibitors (titer ≥5 BU) or low titer inhibitor patients who do not respond to FVIII and require the use of bypassing agents for acute bleeding will be required to utilize rFVIIa as first line therapy for breakthrough bleeding episodes; aPCC (<100 U/kg/day for preferably no more than 1 day) may only be used upon approval of the Study Investigator and under the supervision of a physician. Agents other than Hemlibra (emicizumab) required for hemostatic control will not be supplied by the study; specifically, FVIII concentrate, rFVIIa and (if approved for use by the Study Investigator) aPCC. Reimbursement for subjects' travel to and from the IHTC (or other medical facilities) will not be provided by the study.

Schedule of assessments/events for all visits

Initial study visit

This visit will comprise subject consent and screening.

Subjects will receive their initial screening and be consented by an IHTC staff member/clinician. Screening is expected to take up to 10 days but may be shorter depending on return of required laboratory testing.

The screening visit will include obtaining informed consent; performance of a physical examination, vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight measurement; initiation of safety data collection; and the review/collection of clinical and laboratory data (adequate data in the subject's recent medical files may negate the running of some of laboratory tests) including:

- Baseline FVIII,[*] aPTT, PT and VWF:Ag
- Baseline FVIII inhibitor level
- Baseline CBC w/diff and CMP + direct bilirubin

[*] If the subject has an inhibitor, then testing for FVIII level may not be medically necessary as FVIII is usually undetectable in such cases. Exceptions exist, such as for a patient who has mild hemophilia with an inhibitor that only recognizes infused FVIII and not endogenous FVIII.

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- Serum pregnancy test for female subjects
- Documentation of current or past infection of Hepatitis A, B and C (tests listed below). If documentation is not available, then the tests will be administered as part of the screening process*
    - HAV:Ab
    - HBV:Ag and Ab (Core and Surface); if HBV:Ag positive, HBV viral load
    - HCV:Ab; if HCV:Ab positive, HCV viral load
- Documentation of HIV infection (if Ab positive, viral load and CD4 count)
- Obtain baseline Haem-A-QoL and EQ-5D-5L
- If an activity monitoring device is standardly utilized by the patient, then permission will be requested to access data for the 1-month period prior to study entry and use of data from the device if continued during the study
- Review of at least 16 weeks, and up to 6 months if available, of data on prior use of hemostatic therapy and number of breakthrough bleeding events
- Review of 6 months of data on prior need for hospitalization or for PRBC transfusion
- Review of therapy prior to study entry with dose and interval and trough level if available on prophylaxis
- Review of history of inhibitor including date of first positive test, highest documented titer and date
- Review of concomitant medications and supplements
- Date of development or identification of pseudotumor and documentation of radiologic (CT or MRI) scans
- Review of surgeries and procedures

Second study visit (up to 10 days from screening visit)

The study visit will comprise a 4-week period to administer the 4 loading doses of Hemlibra (emicizumab). This study visit will take place at the IHTC.

- Vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Baseline anti-drug antibody levels for Hemlibra (emicizumab) – banked plasma sample

* Although this testing and documentation is considered standard of care, there are important reasons to include this in the study and budget. There are patients in the US who are not followed at a federally recognized hemophilia treatment center and this testing may be inconsistently available. In addition, there are patients who refuse entry into CDC studies where this testing is performed or refused vaccination to prevent Hepatitis A and/or B transmission. Knowing each patient's viral exposure status and vaccination history will be important to decrease risk of community acquired infections that may lead to development of AEs that could be avoided.

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- Dispensation of a suitable quantity of Hemlibra (emicizumab) (quantity to be determined by the Study Investigator)
- Baseline radiology (CT or MRI) if not performed within one month of study entry or provided scans are deemed inadequate to accurately assess the extent of the pseudotumor
- Weeks 1-4
    - First 4 weekly loading doses to be administered at IHTC
- Week 4
    - Anti-drug antibody levels for Hemlibra (emicizumab) – banked plasma sample
    - Obtain data if applicable from an activity monitoring device if standardly utilized by the patient

Subsequent study visits (annual and study close-out visits at the IHTC; other study visits with local physician)

Subsequent study visits will occur once a quarter, as is the standard of care for patients with hemophilic pseudotumor. These study visits will take place at the medical facilities of the subject's local physician, except for the annual and study close-out visits, which will take place at the IHTC. The first subsequent study visit will be 3 months (±2 weeks) following the first loading dose of Hemlibra (emicizumab).

The specific requirements of each visit are listed below. Depending on when a subject enrolls and when the study ends, the subject might not participate in all study visits beyond month 24.

Study visits at months 3, 9, 15, 21, 27, 33, 39 and 45 (±2 weeks)

The subject will follow-up with their local physician at the intervals specified above.

During this visit:

- Vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Review of patient diary for completeness
- Patient study documentation will be submitted to the IHTC for review of compliance and data collection
- Review of AEs
- Review of concomitant medications and supplements
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

Study visits at months 6, 18, 30 and 42 (±2 weeks)

The subject will follow-up with their local physician for a more detailed clinical review at the intervals specified above.

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During this visit the following data will be collected and/or reviewed and transmitted to the IHTC:

- CBC panel w/diff
- Vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Review of breakthrough bleeding events requiring alternate hemostatic therapy
- Review of the number of hospital admissions
- Review of the development of anemia requiring transfusion or intervention
- Review of AEs
- Review of concomitant medications and supplements
- Review of patient diary for completeness
- Patient study documentation will be submitted to the IHTC for review of compliance and data collection
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

Annual study visits (months 12, 24 and 36 ±2 weeks)[*]
The annual study visit will take place at the IHTC.

During this visit the following data will be collected and/or reviewed at the IHTC:

- Radiologic evaluation (CT and/or MRI) to evaluate control of progression, stabilization or regression (ie changes in size) of the pseudotumor
- Vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Anti-drug antibodies (banked plasma sample)
- Repeated Haem-A-QoL and EQ-5D-5L
- CBC panel w/diff
- Review of breakthrough bleeding events requiring alternate hemostatic therapy
- Review of the number of hospital admissions
- Review of the development of anemia requiring transfusion or intervention
- Review of concomitant medications and supplements
- Review of AEs
- Review of patient diary

[*] Subjects enrolled in the study for the maximum length of time (ie, 48 months) will also participate in an annual visit at approximately the 48-month time point; however, this will be the subject's close-out visit, and the procedures required will be those list in **Section 7.5**. The primary difference between an annual visit and the close-out visit is the collection of used and unused vials of Hemlibra (emicizumab), rather than the dispensation of additional drug

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- Patient study documentation will be collected for review of compliance and data collection
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

During this annual visit, a physical examination will be performed, used/empty vials of Hemlibra (emicizumab) will be collected and a suitable quantity of Hemlibra (emicizumab) will be dispensed.

Unscheduled study visits

- Any unscheduled study visits with the subject's local hemophilia physician will be recorded in the CRF along with all relevant medical information (eg, reason for visit, diagnoses, scans, AEs, lab results, vital signs [blood pressure, pulse, temperature, and respiratory rate], weight, etc)
- If a subject meets with a physician other than their local hemophilia physician, that information should be communicated to their hemophilia physician at the next scheduled quarterly study visit and appropriate medical information recorded in the CRF
- Hospitalizations should be recorded in the CRF along with relevant medical information (see **Section 6.11.3.2d**). These should be reported to the IHTC within 7 days of their occurrence

Surgeries

- All surgeries will be recorded in the CRF, which should minimally include the following information (see **Section 6.11.3** for additional reporting requirements):
    - Procedure type
    - Reason for procedure
    - Planned or unplanned
    - Date of procedure and length of hospitalization
    - Hemostatic therapy provided pre-procedure (type, dose and dates)
    - Hemostatic therapy provided post-procedure (type, dose and dates)
    - Hemostatic outcome immediately post-procedure
    - Hemostatic outcome at the end of hospitalization
    - Adverse events experienced (including, but not limited to clots, thromboses and TMA)
    - Vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight

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Study close-out visit

A study close-out visit will occur at the IHTC for all subjects during the final 2 months prior to the anticipated study termination date.

During this close-out visit the following data will be collected and/or reviewed at the IHTC (depending on when the most recent annual visit took place and at the Study Investigator's discretion, not all specified items may be necessary):

- Radiologic evaluation (CT and/or MRI) to evaluate control of progression, stabilization or regression of pseudotumor
- Vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Anti-drug antibodies (banked plasma sample)
- Repeated Haem-A-QoL and EQ-5D-5L
- CBC panel w/diff
- Review of breakthrough bleeding events requiring alternate hemostatic therapy
- Review of the number of hospital admissions
- Review of the development of anemia requiring transfusion or intervention
- Review of AEs
- Review of concomitant medications and supplements
- Review of patient diary
- Patient study documentation will be collected for review of compliance and data collection
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

Additionally, a physical examination will be performed and all used and unused vials of Hemlibra (emicizumab) will be returned to the IHTC.

Following the close-out visit, all subjects will be requested to meet with their local hemophilia physician to determine their ongoing treatment therapy/regimen.

Dosing Regimen

Genentech drug product

Once weekly US-labeled Hemlibra (emicizumab) using FDA-approved dosing regimen

- Four loading doses: 3 mg/kg once weekly by subcutaneous injection
- Subsequent doses: 1.5 mg/kg once weekly by subcutaneous injection
- *Dose escalation: Should a subject have suboptimal control of breakthrough bleeding (ie, 2 qualifying bleeds within 24 weeks) while on 1.5 mg/kg once weekly Hemlibra*

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*(emicizumab) prophylaxis, the dose may be increased to 3 mg/kg once weekly Hemlibra (emicizumab) prophylaxis upon approval of the Study Investigator (**Section 5.3.3**). If this 3 mg/kg maintenance dose does not result in an improvement in breakthrough bleeding, the subject may return to the standard 1.5 mg/kg maintenance dose upon approval of the Study Investigator, assuming this 1.5 mg/kg dose had resulted in an improvement in breakthrough bleeding compared to their pre-study regimen.*

Non-Genentech drug products

Non-inhibitor subjects and low titer inhibitor subjects (titer <5 BU)

- Breakthrough bleeding events should be treated with a FVIII concentrate, rFVIII or pdFVIII, using the local standard of care at the lowest level expected to achieve hemostasis
- If the subject's standard of care for treatment of bleeding events with low titer inhibitors is a bypassing product, the subject will follow treatment as outlined under high titer inhibitors

High titer inhibitor subjects (titer ≥5 BU)

- Breakthrough bleeding events should be treated with rFVIIa as first line therapy using the local standard of care. aPCC (<100 U/kg/day for preferably no more than 1 day) may only be used upon approval of the Study Investigator and under the supervision of a physician

Dispensation of Hemlibra (Emicizumab)

A suitable quantity of Hemlibra (emicizumab) (to be determined by the Study Investigator) will be dispensed to each subject at study visit 2 and at all annual visits. If necessary, additional Hemlibra (emicizumab) will be dispensed and shipped throughout the year to ensure the subject has a continuous supply.

Duration of Treatment per Subject

Minimum 2 years; maximum 4 years. No follow-up period is planned.

Statistical Considerations

Sample size

Sample size of approximately 10 subjects is based on clinical feasibility and availability of subjects with hemophilia A and pseudotumor rather than statistical considerations.

Statistical Analyses

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Continuous variables will be summarized by descriptive statistics. Categorical variables will be presented with the number and percentage in each category.

Efficacy Analyses

The primary outcome for this study is bleeding events specifically related to the pseudotumor over time; total bleeding events will also be recorded and analyzed. Hemostatic efficacy is defined as the rate of breakthrough bleeding related to the pseudotumor (the number of bleeding episodes while on Hemlibra that require alternative hematinic therapy). Sample size is determined based on clinical feasibility rather than statistical considerations, accounting for the likely possibility of very few bleeding events, the limited number of available subjects with hemophilia A and pseudotumor, and the need to collect sufficient data to assess safety and efficacy.

Safety Analyses

Safety data collection will commence when each individual subject signs and dates the informed consent form and continue until the study ends or the subject withdraws from the study, whichever occurs first. All SAEs will be reported to and reviewed by the Study Investigator. One non-study physician from the IHTC will review all SAEs, deaths or other unexpected events and report to the Study Investigator with recommendations. If a patient dies on study, the case will be evaluated in detail to determine its relatedness to the study drug and to determine if the study warrants stopping in the Study Investigator's opinion. Any death or drug-related SAE will be reported through Genentech's reporting system, as will all other required reportable events (see **Section 6.11.3.2j**). The study site will maintain a record of all SAE reports, interpretations and recommendations which will be available for Genentech to review upon request. In addition, if a greater than expected number of breakthrough bleeding events, or the development of thrombosis, thrombotic microangiopathy (TMA) or anaphylactic reaction to study medication occurs, the treatment of that patient will be halted. The Study Investigator may withdraw a patient based upon their clinical discretion and patient safety.

Planned Interim Analyses

Interim analyses will be conducted yearly at the discretion of the Study Investigator if sufficient patients are enrolled. At a minimum, an interim analysis will occur at the mid-point of the study (2-years following the date of informed consent of the first study subject).

Assessments with brief summary of methods & procedures

Data Safety Monitoring Board (DSMB)

No DSMB will exist for the study. One designated non-study physician from the IHTC will review all safety data and other unexpected events and report to the Study Investigator with recommendations.

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Pharmacokinetics

No pharmacokinetic studies will be performed during the study

Pharmacodynamics

No pharmacodynamics studies will be performed during the study

Quality of Life (QoL)

The change in quality of life and activity with Hemlibra (emicizumab) prophylaxis will be evaluated during the study. QoL and activity will be assessed using Haem-A-QoL and EQ-5D-5L. Activity level may be assessed using a Fitbit or similar device to evaluate daily activity during the course of the study if such a device is standardly utilized by the subject, and the subject provides consent to export data from device.

Biomarker Population

No biomarker population analysis will be performed during the study

Additional Details

Due to the anticipated small study size, there will be no restrictions on BMI and the presence/absence of FVIII inhibitors.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Ab	Antibody
Ag	Antigen
ACT	Activated clotting time
ADA	Anti-drug antibodies
ADR	Adverse drug reactions
AE	adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPCC	Activated prothrombin complex concentrate
APC-R	Activated protein C resistance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BU	Bethesda unit
CBC	Complete blood count
CD4	Cluster of differentiation 4 glycoprotein
CFR	Code of federal regulations
CHO	Chinese hamster ovary
CRF	Case report form
CRO	Contract research organisation
CT	Computed tomography
CTSP	Clinical trial safety portal
CTV	Adverse event case transmission verification
DOB	Date of birth
DSUR	Development safety update report
ELISA	Enzyme linked immunosorbent assay
EMA	European medicines agency
ePS	ePharmaSolutions
EQ-5D-5L	EuroQol Group questionnaire measuring health-related quality of life with 5 dimensions, and responses recording five levels of severity
EtMs	Events to monitor of medical and scientific concern
EU	European Union
EVCTM	Eudravigilance clinical trial module
FDA	Food and drug administration
FVIII	Factor VIII
FVIIIa	Factor VIII activated
FIX	Factor IX
FIXa	Factor IX activated
FX	Factor X

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FXa	Factor X activated
GCP	Good clinical practice
Haem-A-QoL	Haemophilia quality of life questionnaire for adults
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	Head, eyes, ears, nose, throat
HIPAA	Health information portability and accountability act
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IB	Investigator brochure
IHTC	Indiana Hemophilia and Thrombosis Center
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional review board
ISTH	International Society on Thrombosis and Haemostasis
ITI	Immune tolerance induction
MRI	Magnetic resonance imaging
NBU	Nijmegen bethesda unit
PD	Pharmacodynamics
pdFVIII	Plasma-derived factor VIII
PI	Package insert
PK	Pharmacokinetics
PRBC	Packed red blood cells
PRO	Patient reported outcome
PT	Prothrombin time
PT	Preferred term
QoL	Quality of life
rFVIIa	Factor VII activated
rFVIII	Recombinant factor VIII
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TMA	Thrombotic microangiopathy
TT	Thrombin time
U	Unit
ULN	Upper limit of normal
US	United States
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen

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1 INTRODUCTION

1.1 Background Information on the Product

Hemlibra (also known as emicizumab, ACE910 and RO5534262) is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Hemlibra (emicizumab) bridges activated factor IX (FIXa) and factor X (FX) to restore the function of missing activated factor VIII (FVIIIa) that is needed for effective hemostasis.

In patients with hemophilia A, hemostasis can be restored irrespective of the presence of factor VIII (FVIII) inhibitors, as emicizumab shares no sequence homology with FVIII. Due to its pharmacokinetic (PK) properties, emicizumab can be administered subcutaneously at a frequency that is less than that of other currently available therapies for hemophilia A. Therefore, this novel compound may have the potential to significantly change the treatment of patients with hemophilia A, with or without FVIII inhibitors, who are in need of prophylactic treatment to prevent bleeding episodes.

Hemlibra (emicizumab) is currently indicated for prophylactic use in the US and other countries in patients with hemophilia A and FVIII inhibitors to prevent or reduce the incidence of bleeding events.

1.2 Hemophilia

Hemophilia A is an X-linked recessive bleeding disorder characterized by congenital underproduction of or dysfunction of FVIII, an essential protein in promoting clot formation. Hemophilia A accounts for approximately 80% of all cases of hemophilia. The incidence of hemophilia A is approximately 1 in 5,000 live-born male births or 1 out of every 10,000 live births [Franchini and Mannucci 2013, Centers for Disease Control and Prevention 2014, National Institutes of Health 2014]. No racial differences have been reported in the distribution of patients with hemophilia. The number of patients with hemophilia A registered in 2015 in various regions across the world, include 4,986 individuals in Japan (3.9/100,000 people), 17,285 in North America (4.8/100,000 people; [Canada estimate from 2014]), and 21,410 in the five major European nations (United Kingdom, France, Germany, Italy, and Spain; 6.7/100,000 people; [Spain estimate from 2011 and Italy estimate from 2014]) [World Federation of Hemophilia 2012, World Federation of Hemophilia 2013, World Federation of Hemophilia 2016].

The main bleeding sites are intra-articular, intramuscular, subcutaneous, intraoral, intracranial, gastrointestinal, and intranasal. In particular, repeated intra-articular bleeds are a major contributor to decreased HRQoL in patients with hemophilia A, as the joint damage associated with multiple hemarthrosis may progress to hemophilic arthropathy [Gringeri, Leissinger et al. 2013]. In advanced forms, hemophilic arthropathy is associated with significant joint pain, swelling, and limited range of motion, which may ultimately require surgical intervention, including joint replacement. Although less frequently than musculoskeletal bleeds, patients with

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hemophilia A can also develop intracranial or severe gastrointestinal bleeding resulting in death [World Federation of Hemophilia 2012].

The severity of (and bleeding risk associated with) hemophilia A is classified in accordance with endogenous FVIII activity in the plasma. Those with FVIII activity less than 1% have severe disease; between 1% and 5%, moderate disease; and between 5% and 50%, mild disease. Patients with severe hemophilia A can suffer several spontaneous bleeding episodes each month – much more frequently than those with moderate or mild disease. In addition, such patients are at a greater risk for having life-threatening bleeds. Hence, the maintenance of FVIII activity levels about 1-3% with FVIII prophylaxis is desired, in order to effectively reduce bleeding episodes, morbidity (eg, arthropathy), mortality, as well as to improve HRQoL in patients with severe hemophilia A [Srivastava, Brewer et al. 2013].

1.3 Hemophilic Pseudotumor

Hemophilic pseudotumor is a rare complication of hemophilia that occurs in 1-2% of patients with severe hemophilia [van Ommeren, Mooren et al. 2000]. It is observed more frequently in geographic areas where hemophilia is diagnosed late, treatment is inconsistently available, prophylaxis is not used due to resource constraints, and in patients who do not recognize that a bleeding event has occurred (eg, moderate or mild deficient patients who experience infrequent bleeds/injuries). Pseudotumors are more commonly observed in adults than pediatric patients [Magallon, Monteagudo et al. 1994] They may be present in patients with hemophilia either with or without an inhibitor and are more common in patients with inhibitors where hemostasis is less well controlled.

A hemophilic pseudotumor consists of an encapsulated progressive cystic swelling of muscle and/or bone caused by recurrent hemorrhage which can cause a serious complication to both life and limb. Pseudotumors have been reported in a wide variety of bones and soft tissues [Liu, White et al. 1988] where repeated and unresolved hematomas lead to encapsulation, calcification and progressive enlargement, with subsequent erosion of adjacent bone. Most commonly the pseudotumor occurs in the pelvis and long bones of lower extremity; they are also observed in muscles, particularly the iliacus, vastus lateralis and soleus. Pseudotumors are best treated early; if left untreated they can result in compression pressure necrosis of adjacent structures, further bleeding, infection, erosion and loss of function and/or life. Complicating early diagnosis is the fact that patients with pseudotumors may be asymptomatic or stable for long periods of time (sometimes decades) before developing complications [Ahlberg 1975, Magallon, Monteagudo et al. 1994, van Ommeren, Mooren et al. 2000].

Hemophilic pseudotumors are most readily diagnosed and monitored using CT or MRI.

1.4 Current Therapies and Unmet Medical Need

There is no standard treatment for hemophilic pseudotumor; factor replacement therapy and surgical excision are the primary treatment options [van Ommeren, Mooren et al. 2000]. In

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countries lacking significant medical resources, FVIII prophylaxis and surgical intervention are rarely feasible due to availability of factor replacement, lack of local expertise and/or inability to perform the intervention due to extent or site of the pseudotumor. Due to the limited medical resources, hemophilic pseudotumor has a higher incidence in these countries.

It is hypothesized that an agent that confers a consistent FVIII-equivalent level in the mild deficient range that is not associated with trough levels below 10% will confer a higher degree of hemostasis in patients with pseudotumors. It is not practical to achieve such high trough levels over long periods of time using standard factor replacement therapy; instead new products, such as Hemlibra (emicizumab) may provide an alternative approach. If a higher degree of hemostasis is achieved, this is expected to result in a decreased rate of breakthrough bleeding requiring intermittent hemostatic therapy, and an associated decrease in uncontrolled bleeding resulting in anemia, transfusion, and hospitalization. If these endpoints are achieved it is also hypothesized that activity and quality of life may increase or improve respectively.

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2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of the study is:

- To determine the hemostatic efficacy* of prophylactic weekly injections of Hemlibra (emicizumab) in hemophilia A subjects (baseline FVIII level <40%) with pseudotumor, with or without FVIII inhibitors.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To determine the rate of breakthrough bleeding events, either related or unrelated to the pseudotumor, requiring alternate hemostatic therapy
- To evaluate the control of progression, stabilization or regression (ie, change in size) of the pseudotumor
- To determine the safety of Hemlibra (emicizumab) based on adverse events (AEs) and serious adverse events (SAEs) including lack of efficacy and development of anti-drug antibodies (ADA). Samples for ADA will be banked for analysis and performed in conjunction with Genentech/Roche either yearly, at the end of the study, or as determined by the Study Investigator based upon any reported lack of clinical efficacy
- To evaluate the change in quality of life and activity as measured by the Haem-A-QoL and EQ-5D-5L with Hemlibra (emicizumab) prophylaxis. If an activity monitoring device is standardly utilized by the patient (eg, Fitbit) then data from that device will be requested from the patient to assist in activity monitoring as well
- To evaluate the effect of Hemlibra prophylaxis on any surgical procedures, including the use of other hemostatic agents such as FVIII, aPCC or rFVIIa and overall hemostatic efficacy

* Hemostatic efficacy is defined as the rate of breakthrough bleeding related to the pseudotumor; which is defined as the number of bleeding episodes while on Hemlibra that require alternative hematinic therapy.

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3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a single arm, phase 4, prospective, open-label, US single-center study to assess the hemostatic efficacy and safety of Hemlibra (emicizumab) for hemostatic control of hemophilia A patients (baseline FVIII level <40%), children and adults, with and without inhibitors with hemophilic pseudotumors. The study is not randomized.

Subjects will be consented and screened at the IHTC and will be eligible for study participation if they meet all inclusion criteria. Subjects will be excluded from the study if they meet any of the exclusion criteria. US-labeled Hemlibra (emicizumab) will be administered using the FDA-approved once-weekly dosing regimen for loading dose and prophylactic dose. Subjects will administer Hemlibra (emicizumab) for a minimum of 2 years, except in the case of subject withdrawal or early termination of the study, and a maximum of 4 years. Breakthrough bleeding episodes will be treated using the local standard of care subject to the conditions listed in **Sections 5.1.2 and 5.4**.

The proposed study is seeking to address the following knowledge gaps:

- Does weekly prophylactic Hemlibra (emicizumab) reduce the rate of bleeding events in subjects with hemophilia A and pseudotumor, including the rate of hospitalization, anemia and transfusion?
- Does weekly prophylactic Hemlibra (emicizumab) control the progression, stabilization or regression (ie, affect the size) of the hemophilic pseudotumor?
- Does weekly prophylactic Hemlibra (emicizumab) result in an increase in QoL and activity level?

3.1.1 Initial Study Visit (Consent and Screening)

The initial study visit will take place at the IHTC and will comprise subject consent and screening. The subject will be screened per the criteria listed in **Section 4** of this protocol and will include a physical examination and the review/collection of clinical and laboratory data (if not included in the subject's medical records) including:

- Baseline FVIII,[*] aPTT, PT and VWF:Ag
- Baseline FVIII inhibitor level
- Baseline CBC w/diff and CMP + direct bilirubin
- Vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight

[*] If the subject has an inhibitor, then testing for FVIII level may not be medically necessary as FVIII is usually undetectable in such cases. Exceptions exist, such as for a patient who has mild hemophilia with an inhibitor that only recognizes infused FVIII and not endogenous FVIII.

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- Serum pregnancy test for female subjects
- Documentation of current or past infection of Hepatitis A, B and C (tests listed below). If documentation is not available, then the tests will be administered as part of the screening process*
    - HAV:Ab
    - HBV:Ag and Ab (Core and Surface); if HBV:Ag positive, HBV viral load
    - HCV:Ab; if HCV:Ab positive, HCV viral load
- Documentation of HIV infection (if Ab positive, viral load and CD4 count)
- Baseline Haem-A-QoL and EQ-5D-5L
- If an activity monitoring device is standardly utilized by the patient, then permission will be requested to access data for the 1-month period prior to study entry and use of data from the device if continued during the study
- Review of at least 16 weeks, and up to 6 months if available, of data on prior use of hemostatic therapy and number of breakthrough bleeding events
- Review of 6 months of data on prior need for hospitalization or for PRBC transfusion
- Review of therapy prior to study entry with dose and interval and trough level if available on prophylaxis
- Review of history of inhibitor including date of first positive test, highest documented titer and date
- Review of concomitant medications and supplements
- Determination of the date of development or identification of pseudotumor and documentation of radiologic (CT or MRI) scans
- Review of surgeries and procedures

If the subject is not vaccinated, previously exposed, or immune to HAV and/or HBV then they will receive the first dose of the HAV and/or HBV vaccine during screening. Subjects must follow up with their local provider to complete the recommended vaccination schedule.†

Safety data reporting will commence at the time of subject consent and study procedures and will end at study discontinuation/termination or 24 weeks following the last administration of study treatment, whichever occurs first. Extensions to this time will be made in certain situations (eg, **Sections 6.11.3.2.f and 6.11.3.2g**).

* Although this testing and documentation is considered standard of care, there are important reasons to include this in the study and budget. There are patients in the US who are not followed at a federally recognized hemophilia treatment center and this testing may be inconsistently available. In addition, there are patients who refuse entry into CDC studies where this testing is performed or refused vaccination to prevent Hepatitis A and/or B transmission. Knowing each patient's viral exposure status and vaccination history will be important to decrease risk of community acquired infections that may lead to development of AEs that could be avoided.
† Vaccinations will not be charged to the study.

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Screening is expected to take up to 10 days but may be shorter depending on the return of required laboratory testing. If successfully screened, the subject may then be enrolled in the study and receive Hemlibra (emicizumab) loading doses during the second study visit

3.1.2 Second Study Visit [Hemlibra (emicizumab) Loading Doses]

The second study visit will take place at the IHTC up to 10 days after the initial screening visit. The purpose of the second study visit is to administer the 4 weekly loading doses of Hemlibra (emicizumab); acquire ADA data, vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight; and complete baseline radiology.

Prior to the first loading dose, a banked plasma sample will be obtained to determine baseline anti-drug antibody levels for Hemlibra (emicizumab). Baseline radiology (CT and/or MRI) will also be obtained if not previously performed within one month of study entry or if provided scans are deemed inadequate to accurately assess the extent of the pseudotumor.

Subjects/caregivers will be instructed on how to inject Hemlibra (emicizumab) and how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. The Study Investigator has the discretion to provide additional training or include additional observation (eg, after the fourth loading dose), if deemed appropriate, and each subject/caregiver will be able to ask any question he or she may have prior to being deemed capable of performing subcutaneous Hemlibra (emicizumab) injections. If, despite additional training, the investigator determines that the subject/caregiver is unable to inject Hemlibra (emicizumab), a trained and proficient caregiver or local healthcare provider should be identified to administer the prophylaxis injections.

The 4 loading doses will be administered once weekly for 4 weeks using the FDA-approved regimen (3 mg/kg once weekly by subcutaneous injection). Following the 4th loading dose a second banked plasma sample will be obtained to determine anti-drug antibody levels for Hemlibra (emicizumab). If the subject routinely uses an activity monitoring device and has consented to the use of data from that device during the study, then data from the time of informed consent will be collected.

During study visit 2 suitable quantities (to be determined by the Study Investigator) of Hemlibra (emicizumab) will be dispensed to the subject (see **Section 6.7**).

3.1.3 Subsequent Scheduled Study Visits

Subsequent study visits will occur once a quarter, as is the standard of care for patients with hemophilic pseudotumor. These study visits will take place at the medical facilities of the subject's local physician, except for the annual and study close-out visits, which will take place at the IHTC. The first subsequent study visit will be 3 months (±2 weeks) following the first loading dose of Hemlibra (emicizumab).

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The specific requirements of each visit are listed below. Depending on when a subject enrolls and when the study ends, the subject might not participate in all study visits beyond month 24. See **Appendix 2**.

3.1.3.1 Study visits at months 3, 9, 15, 21, 27, 33, 39 and 45 (±2 weeks)

The subject will follow-up with their local physician at the intervals specified above.

During this visit:

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Review of patient diary for completeness
- Patient study documentation will be submitted to the IHTC for review of compliance and data collection
- Review of AEs
- Review of concomitant medications and supplements
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

3.1.3.2 Study visits at months 6, 18, 30 and 42 (±2 weeks)

The subject will follow-up with their local physician for a more detailed clinical review at the intervals specified above.

During this visit the following data will be collected and/or reviewed and transmitted to the IHTC:

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- CBC panel w/diff
- Review of breakthrough bleeding events requiring alternate hemostatic therapy
- Review of the number of hospital admissions
- Review of the development of anemia requiring transfusion or intervention
- Review of AEs
- Review of concomitant medications and supplements
- Review of patient diary for completeness
- Patient study documentation will be submitted to the IHTC for review of compliance and data collection
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

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3.1.3.3 Annual study visits (months 12, 24 and 36 ±2 weeks)[*]

The annual study visit will take place at the IHTC.

During this visit the following data will be collected and/or reviewed at the IHTC:

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Radiologic evaluation (CT and/or MRI) to evaluate control of progression, stabilization or regression of pseudotumor
- Anti-drug antibodies (banked plasma sample)
- Repeated Haem-A-QoL and EQ-5D-5L
- CBC panel w/diff
- Review of breakthrough bleeding events requiring alternate hemostatic therapy
- Review of the number of hospital admissions
- Review of the development of anemia requiring transfusion or intervention
- Review of AEs
- Review of concomitant medications and supplements
- Review of patient diary
- Patient study documentation will be collected for review of compliance and data collection
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

During this annual visit, a physical examination will be performed, used/empty vials of emicizumab will be collected and a suitable quantity of Hemlibra (emicizumab) will be dispensed (see **Section 6.7**).

3.1.3.4 Study close out visit

See **Section 7.5**

3.1.4 Unscheduled Study Visits

Any unscheduled study visits with the subject's local hemophilia physician will be recorded in the CRF along with all relevant medical information (eg, reason for visit, diagnoses, scans, AEs, lab results, vital signs [blood pressure, pulse, temperature, and respiratory rate], weight, etc).

[*] Subjects enrolled in the study for the maximum length of time (ie, 48 months) will also participate in an annual visit at approximately the 48-month time point; however, this will be the subject's close-out visit, and the procedures required will be those list in **Section 7.5**. The primary difference between an annual visit and the close-out visit is the collection of used and unused vials of Hemlibra (emicizumab), rather than the dispensation of additional drug

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If a subject meets with a physician other than their local hemophilia physician, that information should be communicated to their hemophilia physician at the next scheduled quarterly study visit and appropriate medical information recorded in the CRF.

Hospitalizations should be recorded in the CRF along with relevant medical information (see **Section 6.11.3.2d**). These should be reported to the IHTC within 7 days of their occurrence.

AEs should be reported using the instructions in **Section 6.11.3**.

3.1.5 Surgeries

All surgeries will be recorded in the CRF, which should minimally include the following information (see **Section 6.11.3** for additional reporting requirements):

- Procedure type
- Reason for procedure
- Planned or unplanned
- Date of procedure and length of hospitalization
- Hemostatic therapy provided pre-procedure (type, dose and dates)
- Hemostatic therapy provided post-procedure (type, dose and dates)
- Hemostatic outcome immediately post-procedure
- Hemostatic outcome at the end of hospitalization
- Adverse events experienced (including, but not limited to clots, thromboses and TMA)
- Vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight

Hemostatic outcome for surgical treatment is defined using the standard ISTH rating scale shown below [Blanchette, Key et al. 2014].

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

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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

Medical details and outcome of all surgeries should be reported to the IHTC within 7 days of their occurrence.

3.1.6 Subject Withdrawal/Study Termination Procedures

See **Section 7.6**

3.1.7 Follow-up Period

No follow-up period is planned with the exception of post-study adverse events listed in **Sections 6.11.2.1** and **6.11.3.2g**.

3.2 Rationale for Study Design

Hemophilic pseudotumor is a complication of hemophilia (1-2% of patients) that consists of a progressive cystic swelling of muscle and/or bone caused by recurrent hemorrhage. It is observed more frequently in geographic areas where hemophilia is diagnosed late, treatment is inconsistently available, prophylaxis is not used due to resource constraints, and in patients who do not recognize that a bleeding event has occurred (eg, moderate or mild deficient patients who experience a bleed/injury). FVIII prophylaxis has been used in patients with hemophilia A with pseudotumors when surgical intervention is not feasible either due to lack of local expertise or inability to perform the intervention due to extent or site of the pseudotumor. Pseudotumors may be present in patients with hemophilia either with or without an inhibitor and are more common in patients with inhibitors where hemostasis is less well controlled.

It is hypothesized that an agent that confers a consistent FVIII level in the mild deficient range that is not associated with trough levels below 10% will confer a higher degree of hemostasis in patients with pseudotumors; this will result in a decreased rate of breakthrough bleeding requiring intermittent hemostatic therapy, and an associated decrease in uncontrolled bleeding resulting in anemia, transfusion, and hospitalization. If these endpoints are achieved it is also hypothesized that activity and quality of life may increase or improve respectively.

The purpose of this study is to prospectively investigate the hemostatic efficacy and safety of weekly prophylactic Hemlibra (emizicumab) in the treatment/control of pseudotumors in children and adults with FVIII deficiency (baseline FVIII level <40%) either with or without an inhibitor; in addition, changes in quality of life and activity level in subjects with hemophilia A and pseudotumor will be assessed.

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3.3 Study Duration and Dates

The enrollment period for this study will last 2 years and is planned to start in the first quarter of 2019.

Each subject will receive Hemlibra (emicizumab) therapy for a minimum of 2 years unless they voluntarily withdraw, are involuntarily withdrawn by the Study Investigator, or the study is terminated early. The maximum duration of Hemlibra (emicizumab) therapy on study is 4 years. The maximum time on study for each subject is dependent on when they enroll.

The study will last a maximum of 4 years from the date of the first signed consent form from the first subject, to the last administration of Hemlibra (emicizumab) to any subject.

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4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 10 subjects will be enrolled in this study and receive study medication. There are no restrictions on weight or BMI.

4.2 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent form from the subject, parent or guardian
- Diagnosis of congenital hemophilia A (baseline FVIII level <40%) with or without FVIII inhibitor, either high or low responding, regardless of titer
- Diagnosis of a hemophilic pseudotumor confirmed by radiologic assessment such as CT or MRI
- Any weight or BMI
- Medical documentation of prophylactic or episodic treatment (FVIII or bypassing agent) and the number of bleeding episodes for at least 16 weeks, and up to 6 months if available, prior to entry into the study
- Medical documentation of any need for PRBC transfusion or hospitalization for 6 months prior to entry into the study
- Subjects with a history of an inhibitor should provide documentation of the inhibitor history including date of initial diagnosis of inhibitor, peak titer, and agent utilized for hemostatic control
- Subjects with high titer inhibitors or those with low titer inhibitors who do not respond to FVIII must be willing to use rFVIIa as first line therapy for the treatment of breakthrough bleeding events
- Medical documentation of ITI therapy for subjects with a history of a FVIII inhibitor and ITI, including current FVIII inhibitor titer
- Willingness to discontinue any current prophylactic hemostatic regimen (FVIII or bypassing agent) and/or FVIII ITI therapy for the duration of the study
    - Subjects receiving FVIII prophylaxis must be willing to discontinue their FVIII prophylactic regimen immediately prior to their second loading dose of Hemlibra (emicizumab)
    - Subjects receiving bypassing agent prophylaxis must be willing to discontinue their prophylactic regimen at least 24 hours prior to their first loading dose of Hemlibra (emicizumab)

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    - Subjects receiving FVIII ITI therapy must be willing to discontinue ITI immediately prior to their first loading dose of Hemlibra (emicizumab)
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the health-related questionnaires, activity tracking, and bleed diaries, using systems provided during the study
- Adequate hepatic function, defined as total bilirubin ≤1.5 × age-adapted upper limit of normal (ULN) (excluding Gilbert's syndrome) and both AST and ALT ≤3 × age-adapted ULN at the time of screening, and no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Subjects must be willing to be vaccinated against HAV and HBV if not previously vaccinated, exposed or immune to HAV or HBV*
- Adequate hematologic function, defined as a platelet count ≥100,000/μL and a PT≤1.5 times the ULN at the time of screening
- Adequate renal function, defined as serum creatinine ≤2.5 × age-adapted ULN and creatinine clearance ≥30 mL/min by Cockcroft-Gault formula
- For women with hemophilia of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

4.3 Exclusion Criteria

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

- Inherited or acquired bleeding disorder other than congenital hemophilia A
- Lack of a documented diagnosis of hemophilic pseudotumor
- Patients who are at high risk for TMA (eg, have a previous medical or family history of TMA), in the Study Investigator's judgment
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the Study Investigator's judgment
- Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (eg, certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis

* Vaccinations will not be charged to the study.

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- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the Emicizumab injection
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Known HIV infection with CD4 counts <200 cells/μL. HIV infection with CD4 counts ≥200 cells/μL permitted
- Use of systemic immunomodulators (eg, interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- Concomitant disease, condition, significant abnormality on screening evaluations or laboratory tests, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the Study Investigator, pose an additional unacceptable risk in administering study drug to the patient
- Receipt of any of the following:
    - Hemlibra (emicizumab) in a prior investigational study
    - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration
    - A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
    - Any other investigational drug currently being administered or planned to be administered
- Inability to comply with the study protocol in the opinion of the Study Investigator
- Pregnancy or lactation or intention to become pregnant during the study
- Women with a positive serum pregnancy test result within 10 days prior to initiation of study drug

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5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Study Drug

The study drug is US-labeled Hemlibra (emicizumab). It will be administered using the FDA approved once-weekly doing regimen for loading dose (3 mg/kg) and prophylactic dose (1.5 mg/kg, *or 3 mg/kg kg if dose escalation is determined appropriate by the Study Investigator*). Hemlibra (emicizumab) will be provided in a clear vial as a solution. Hemlibra (emicizumab) will be provided by the study.

5.1.2 Non-study Drugs

Should a breakthrough bleed occur, then any locally approved pdFVIII or rFVIII may be used in subjects without a FVIII inhibitor or with a low titer inhibitor (titer <5BU) using the local standard of care; if the subject's standard of care for treatment of bleeding events with low titer inhibitors is a bypassing product, the subject will follow treatment as outlined under high titer inhibitors (below).

Should a breakthrough bleed occur in subjects with a high titer FVIII inhibitor (titer ≥5BU), then any locally approved rFVIIa concentrate may be used using the local standard of care. Other bypassing agents (eg, aPCC) may only be used with the approval of the Study Investigator. Agents to treat breakthrough bleeds or other sequelae (including, but not limited to pdFVIII, rFVIII, rFVIIa, and aPCC) will not be provided by the study.

5.2 Packaging and Labeling

US-labeled Hemlibra (emicizumab) will be supplied as a solution in clear glass vials at nominal doses of 30mg, 60mg, 105mg and 150mg. Vials will be packaged in an outer box. In addition, supplies for administration of Hemlibra (emicizumab) will be provided (eg, syringes, transfer needles, injection needles, alcohol wipes, etc).

5.3 Treatments Administered

5.3.1 Loading Doses of Hemlibra (emicizumab)

After obtaining informed consent and the performance of screening procedures, patients who (at the discretion of the Study Investigator) meet all inclusion and exclusion will be eligible for study medication.

The 4 loading doses of Hemlibra (emicizumab) will be administered as 3 mg/kg subcutaneous injections, dosed once-weekly over a 4-week period during study visit 2 (**Section 7.2**).

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5.3.2 Prophylactic Doses of Hemlibra (emicizumab)

Prophylactic administration of Hemlibra (emicizumab) will continue on a weekly basis (1.5 mg/kg subcutaneous dosing, *or 3 mg/kg kg if dose escalation is determined appropriate by the Study Investigator [**Section 5.3.3**]*) until the subject withdraws from the study, is involuntarily withdrawn from the study, or the study is terminated, whichever occurs first (**Section 7.3**). All used and unused vials of Hemlibra (emicizumab) should be returned to the IHTC once a subject is no longer enrolled.

5.3.3 Dose Escalation of Prophylactic Hemlibra (emicizumab)

All subjects with suboptimal control of bleeding as defined by the protocol will be offered the option to increase their Hemlibra (emicizumab) maintenance dose to 3 mg/kg QW, with approval from the Study Investigator. Suboptimal response is defined as follows:

- *Two qualifying bleeds within 24 weeks while on prophylactic Hemlibra (emicizumab)*

A qualifying bleed is defined as spontaneous, verified by an investigator (eg, by imaging or physical examination or reliable symptoms reported by patient including increased pain with swelling, decreased ability to function etc clearly related to presence/site of pseudotumor), and occurring while on prophylactic Hemlibra (emicizumab) at steady state (after week 5). If the investigator believes that a specific subject warrants dose escalation on the basis of a different reason, he or she may discuss the case with the Study Investigator for consideration and potential approval.

If this 3 mg/kg maintenance dose does not result in increased control of breakthrough bleeding, the subject may return to the standard 1.5 mg/kg maintenance dose upon approval of the Study Investigator, assuming this 1.5 mg/kg dose had resulted in an improvement in breakthrough bleeding compared to their pre-study regimen.

5.4 Treatment of Breakthrough Bleeds and Concomitant Therapies

No pdFVIII, rFVIII, rFVIIa or aPCC shall be administered unless required to treat a breakthrough bleed. **The use of aPCC should be avoided and may only be administered if approved by the Study Investigator. The use of any bypassing agent, other than rFVIIa (eg, NovoSeven®), requires approval of the Study Investigator.**

Drugs intended to control or prevent bleeds, including bypassing agents, should be used at the lowest dose expected to achieve hemostasis according to the local standard of care. Given that circulating Hemlibra (emicizumab) may increase the patient's coagulation potential, the usual doses of hemostatic medication (ie, bypassing agents, FVIII, antifibrinolytics, etc) required to achieve hemostasis may be lower than the doses used prior to starting Hemlibra (emicizumab). Use of aPCC in combination with Hemlibra (emicizumab) should be avoided in patients who have the option of using other bypassing agents to treat bleeds. In the event that aPCC is the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed,

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with no more than 50 U/kg aPCC to be administered as an initial dose. The total dose of aPCC must be <100 U/kg/day for preferably less than 1 day. **aPCC may only be administered if approved by the Study Investigator and may only be administered by a physician.**

Caution should be taken for patients who are using rFVIIa (eg, consideration of using no more than 90 μg/kg of rFVIIa as an initial dose). Other bypassing agents should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose. **Bypassing agents other than rFVIIa may only be administered if approved by the Study Investigator.**

The exact dose and schedule of bypassing agents should be discussed with subjects at the beginning and throughout the study. Repeated dosing of rFVIIa, aPCC, or other bypassing agents should be performed only under medical supervision, which could include laboratory monitoring by additional local and central laboratory assessments, and consideration should be given to verifying bleeds prior to repeated dosing.

Caution should be taken if antifibrinolytics are used in conjunction with bypassing agents including rFVIIa and aPCC in patients receiving Hemlibra (emicizumab). Use of antifibrinolytics after one dose of bypassing agent (eg, as done for dental extractions) is allowed; concomitant use of rFVIIa and antifibrinolytics should be avoided if at all possible and concomitant use of aPCC and antifibrinolytics is not allowed. (see Restrictions, **Section 5.5**)

Drugs and therapies to treat AEs and use of topical antiseptics, anesthetics, eye drops, etc, that are not considered to result in systemic exposure are permitted.

All concomitant medications need to be registered in the subject's medical files and the patient diaries and recorded in the CRF.

5.5 Restrictions

Use of the following therapies may be prohibited for subjects enrolled in ongoing studies and for at least 4 weeks prior to the initiation of study treatment.

- Use of drugs that would affect hemostasis (eg, aspirin, non-steroidal anti-inflammatory drugs, or anticoagulants [other than to flush, dwell, or de-clot a central venous access device]) but excluding drugs intended to control bleeding episodes or used in the context of minor surgery (eg, tooth extraction) or injuries (eg, concussion) to prevent deterioration
- Use of systemic immunomodulators (eg, rituximab, interferon) other than antiretroviral therapy from enrollment to last observation
- Elective surgery (excluding minor procedures such as tooth extraction, central venous access device removal, or incision and drainage as well as emergency surgeries) from enrollment to last observation

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- Use of aPCC for short-term or long-term prophylaxis
- Use of antifibrinolytics concomitantly with aPCC
- Use of other investigational drugs from enrollment to last observation

5.6 Treatment Compliance

All subjects will either self-administer Hemlibra (emicizumab) in an at-home setting, or have Hemlibra (emicizumab) administered by a trained caregiver or healthcare provider (either at home or at a local physician's office) on a weekly basis.[*] Agents required to treat a breakthrough bleed may also be self-administered by the subject or a caregiver in an at-home setting, except aPCC, which if approved by the Study Investigator may only be administered by a physician.

The following will be recorded by the subject in their patient diary:

- The date and time of Hemlibra (emicizumab) administration
- The exact dose of Hemlibra (emicizumab) administered
- Any adverse events, duration and actions taken

Additionally, the subject will record the following for all bleeding events

- The date and time of onset
- The anatomical location and severity
- The agent(s) used to control the bleed, the exact dose(s), the number of doses and the time(s) of administration
- The Study Investigator will determine whether the bleeding event was related to the pseudotumor based on a retrospective review of the clinical data

Should the subject be admitted to a hospital or medical facility this should be recorded as described in **Section 6.11.3**, as should any incidences of anemia that require transfusion or intervention. All surgeries or deaths should also be recorded. Medical details of these events should be transmitted to the IHTC within 7 days of their occurrence

The patient diary will be checked by the subject's local physician during the quarterly study visits that take place at their local facilities and transmitted to the IHTC at that time. The patient diary will be reviewed by IHTC staff during the annual and study close-out visits at the IHTC.

5.7 Storage and Accountability

Hemlibra (emicizumab) must be stored in a safe and secure place at the subject's home or local clinic. Hemlibra (emicizumab) should be stored between 2°C (36°F) and 8°C (46°F) in the

[*] Weekly injections of Hemlibra (emicizumab) by a nurse or qualified healthcare provider is not required by the study and therefore is not included in the budget. Travel by the subject to receive injections of Hemlibra (emicizumab) is not required by the study and therefore is not included in the budget.

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original carton and protected from light. The product is stable at room temperature (below 30°C, 86ºF) for up to 7 days. The product should not be frozen or shaken.

The Study Investigator is fully responsible for all study supply of Hemlibra (emicizumab) stored at the IHTC. Access should be strictly limited to the Study Investigator and designated staff.

All study supply of Hemlibra (emicizumab) received at the IHTC, dispensed to and returned from a subject will be documented. All empty vials will be returned to the IHTC and documented. This documentation must be available for review by Genentech to confirm proper investigational product management.

5.8 Investigational Product Retention at Study Site

All used and unused vials of Hemlibra (emicizumab) will be retained until accountability has been performed and recorded by the IHTC pharmacy. For this purpose, study staff will keep all used vials to perform the treatment compliance check and store them for a final accountability check by Genentech.

All unused vials of Hemlibra (emicizumab) will be returned to Genentech or destroyed by the IHTC pharmacy.

5.9 Dispensation of Hemlibra (emicizumab)

See **Section 6.7**.

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6 STUDY PROCEDURES

6.1 Informed Consent

Informed consent will be in English. The subject and/or their caregiver must be sufficiently proficient in English to read, understand and sign the informed consent form.

All subjects will be informed of the aims of study, the possible adverse events, the procedures and possible risks to which they will be exposed, and how treatment and dose will be determined. They will be informed as to the strict confidentiality of their personal data, and that their medical records may be reviewed for study purposes by authorized individuals other than their treating physicians. It will be emphasized that the participation is voluntary and that the subject is allowed to refuse further participation in the protocol whenever they want. Once the subject completely understands the study and its procedures and risks they will be asked to sign and date the informed consent form. Study procedures may only occur after the informed consent form has been signed and dated.

Any subject who provides informed consent (ie, signs and dates the informed consent form) will be screened, and if screening is successful they will be enrolled in the study. Screening is expected to take less than 10 days. Recording of safety observations will commence immediately with the signing and dating of the informed consent form and the initiation of study procedures.

6.2 Medical History/Demographics

The medical history of the subject will be obtained. Specific information will be recorded on the CRF relating to any prior or existing medical conditions/surgical procedures involving the following: Infectious Diseases (including viral infections, such as Hepatitis and HIV), Allergies, Metabolic/Endocrine/Nutritional, Hematopoietic, Musculoskeletal, Dermatologic, Head, Ears, Eyes, Nose, and Throat (HEENT), Breasts, Respiratory, Cardiovascular, Gastrointestinal/Hepatic, Genitourinary/Renal, Neurologic, and Psychiatric/Psychosocial.

Specific documentation for the following should be provided to the IHTC:

- Medical documentation of any prophylactic (FVIII or bypassing agent) therapy for at least 16 weeks, and up to 6 months if available, prior to entry into the study
- Medical documentation for the number of bleeding episodes (including location, severity, duration and treatment) for at least 16 weeks, and up to 6 months if available, prior to entry into the study. If available, the hemostatic agent, number of infusions and quantity of drug infused for each bleeding episode will be collected
- Medical documentation of any complications related to the pseudotumor (including any incidences of anemia, the need for PRBC transfusion or hospitalization) for 6 months prior to entry into the study

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- Subjects with a history of an inhibitor should provide documentation of the inhibitor history including date of initial diagnosis of inhibitor, peak titer, and agent utilized for hemostatic control
- Medical documentation of ITI therapy for subjects with a history of a FVIII inhibitor and ITI, including current FVIII inhibitor titer
- Documentation of current concomitant medications and supplements
- Date of development or identification of pseudotumor and documentation of radiologic (CT and/or MRI) scans

Demographics (date of birth, race/ethnicity, gender, height, weight, etc) and vital signs (blood pressure, pulse, temperature, and respiratory rate) will also be collected.

6.3 Physical Examination

Standard physical examinations will be performed during the study. All findings from this examination will be recorded on source documents and entered into the CRF. The standard physical examination will minimally include the following observations/measurements: General Appearance, Skin, HEENT, Thyroid, Lymph Nodes, Heart, Lungs, Abdomen, Extremities/Joints, Neurological, and Mental Status.

6.4 Events of Special Interest

During the study the subject will be checked for the Hemlibra (emicizumab) Events of Special Interest (**Section 6.11.3.2i**), which are clinical signs of thrombotic microangiopathy, thromboembolic events, systemic hypersensitivity reactions and anaphylactic/anaphylactoid reactions. If observed, ongoing monitoring and rapid communication by the Study Investigator to Genentech is required. Such an event might require further investigation in order to characterize and understand it. If any of the above are observed, appropriate laboratory tests should be pursued.

6.5 Quality of Life and Activity Assessments

6.5.1 Haem-A-QoL and EQ-5D-5L

Quality of life assessments will be completed by adult subjects using the Haem-A-QoL (Haem-A-QoL Group) and EQ-5D-5L (EuroQol Group) questionnaires. They will be completed in English or in the subject's native language if available and validated in that language. These assessments will be repeated at every annual study visit and the study close-out visit.

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6.5.2 Activity Monitoring Device

If the subject routinely uses an activity monitoring device (eg, Fitbit or similar) and plans to remain doing so during the study, then permission will be requested to access the data for the 1-month period prior to enrollment in the study (baseline data) and continued access from enrollment until the end of their participation in the study (study data). These data will be collected and transmitted to the IHTC on at least a quarterly basis for analysis.

6.6 Clinical Laboratory Tests

6.6.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. Clinical laboratory tests will include the following, and unless otherwise noted, will be carried out by the local laboratory of the study site. Not all of these tests will be performed at screening if there are acceptable results available in the subject's medical files, or if they are considered medically unnecessary for a specific patient at the discretion of the Study Investigator. See **Section 7** for specific details on when these tests might be performed.

List of Laboratory Tests

- FVIII level[*]
- aPTT
- PT
- VWG:Ag
- FVIII inhibitor level (Bethesda assay)
- CBC w/diff
- CMP + direct bilirubin
- ADA for Hemlibra (emicizumab) – banked sample for analysis at central laboratory
- HAV:Ab
- HBV:Ag and Ab (Core and Surface); If HBV:Ag positive, then HBV viral load
- HCV:Ab; If HCV:Ab positive, then HCV viral load
- HIV:Ab; if HIV:Ab positive, then HIV viral load and CD4 count
- Serum pregnancy test for female subjects

[*] If the subject has an inhibitor, then testing for FVIII level may not be medically necessary as FVIII is usually undetectable in such cases. Exceptions exist, such as for a patient who has mild hemophilia with an inhibitor that only recognizes infused FVIII and not endogenous FVIII.

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6.6.2 Life-threatening Bleeding Due to Unreliable Standard Coagulation Tests in the Setting of Hemlibra (emicizumab)

Emicizumab affects assays for non-bovine reagent aPTT and all assays based on non-bovine reagent aPTT, such as one-stage FVIII activity. Therefore, non-bovine aPTT-based coagulation laboratory test results in patients who have been treated with emicizumab prophylaxis will not be used to monitor either emicizumab activity or determine dosing for factor replacement, or measure FVIII inhibitor titers. If required for clinical care, specific specialized testing such as the chromogenic FVIII assay with bovine FIXa/FX to measure exogenous FVIII replacement, or a bovine based aPTT for inhibitor analysis will be recommended to be utilized as available; these analyses are not required by the study and therefore not included in the budget.

There is a risk of life-threatening bleeding due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab if a patient is treated by a practitioner other than the emicizumab-prescribing practitioner in settings such as an emergency room or in an acute care setting.

For recommendations on the use and interpretation of coagulation assays for patients receiving emicizumab, see **Section 6.6.3**.

6.6.3 Use & Interpretation of Coagulation Assays

Most coagulation assays may be performed in a local laboratory for screening. Once administration of Hemlibra (emicizumab) has been initiated, certain coagulation assays should not be used due to interference; instead alternative assays at a local or central laboratory should be used.

Based on its mechanism, Hemlibra (emicizumab) is expected to interfere with any laboratory coagulation test that is based on the intrinsic pathway. This section explains the effects of Hemlibra (emicizumab) on the tests most commonly used in hemophilia A.

The following table summarizes the coagulation tests affected and unaffected by emicizumab. Due to the long half-life of Hemlibra (emicizumab), these effects on coagulation assays may persist for up to 6 months after the last dose.

Results affected by Hemlibra (emicizumab)	**Results unaffected by Hemlibra (emicizumab)**
Activated partial thromboplastin time (aPTT) Activated clotting time (ACT) One-stage, aPTT-based, single-factor assays aPTT-based Activated Protein C Resistance (APC-R)	Thrombin time (TT) One-stage, PT-based, single-factor assays Chromogenic-based single-factor assays other than FVIII*

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Bethesda assays (clotting-based) for FVIII inhibitor titers	Immuno-based assays (eg, ELISA, turbidometric methods) Bethesda assays (bovine chromogenic) for FVIII inhibitor titers Genetic tests of coagulation factor mutations (eg, Factor V Leiden, Prothrombin 20210)

ACT, activated clotting time; APC-R, Activated Protein C Resistance; aPTT, activated partial thromboplastin time; ELISA, enzyme linked immunosorbent assay; FVIII, factor VIII; PT, prothrombin time; TT, thrombin time
[*] For important considerations regarding FVIII chromogenic activity assays, please see **Section 6.6.3.3**

6.6.3.1 aPTT assay

The total clotting time as measured by aPTT is dependent on a large number of coagulation factors, including the feedback activation of FVIII by thrombin, which is a rate-limiting step. Hemlibra (emicizumab) does not require activation, resulting in a supra-physiologically short time to clot formation. Thus, aPTT is normalized by sub-therapeutic concentrations of emicizumab (as low as 5 µg/mL) and does not accurately indicate the patient's coagulation status or the activity of emicizumab.

6.6.3.2 One-stage FVIII activity assay

This assay utilizes aPTT reagents and thus is subject to interference by Hemlibra (emicizumab). Very rapid clotting times result in overly high reported FVIII activity values, which do not correctly reflect the patient's coagulation status or the activity of Hemlibra (emicizumab).

6.6.3.3 FVIII chromogenic activity assay ("two-stage")

As an antibody, Hemlibra (emicizumab) exhibits very specific binding to its targets, human FIXa and FX, and it does not exhibit cofactor activity with the respective bovine proteins. Most commercially available chromogenic activity assays are manufactured using purified bovine FIXa and FX. Hemlibra (emicizumab) activity cannot be detected in these assays and can only be detected using a chromogenic assay composed of human proteins (Hyphen Biophen).

6.6.3.4 Bethesda assay

Hemlibra (emicizumab) is not inactivated by heat treatment and is not neutralized by FVIII inhibitors. Hemlibra (emicizumab) will cause plasma samples to clot irrespective of the presence FVIII inhibitors. Therefore, FVIII inhibitors cannot be detected by functional tests, such as Bethesda or Nijmegen-Bethesda assays, which use a one-stage clotting based readout. A Chromogenic Bethesda Assay using bovine FIXa and FX is required since Hemlibra (emicizumab) does not bind to bovine factors (Chromogenic Bethesda Assay using human FIXa

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and FX should not be used for FVIII inhibitor detection). Immunoassays for FVIII inhibitors may also be used.

6.6.4 Central Laboratory Assays

Samples that require analysis in centralized laboratories will be appropriately processed according to standardized methods and stored at the IHTC based upon sample requirements until shipment occurs. In the case that a bovine based inhibitor titer is required, the sample will be sent to a laboratory with established methodology (eg, CDC) for analysis. The IHTC has experience with drawing, processing, storage and shipment of a wide variety of research samples. The IHTC has on-site equipment and SOPs for such procedures and has a -70ºC monitored freezer to store samples as well as an off-site secure sample storage facility agreement in place for longer term storage (BioStorage Technologies, Inc.) which can retrieve needed samples and/or ship per IHTC requirements.

6.7 Dispensation of Study Drug

Hemlibra (emicizumab) drug will be dispensed to the subject by the IHTC. Dispensation will take place at study visit 2, during annual visits to the IHTC and at other periods throughout the year to ensure adequate supply for the subject.

The quantity of Hemlibra (emicizumab) dispensed will depend on the storage capacity at the subject's home. It is preferred that study Hemlibra (Emicizumab) be stored in the patient's home unless extenuating circumstances exist; in these circumstances a discussion with the study investigator will occur and a solution developed to allow local access to study medication.

The quantity dispensed will be at the discretion of the Study Investigator and may vary from subject to subject. Additional quantities (ie, quantities dispensed at times other than study visit 2 and annual visits at the IHTC) may be dispensed and shipped to the subject throughout the year to ensure adequate supply for the subject using standard protocols for the shipment/transport of medicines.

The subject shall also receive appropriate materials for administration (eg, alcohol swabs, syringes, needles, etc.)

6.8 Pharmacokinetic Assessments

No pharmacokinetic assessments will be performed as part of the study

6.9 Pharmacodynamic Assessments

No pharmacodynamic assessments will be performed as part of the study

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6.10 Efficacy and Quality of Life Assessments

The primary outcome for this study is bleeding events specifically related to the pseudotumor over time; total bleeding events will also be recorded and analyzed.

All bleeding events will be recorded in the patient diary along with the following:

- The date and time of onset
- The anatomical location and severity
- The agent(s) used to control the bleed, the exact dose(s), the number of doses and the time(s) of administration
- The Study Investigator will determine whether the bleeding event was related to the pseudotumor based on a retrospective review of the clinical data

The efficacy of Hemlibra (emicizumab) will be determined by comparing the incidence of bleeding events and use of alternate hemostatic medication on study to the incidences prior to study enrollment and by changes over time.

The following should also be recorded and transmitted to the IHTC within 7 days of their occurrence:

- The admission of the subject to a hospital or medical facility (described in **Section 6.11.3**)
- Incidences of anemia that require transfusion or intervention
- All surgeries or deaths
- Any other AEs or SAEs noted and recorded by a physician

The efficacy of Hemlibra (emicizumab) will be determined by comparing the incidence of hospitalization and anemia that require transfusion or intervention on study to the incidences prior to study enrollment and by changes over time.

The following should be acquired during study visit 2 (if they were not performed within 1 month of study entry and if they are not considered suitable for study purposes) and at every annual study visit and the study close-out visit:

- Radiology (CT and/or MRI) to observe change in the size of the pseudotumor over time (ie, the progression, stabilization or regression of the pseudotumor)

The efficacy of Hemlibra (emicizumab) will be determined by the change in the size of the pseudotumor over time (ie, the control of progression, stabilization or regression of the pseudotumor).

The following will be used to determine changes in quality of life and activity level:

- Haem-A-QoL and EQ-5D-5L will be completed following screening and at every annual study visit and the study close-out visit

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- If an activity monitoring device is standardly utilized by the patient (eg, Fitbit) and the subject has provided consent to use that data in the study, then data from that device will be transmitted to the IHTC on a quarterly basis to assist in activity monitoring

The efficacy of Hemlibra (emicizumab) will be determined by comparing changes in activity and quality of life over time.

6.10.1 Primary Endpoints

The primary endpoints are:

- The number of breakthrough bleeding events over time requiring the use of alternate hemostatic therapy (bleed rate) related to the pseudotumor
- The number of hospital admissions related to the pseudotumor
- The number of incidences of anemia requiring transfusion or intervention related to the pseudotumor
- The change in the size of the pseudotumor over time (ie, the control of progression, stabilization or regression of the pseudotumor) as measured by yearly assessments including CT or MRI

The study investigator will determine whether the reported event was related to the pseudotumor based on a retrospective review of the medical data (eg, bleed location, patient symptoms, etc).

6.10.2 Secondary Endpoints

The secondary endpoints are:

- The impact of weekly prophylaxis on quality of life and activity level
- Safety including development of AEs, SAEs, and ADA
- The dose(s) and number of infusions of alternate hemostatic therapy (FVIII, rFVIIa or aPCC) required to treat a breakthrough bleeding event either unrelated or related to the pseudotumor
- The number of breakthrough bleeding events over time requiring the use of alternate hemostatic therapy (bleed rate) unrelated to the pseudotumor
- The use of alternate hemostatic therapies (eg, FVIII, rFVIIa or aPCC) during surgeries and the hemostatic efficacy

The study investigator will determine whether the reported event was related to the pseudotumor based on a retrospective review of the medical data (eg, bleed location, patient symptoms, etc).

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6.11 Safety Reporting of Adverse Events

6.11.1 Assessment of Safety

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on radiologic (CT and/or MRI) scans. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

6.11.1.1 Specification of safety variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

6.11.1.2 Adverse events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with hemophilia that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- Preexisting medical conditions (other than the condition being studied) judged by the Study Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

6.11.1.3 Serious adverse events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (ie, the AE actually causes or leads to death)

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- It is life threatening (ie, the AE, in the view of the Study Investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP
- It is considered a significant medical event by the Study Investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

6.11.2 Methods and Timing for Assessing and Recording Safety Variables

The Study Investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

6.11.2.1 Adverse event reporting period

The study period during which AEs and SAEs as described in **Section 6.10.3.2j** where the patient has been exposed to Genentech product must be reported. Reporting period begins after informed consent is obtained and initiation of any study procedures and ends 24 weeks following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment (eg, AEs such as those described in **Section 6.11.3.2g**).

6.11.2.2 Assessment of adverse events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (ie, start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the Hemlibra (emicizumab) (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, Study Investigators should apply the following general guideline:

- **Yes**
  There is a plausible temporal relationship between the onset of the AE and administration of the Hemlibra (emicizumab), and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the

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AE follows a known pattern of response to the Hemlibra (emicizumab); and/or the AE abates or resolves upon discontinuation of the Hemlibra (emicizumab) or dose reduction and, if applicable, reappears upon re-challenge.

- **No**
  Evidence exists that the AE has an etiology other than the Hemlibra (emicizumab) (eg, preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to Hemlibra (emicizumab) administration (eg, cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (PI) or current Investigator Brochure (IB).

Unexpected adverse events are those not listed in the PI or current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the PI or IB. For example, under this definition, hepatic necrosis would be unexpected if the PI or IB only referred to elevated hepatic enzymes or hepatitis.

Specific unexpected adverse events include, but are not limited to:

- Fracture of a bone related to the erosion/weakening of osseous structures due to the pseudotumor
- Infection of pseudotumor especially if a fistula is present
- Requirement for emergent surgery due to expansion of pseudotumor or uncontrolled bleeding
- Requirement of amputation due to expansion of pseudotumor or uncontrolled bleeding

6.11.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

6.11.3.1 Eliciting adverse events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- “How have you felt since your last clinical visit?”
- “Have you had any new or changed health problems since you were last here?”

6.11.3.2 Specific instructions for recording adverse events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

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6.11.3.2a Diagnosis vs. signs and symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (eg, 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, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

6.11.3.2b Deaths

All deaths that occur during the protocol-specified AE reporting period (see **Section 6.11.3.2i**), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

6.11.3.2c Preexisting medical conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

6.11.3.2d Hospitalizations for medical or surgical procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

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6.11.3.2e Assessment of severity of adverse events

The adverse event severity grading scale for the NCI CTCAE will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse event severity grading scale for events not specifically listed in NCI CTCAE:

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE, which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event" it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

6.11.3.2f Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 24 weeks after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

6.11.3.2g Post-study adverse events

The Study Investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior Hemlibra (emicizumab) exposure. If the Study Investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject or of the female

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partner of a male study subject who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period

6.11.3.2h Case transmission verification of single case reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via the IHTC emailing Genentech a Quarterly line-listing documenting single case reports sent by the IHTC to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by the IHTC to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

6.11.3.2i AEs of special interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Study Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (eg, Regulatory Authorities) may also be warranted.

The Hemlibra (emicizumab) Events of Special Interest are:

- Thrombotic Microangiopathy
- Thromboembolic Events
- Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions

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:
    - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN

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- Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

- Suspected transmission of an infectious agent by the study drug, as defined below:
  - Any organism, virus, or infectious particle (eg, 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

6.11.3.2j Exchange of single case reports

IHTC will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

Study Investigators must report all *the above-mentioned single case reports* adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed*/emailed* immediately upon completion to Genentech at *the following contacts*:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints <u>with</u> an AE should be sent to:

Fax: 650-238-6067

Email: usds_aereporting-d@gene.com

All Product Complaints <u>without</u> an AE should be called into:

Product Complaint Hotline Phone Number: (800) 334-0290

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Serious adverse events (SAEs), pregnancy reports, AEs of special interest (AESIs), Special Situation Reports *and Product Complaints (with or without an AE)*, where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports

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(initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- **SADRs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.
- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.
- **AESIs**
  AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.
- **Pregnancy reports**
  While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.
- **Special situation reports**
  In addition to all SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
    - Data related to the Product usage during pregnancy or breastfeeding
    - Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
    - Lack of therapeutic efficacy
    - Drug interaction
    - Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)
- ***Product Complaints***
  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

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A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

All other AEs will be reported via CTV reconciliation process (a list of all AEs) on a quarterly basis.

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported

6.11.3.2k Disease progression

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on radiologic (CT and/or MRI) scans. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

6.11.4 Reporting Requirements for Adverse Events Originating from Patient Reported Outcomes

Although sites are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during site review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Adverse Event and Special Situation Reporting Form or MedWatch form.

6.11.5 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Study Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

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6.11.5.1 Follow-up information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (ie, DOB initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (the patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

6.11.5.2 Reporting to regulatory authorities, ethics committees and investigators

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations

Genentech will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM).

The IHTC will be responsible for the distribution of safety information to its own investigators, where relevant.

The IHTC will be responsible for the distribution of safety information to the IHTC IRB:

For questions related to safety reporting, please contact Genentech/Roche Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

6.11.6 Aggregate Reports

6.11.6.1 Development safety update report

The IHTC as the Sponsor of the study, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. The IHTC agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion.

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Genentech agrees to forward to the IHTC an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees that the IHTC may cross-reference the executive summary of the Genentech/Roche DSUR, as applicable.

6.11.6.2 Other reports

The IHTC will forward a copy of the Final Study Report to Genentech/Roche upon completion of the study. The IHTC will also forward a copy of any publications developed and accepted for publication to Genentech/Roche.

6.11.7 Study Close-out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Emicizumab IIS Clinical Operations

Email: emicizumab-gsur-d@gene.com

And to Genentech Drug Safety CTV oversight mail box at:

ctvist_drugsafety@gene.com

6.11.8 Queries

Queries related to the study will be answered by the IHTC. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to the Product. The IHTC agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

6.11.9 Safety Crisis Management

In case of a safety crisis, eg, where safety issues have a potential impact on the indication(s), on the conduct of the study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

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The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. The IHTC agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

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7 STUDY ACTIVITIES

7.1 Study Visit 1: Informed Consent and Screening

- Informed consent signature and date
- Determination of eligibility
- Demographics (date of birth, race, gender, height)
- Weight
- Vital signs (blood pressure, pulse, temperature, and respiratory rate)
- Medical history review, including
    - Documentation of current or past infection of Hepatitis A, B and C
        - HAV:Ab
        - HBV:Ag and Ab (Core and Surface); if HBV:Ag positive, HBV viral load
        - HCV:Ab; if HCV:Ab positive, HCV viral load
    - Documentation of HIV infection (if Ab positive, viral load and CD4 count)
    - Review of at least 16 weeks, and up to 6 months if available, of data on prior use of hemostatic therapy and number of breakthrough bleeding events
    - Review of 6 months of data on prior need for hospitalization or for PRBC transfusion
    - Review of therapy prior to study entry with dose and interval and trough level if available on prophylaxis
    - Review of history of inhibitor including date of first positive test, highest documented titer and date
    - Review of concomitant medications and supplements
    - Date of development or identification of pseudotumor and documentation of radiologic (CT or MRI) scans
    - Review of surgeries and procedures
- Physical examination
- Lab screening (if adequate results are not available in the subject's medical records):
    - FVIII[*]
    - aPTT
    - PT
    - VWF:Ag
    - FVIII inhibitor level (Bethesda assay)

[*] If the subject has an inhibitor, then testing for FVIII level may not be medically necessary as FVIII is usually undetectable in such cases. Exceptions exist, such as for a patient who has mild hemophilia with an inhibitor that only recognizes infused FVIII and not endogenous FVIII.

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  - CBC w/diff
  - CMP + direct bilirubin
  - Serum pregnancy test for female subjects
- Lab screening for hepatitis (if adequate results are not available in the subject's medical records):
  - HAV:Ab
  - HBV:Ag and Ab (Core and Surface); If HBV:Ag positive, HBV viral load
  - HCV:Ab; If HCV:Ab positive, HCV viral load
- Lab screening for HIV (if adequate results are not available in the subject's medical files):
  - HIV:Ab; if HIV:Ab positive then HIV viral load and CD4 count
- Vaccinations: If the subject is not vaccinated, previously exposed, or immune to HAV and/or HBV then they will receive the first dose of the HAV and/or HBV vaccine. Subjects must follow up with their local provider to complete the recommended vaccination schedule[*]
- Baseline Haem-A-QoL and EQ-5D-5L surveys
- Assessment of concomitant medication and supplements
- If an activity monitoring device is standardly utilized by the patient, then permission will be requested to access data for the 1-month period prior to study entry and use of data from the device if continued during the study
- Assessment of adverse events

7.2 Study Visit 2: Loading Doses

Study visit 2 will comprise 4 weeks during which the 4 loading doses of Hemlibra (emicizumab) will be administered. During study visit 2, baseline radiology (CT and/or MRI scan) will be acquired if they were not performed within 1 month of study entry and if they are not considered suitable for study purposes. The subject and/or caregiver will also be trained for self-infusion of Hemlibra (emicizumab) and trained to look for signs of adverse events.

Subjects/caregivers will be instructed on how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. The Study Investigator has the discretion to provide additional training or include additional observation (eg, after the fourth loading dose), if deemed appropriate, and each subject/caregiver will be able to ask any question he or she may have prior to being deemed capable of performing subcutaneous Hemlibra (emicizumab) injections. If, despite additional training, the investigator

[*] Vaccinations will not be charged to the study

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determines that the subject/caregiver is unable to inject Hemlibra (emicizumab), a trained and proficient caregiver or local healthcare provider should be identified to administer the injections.

Subjects will be observed for a minimum of 30 minutes after the first three loading doses of Hemlibra (emicizumab).

Following each of the first 3 loading doses of Hemlibra (emicizumab), the site will call a subject who has a previous history of a clinically significant hypersensitivity reaction 24 hours after each dose to assess the status of the subject.

Additional precautions following each of these doses may also be considered, including having an extended observation period or IV access prior to dosing, etc. The Study Investigator may include these or other precautions, as deemed appropriate.

A subject utilizing a prophylactic FVIII regimen, a prophylactic bypassing agent regimen or ITI therapy must discontinue those regimens according to the schedule below and for the duration of the study.

- Subjects receiving FVIII prophylaxis must discontinue their FVIII prophylactic regimen immediately prior to their second loading dose of Hemlibra (emicizumab)
- Subjects receiving bypassing agent prophylaxis must discontinue their prophylactic regimen at least 24 hours prior to their first loading dose of Hemlibra (emicizumab)
- Subjects who are receiving FVIII ITI therapy must discontinue ITI immediately prior to their first loading dose of Hemlibra (emicizumab)

During study visit 2, a suitable quantity (at the discretion of the Study Investigator) of Hemlibra (emicizumab) will be dispensed (see **Section 6.7**).

7.2.1 Day -1 Procedures

If the subject is on a bypassing agent prophylactic regimen, that regimen must be discontinued at least 24 hours prior to the administration of the first loading dose of Hemlibra (emicizumab). Bypassing agent prophylaxis must remain discontinued for the duration of the study.

7.2.2 Day 0 Procedures

7.2.2.1 Pre-treatment

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Confirmation of eligibility
    - Subject should not have received aPCC or rFVIIa within 24 hours prior to study drug administration
    - Subject should not have an active bleeding event

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    - Subject should not have any other temporary or permanent exclusionary event (at the discretion of the Study Investigator)
- Subjects who are receiving FVIII ITI therapy must discontinue ITI at this time and ITI must remain discontinued for the duration of the study
- Assessment of concomitant medication and supplements
- Assessment of adverse events
- Banked plasma sample [baseline antidrug antibody levels for Hemlibra (emicizumab)] for testing at the central laboratory
- Other diagnostic procedures as needed and ordered by the Study Investigator and recommended by the standard of care

7.2.2.2 Drug administration

- The loading dose for Hemlibra (emizicumab) is 3 mg/kg
- The vial(s) of Hemlibra (emicizumab) should be removed from the refrigerator and warmed to room temperature at least 15 minutes prior to administration
- Hemlibra (emicizumab) should be administered subcutaneously to the thigh, abdomen or upper arm

7.2.2.3 Following drug administration

- Observation at the IHTC for 30 minutes and assessment of adverse events
- For subjects with a history of hypersensitivity, the IHTC should follow up with the subject 24 hours after administration of Hemlibra (emicizumab) for assessment of adverse events

7.2.3 Day 7 Procedures

7.2.3.1 Pre-treatment

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Assessment of concomitant medication and supplements
- Assessment of adverse events
- Subjects who are receiving FVIII prophylaxis must discontinue their FVIII prophylactic regimen at this time and FVIII prophylaxis must remain discontinued for the duration of the study

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- Other diagnostic procedures as needed and ordered by the Study Investigator and recommended by the standard of care

7.2.3.2 Drug administration

- The loading dose for Hemlibra (emizicumab) is 3 mg/kg
- The vial(s) of Hemlibra (emicizumab) should be removed from the refrigerator and warmed to room temperature at least 15 minutes prior to administration
- Hemlibra (emicizumab) should be administered subcutaneously to the thigh, abdomen or upper arm at least 1-inch away from the previous site of administration

7.2.3.3 Following drug administration

- Observation at the IHTC for 30 minutes and assessment of adverse events
- For subjects with a history of hypersensitivity, the IHTC should follow up with the subject 24 hours after administration of Hemlibra (emicizumab) for assessment of adverse events

7.2.4 Day 14 Procedures

7.2.4.1 Pre-treatment

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Assessment of concomitant medication and supplements
- Assessment of adverse events
- Other diagnostic procedures as needed and ordered by the Study Investigator and recommended by the standard of care

7.2.4.2 Drug administration

- The loading dose for Hemlibra (emizicumab) is 3 mg/kg
- The vial(s) of Hemlibra (emicizumab) should be removed from the refrigerator and warmed to room temperature at least 15 minutes prior to administration
- Hemlibra (emicizumab) should be administered subcutaneously to the thigh, abdomen or upper arm at least 1-inch away from the previous site of administration

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7.2.4.3 Following drug administration

- Observation at the IHTC for 30 minutes and assessment of adverse events
- For subjects with a history of hypersensitivity, the IHTC should follow up with the subject 24 hours after administration of Hemlibra (emicizumab) for assessment of adverse events

7.2.5 Day 21 Procedures

7.2.5.1 Pre-treatment

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Assessment of concomitant medication and supplements
- Assessment of adverse events
- Other diagnostic procedures as needed and ordered by the Study Investigator and recommended by the standard of care

7.2.5.2 Drug administration

- The loading dose for Hemlibra (emizicumab) is 3 mg/kg
- The vial(s) of Hemlibra (emicizumab) should be removed from the refrigerator and warmed to room temperature at least 15 minutes prior to administration
- Hemlibra (emicizumab) should be administered subcutaneously to the thigh, abdomen or upper arm at least 1-inch away from the previous site of administration
- Assessment of adverse events

7.2.5.3 Following drug administration

- Assessment of adverse events
- Banked plasma sample [antidrug antibody levels for Hemlibra (emicizumab)] for testing at the central laboratory
- Obtain data from an activity monitoring device (for the period from informed consent to Day 21) if standardly utilized by the patient and prior consent has been provided

7.3 Prophylactic Administration of Hemlibra (emicizumab)

Prophylactic administration of Hemlibra (emicizumab) will continue on a weekly basis (1.5 mg/kg subcutaneous dosing, *or 3 mg/kg kg if dose escalation is determined appropriate by the*

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*Study Investigator [**Section 5.3.3**]*) until subject withdrawal or study termination, whichever occurs first. The weekly injections will be administered by the subject, a trained caregiver, or a local healthcare provider, depending on the needs of the subject. Each subject will receive Hemlibra (emicizumab) for a minimum of 2 years and a maximum of 4 years based upon time of enrollment.

The subject will record the following in the patient diary at the time of each Hemlibra (emicizumab) infusion

- Adverse event assessment
- Any concomitant medication or supplement
- Date, time and quantity of Hemlibra (emicizumab) infused

7.4. Subsequent Study Visits

Subsequent study visits will be scheduled once a quarter, as is the standard of care for patients with hemophilic pseudotumor. These study visits will take place at the medical facilities of the subject's local physician, except for the annual and study close-out visits, which will take place at the IHTC. The first subsequent study visit will be 3 months (±2 weeks) following the first loading dose of Hemlibra (emicizumab).

The specific requirements of each visit are listed below. Depending on when a subject enrolls and when the study ends, the subject might not participate in all study visits beyond month 24. See **Appendix 2**.

7.4.1 Study Visits at Months 3, 9, 15, 21, 27, 33, 39 and 45 (±2 Weeks)

The subject will follow-up with their local physician at the intervals specified above.

During this visit:

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Review of patient diary for completeness
- Patient study documentation will be submitted to the IHTC for review of compliance and data collection
- Review of AEs
- Review of concomitant medications and supplements
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

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7.4.2 Study Visits at Months 6, 18, 30 and 42 (±2 Weeks)

The subject will follow-up with their local physician for a more detailed clinical review at the intervals specified above.

During this visit the following data will be collected and/or reviewed and transmitted to the IHTC:

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- CBC panel w/diff
- Review of breakthrough bleeding events requiring alternate hemostatic therapy
- Review of the number of hospital admissions
- Review of the development of anemia requiring transfusion or intervention
- Review of AEs
- Review of concomitant medications and supplements
- Review of patient diary for completeness
- Patient study documentation will be submitted to the IHTC for review of compliance and data collection
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

7.4.3 Annual Study Visits (Months 12, 24 and 36 ±2 Weeks)

The annual study visit will take place at the IHTC.

During this visit the following data will be collected and/or reviewed at the IHTC:

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Radiologic evaluation (CT and/or MRI) to evaluate control of progression, stabilization or regression of pseudotumor
- Anti-drug antibodies (banked plasma sample)
- Repeated Haem-A-QoL and EQ-5D-5L
- CBC panel w/diff
- Review of breakthrough bleeding events requiring alternate hemostatic therapy
- Review of the number of hospital admissions
- Review of the development of anemia requiring transfusion or intervention
- Review of AEs
- Review of concomitant medications and supplements

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- Patient diary will be collected for review
- Patient study documentation will be collected for review of compliance and data collection
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

During this annual visit, a physical exam will be performed, used/empty vials of Hemlibra (emicizumab) will be collected, and a suitable quantity of Hemlibra (emicizumab) will be dispensed (see **Section 6.7**).

7.4.4 Unscheduled Study Visits

Any unscheduled study visits with the subject's local hemophilia physician will be recorded in the CRF along with all relevant medical information (eg, reason for visit, diagnoses, scans, AEs, lab results, vital signs [blood pressure, pulse, temperature, and respiratory rate], weight, etc).

If a subject meets with a physician other than their local hemophilia physician, that information should be communicated to their hemophilia physician at the next scheduled quarterly study visit and appropriate medical information recorded in the CRF.

Hospitalizations should be recorded in the CRF along with relevant medical information (see **Section 6.11.3.2d**). These should be reported to the IHTC within 7 days of their occurrence.

AEs should be reported using the instructions in **Section 6.11.3**.

7.4.5 Surgeries

All surgeries will be recorded in the CRF, which should minimally include the following information (see **Section 6.11.3** for additional reporting requirements):

- Procedure type
- Reason for procedure
- Planned or unplanned
- Date of procedure and length of hospitalization
- Hemostatic therapy provided pre-procedure (type, dose and dates)
- Hemostatic therapy provided post-procedure (type, dose and dates)
- Hemostatic outcome immediately post-procedure
- Hemostatic outcome at the end of hospitalization
- Adverse events experienced (including, but not limited to clots, thromboses and TMA)
- Vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight

Hemostatic outcome for surgical treatment is defined using the standard ISTH rating scale shown below [Blanchette, Key et al. 2014].

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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

Medical details and outcome of all surgeries should be reported to the IHTC within 7 days of their occurrence.

7.5 Study Close-out Visit

All subjects will participate in a study close-out visit at the IHTC within 2 months of the planned study termination date.

During this close-out visit the following data will be collected and/or reviewed at the IHTC (depending on when the most recent annual visit took place and at the Study Investigator's discretion, not all specified items may be necessary):

- Measurement of vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight
- Radiologic evaluation (CT and/or MRI) to evaluate control of progression, stabilization or regression of pseudotumor
- Anti-drug antibodies (banked plasma sample)
- Repeated Haem-A-QoL and EQ-5D-5L
- CBC panel w/diff

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- Review of breakthrough bleeding events requiring alternate hemostatic therapy
- Review of the number of hospital admissions
- Review of the development of anemia requiring transfusion or intervention
- Review of AEs
- Review of concomitant medications and supplements
- Review of patient diary
- Final Haem-A-QoL and EQ-5D-5L
- Patient study documentation will be collected for review of compliance and data collection
- Data will be obtained from an activity monitoring device if standardly utilized by the patient (if applicable)

Additionally, a physical exam will be performed and all used and unused vials of Hemlibra (emicizumab) will be returned to the IHTC.

Following the close-out visit, all subjects will be requested to meet with their local hemophilia physician to determine their ongoing treatment therapy/regimen.

7.6 End of Study/Early Termination Procedures

The subject has the right to withdraw consent and exclude him/herself from the study at any time. The Study Investigator has the right to involuntarily withdraw a subject from the study at any time for any reason (eg, lack of compliance, unwillingness to complete study visits, SAEs, etc). The study may also be terminated early by Genentech as detailed in **Section 10.11**.

If the study is not terminated early, then the study will end 4 years following the date on the informed consent form of the first subject.

At subject withdrawal or study end/termination:

- All unused vials of Hemlibra (emicizumab) will be returned to the IHTC
- All empty vials of Hemlibra (emicizumab) will be returned to the IHTC
- The patient diary, study medical files and any activity data covering the final partial quarter of the study will be transmitted to the IHTC

Following subject withdrawal, the subject will be requested to meet with their local hemophilia physician to determine their ongoing treatment therapy/regimen.

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8 QUALITY CONTROL AND ASSURANCE

This study will be sponsored by the IHTC. The IHTC research personnel undergo comprehensive clinical research training per Standard Operating Procedure (SOP) "Personnel Training, Competency and Qualifications" and comply with Food and Drug Administration (FDA), GCP and Institutional Review Board (IRB) regulations. All study staff will be CITI Trained

The Investigator will conduct the study in compliance with the protocol. Modifications to the protocol should not be made without agreement of the Investigator, the Sponsor, and Genentech. Changes to the protocol will require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The Sponsor will ensure the study is conducted in compliance with the protocol through various quality processes, including:

- Creating, implementing, and upholding SOPs for trial execution
- A quality scientific and medical design of the protocol
- Clinical investigator and site pre-assessment and selection
- Regulatory agency and ethics committee approval
- Developing and providing appropriate informed consent (language, transparency of benefits and risks) and obtaining IRB approval of the informed consent process
- Investigator meetings and training
- Adequate recording and reporting of data
- Periodic monitoring
- Audits

Regulatory authorities, the IRB, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, database, and any other applicable study documentation for an on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. All study sites may be audited by Genentech. Study sites will receive written notice in advance of any audit.

Additional standards and resources for Quality Assurance and Quality Control will be employed by the Sponsor during this study as appropriate.

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9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the sample size (n), mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages.

9.2 Determination of Sample Size

Sample size is based on clinical feasibility rather than statistical considerations, accounting for the likely possibility of very few bleeding events, the limited number of available subjects with hemophilia A and pseudotumor, and the need to collect sufficient data to assess safety and efficacy. Approximately 10 subjects will receive study medication (the Treated Population).

9.3 Analysis Populations

The Study population is defined as all subjects who provide informed consent. The Treated Population is defined as all subjects who receive study medication. All analyses of efficacy, quality of life and safety will be performed based on the Treated Population.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics for all subjects will be summarized using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

9.5 Primary Endpoints

The primary endpoints are:

- The number of breakthrough bleeding events over time requiring the use of alternate hemostatic therapy (bleed rate) related to the pseudotumor
- The number of hospital admissions related to the pseudotumor
- The number of incidences of anemia requiring transfusion or intervention related to the pseudotumor
- The control of progression, stabilization or regression of the pseudotumor (ie, changes in size) as measured by yearly assessments including CT and/or MRI

The study investigator will determine whether the reported event was related to the pseudotumor based on a retrospective review of the medical data (eg, bleed location, patient symptoms, etc).

Efficacy analyses will be performed based on the parameters listed above. As there is no control group or placebo in the study, the on-study data will be compared to that listed in the subject's

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medical files prior to study enrollment. The efficacy analyses will exclude data acquired during the 4 loading doses (study visit 2). Analyses will be performed on a per-subject basis and in aggregate. Sub-analyses will be considered based upon the included study population.

Demographic and baseline characteristics for all subjects will be summarized using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

9.6 Secondary Endpoints

The secondary endpoints are:

- The impact of weekly prophylaxis on quality of life and activity level
- Safety including development of AEs, SAEs, and ADA
- The number of infusions of alternate hemostatic therapy required (FVIII preparation, rFVIIa or aPCC) to treat a breakthrough bleeding event either unrelated or related to the pseudotumor
- The number of breakthrough bleeding events over time requiring the use of alternate hemostatic therapy (bleed rate) unrelated to the pseudotumor.
- The use of alternate hemostatic therapies (eg, FVIII, rFVIIa or aPCC) during surgeries and the hemostatic efficacy.

The study investigator will determine whether the reported event was related to the pseudotumor based on a retrospective review of the medical data (eg, bleed location, patient symptoms, etc).

Efficacy analyses will be performed based on the parameters listed above. As there is no control group or placebo in the study, the on-study data will be compared to that listed in the subject's medical files prior to study enrollment. The efficacy analyses will exclude data acquired during the 4 loading doses (study visit 2). Analyses will be performed on a per-subject basis and in aggregate. Sub-analyses will be considered based upon the included study population.

Changes in quality of life will be determined using the Haem-A-QoL and EQ-5D-5L assessments. The Haem-A-QoL scales range from 0 to 100, with lower scores reflecting better health-related quality of life. Clinically meaningful differences are 10 points for the score on the physical health subscale and 7 points for the total score. Scores on the EQ-5D-5L visual-analogue scale range from 0 to 100, and index utility scores range from -0.4 to 1.0; higher scores indicate better health status. Clinically meaningful differences are 7 and 0.07 points, respectively.

9.7 Safety Analyses

The number and percentage of subjects with any AEs, any serious AEs (SAEs), and any treatment related AEs/SAEs will be presented for all subjects. AEs will be summarized at the subject level by MedDRA system organ class (SOC) and preferred term (PT) using frequencies

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and percentages. AEs will also be tabulated at the event level by SOC, PT and severity and by SOC, PT and relationship to study treatment.

9.8 Interim Analysis

Interim analyses will be conducted yearly at the discretion of the study investigator if sufficient patients are enrolled. At a minimum, an interim analysis will occur at the mid-point of the study (2-years following the date of informed consent of the first study subject). This will include a detailed review of safety data. Depending on the number of subjects enrolled, an interim review of additional data may also be considered.

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10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Genentech may contract a CRO to perform specific study related tasks. The division of responsibilities will be documented in mutually agreed documents. Written procedures will be used to assure that the study is conducted according to all applicable rules and regulations.

The Study Investigator will ensure that this study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and any other local regulations and guidelines.

The Study Investigator will review all study related documents including the protocol and the current version of the Investigator's Brochure. It is obligatory that the Study Investigator be familiar with the protocol and all sections of the Investigator's Brochure prior to initiation of the study.

10.2 Institutional Review Board (IRB) Approval

A copy of the protocol, Investigator's Brochure, proposed Informed Consent Form and any other written subject information must be submitted to the IHTC IRB for written approval. A copy of the written IRB approval of the protocol and Informed Consent Form must be received by Genentech before recruitment of subjects into the study and shipment of investigational drug.

The Study Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The Study Investigator should notify the IRB of deviations from the protocol or SAEs/reportable safety events at the site or reports of such events received from Genentech in accordance with local procedures.

The Study Investigator will be responsible for obtaining annual IRB approval and renewal throughout the duration of the study.

The Study Investigator will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects and will not make any changes in the research without prior approval from Genentech and the IRB, except where necessary to eliminate immediate hazards to human subjects.

10.3 Ethical Conduct of the Study

This study will be conducted in compliance with Good Clinical Practice (GCP) as described in the International Conference on Harmonisation (ICH) document Guidance for Industry-E6 Good Clinical Practice: Consolidated Guidance dated April 1996. These practices are consistent with the principles stated in the Declaration of Helsinki (October 2000 revised version). All other applicable regulations will be adhered to.

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10.4 Clinical Trial Safety Portal (CTSP)

The Study Investigator is required to complete CTSP training to access the safety documents required for the study. It is the sponsor's responsibility to ensure that all safety documents are obtained from CTSP and submitted to the appropriate authorities such as your institution's IRB. The Sponsor will receive an email from ePharmaSolutions (ePS) with details of training sessions. This training should be completed as quickly as possible.

10.5 Subject Information and Consent

Written informed consent must be obtained for all subjects who are potential study candidates before any study-specific tests or procedures are performed. Subjects who meet general entry criteria will be asked to sign and date the study specific, IRB-approved Informed Consent form before any study-specific test or procedures are performed. The written informed consent should be obtained after the context of the study has been fully explained to the subject/legal guardian in a language that is easily understood by the subject/legal guardian. There must also be adequate opportunity to ask questions and have those questions answered to their satisfaction. Study personnel should explain that even if a subject agrees to participate in the study and signs an Informed Consent form, the study specific test or procedures may demonstrate that the subject is not a candidate for the study.

The written informed consent will be in English and will be administered according to national requirements. All subjects and/or caregivers must be proficient in English and able to read and understand the informed consent for participation in the study.

10.6 Subject Confidentiality

Subject participation is voluntary; subjects may refuse to participate or withdraw from the study at any time and for any reason. Subjects who participate in the study will be informed that information about them is being entered into a study database and their consent will be obtained and recorded. Subjects will be identified only by a subject number and date of birth. They will be informed as to the strict confidentiality of their subject data, and that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.

10.7 Study Monitoring

The IHTC is responsible for study monitoring which will be conducted periodically to ensure that all aspects of the current, approved protocol are being followed. The study monitor will be a non-study physician from the IHTC.

The study monitor should be given direct access to original source documents and the Case Report Form (CRF). For this study, source documents include but are not limited to the Informed Consent Form, subject's medical records, patient diaries, laboratory results, reports of AEs, and drug accountability logs.

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10.8 Case Report Forms and Study Records

Subject data will be collected electronically and/or on paper. The Study Investigator must ensure the accuracy and completeness of the recorded data and provide his/her signature on the appropriate CRFs and/or in the electronic system. The Study Investigator's signature for specific CRFs will be documented in compliance with ICH/GCP guidelines. Visual and/or computer data review will be performed to identify possible data discrepancies. Data cleaning will be performed on all data in the CRF. Queries will be created in the data management system and will be issued for appropriate response.

10.9 Data Monitoring

The IHTC is responsible for the oversight of subject safety.

Safety data collection will commence when each individual subject signs and dates the informed consent form and initiates study procedures and will continue until the study ends or the subject withdraws from the study, whichever occurs first. All SAEs will be reported to and reviewed by the Study Investigator. One non-study physician from the study site will review all SAEs, deaths or other unexpected events and report to the Study Investigator with recommendations. If a patient dies on study, the case will be evaluated in detail to determine its relatedness to the study drug and to determine if the study warrants stopping in the opinion of the Study Investigator.

Any drug-related SAE (SADR) will be reported through Genentech's reporting system, as will all AEs stipulated in **Section 6.11.3.2j**. The study site will maintain a record of all SAE reports, interpretations and recommendations which will be available for Genentech to review upon request. In addition, if a greater than expected number of breakthrough bleeding events, or the development of thrombosis or thrombotic microangiopathy (TMA) outside of the established associations occurs, treatment of the subject with Hemlibra (emicizumab) may be halted. If an anaphylactic reaction to Hemlibra (emicizumab) occurs, then treatment of that patient may be halted. The Study Investigator may withdraw a patient based upon their clinical discretion and patient safety.

During the course of the trial, the IHTC will review safety data at least at the following time points:

- On the occasion of every SAE, death or other unexpected event. The event will be assessed by a non-study physician from the IHTC who will report their findings to the Study Investigator. Any drug-related SAE (SADR) will also be reported through Genentech's reporting system
- Every 3 months on a subject-by-subject basis by a non-study physician from the IHTC
- Comprehensively by a non-study physician from the IHTC during every interim analysis (minimally at the 2-year midpoint of the study).

A non-study physician from the study site and the Study Investigator will make recommendations, if necessary, for study modification or termination because of concerns over

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subject safety or issues relating to data monitoring or quality control. This will be submitted in writing to Genentech for consideration and final decision. However, if the Study Investigator at any time determines that a potential serious risk exists to subjects in the trial, the Study Investigator will immediately notify Genentech.

10.10 Protocol Violations/Deviations

Deviations from clinical protocol requirements will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective actions put into place.

10.11 Criteria for Terminating Study

Genentech reserves the right to terminate the study but only intends to exercise this right for valid scientific or administrative reasons and reasons related to subject safety and protection. Investigators and the associated IRB will be notified in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Genentech to suspend or discontinue development of the investigational product

10.12 Access to Source Documentation

The non-study IHTC physician monitoring the study will check the CRF form entries against the original source documents. The consent form will include a statement by which the subjects allow the non-study physician access to source data (eg, original laboratory reports, etc) which substantiate information in the CRF. These personnel, bound by professional confidentiality, will not disclose any personal information.

10.13 Data Generation and Analysis

See the Statistical section of this protocol (Section 9).

10.14 Retention of Data

The IHTC should maintain the trial documents as specified in ICH E6 Good Clinical Practice Consolidated Guidance and as required by the applicable regulatory requirement(s). The Study Investigator and the IHTC should take measures to prevent accidental or premature destruction of these documents. If for any reason the Study Investigator withdraws responsibility for maintaining the trial documents, custody must be transferred to an individual who will assume responsibility. Genentech must receive written notification of this custodial change.

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Essential documents should be retained for as long as necessary to meet applicable regulatory requirements or as required by agreement with Genentech.

10.15 Financial Disclosure

All rules and regulations on the documentation and disclosure of any potential financial conflicts will be adhered to.

10.16 Publication and Disclosure Policy

The study will be listed in the public database on clinical studies *www.clinicaltrials.gov*. A summary report of the study will be made available after the conclusion of the study. It is the intention of the IHTC to publish the results of this study in a peer reviewed journal.

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11 APPENDIX 1: Safety Reporting FAX Cover Sheet

Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	Amy D. Shapiro, MD
Site Name	The Indiana Hemophilia & Thrombosis Center
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

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12 APPENDIX 2: Schedule of Study Visits (per Subject)

Evaluation	**Study Visit 1**		**Study Visit 2***						
	Day -10	Day -1†	Day 0			Day 7			
Visit Window:	*n/a*	*n/a*	*n/a*			*±2 days*			*±2 we*
	Screening		Pretreatment	Treatment	Post-treatment	Pretreatment	Treatment	Post-treatment	
Informed consent	X								
I/E criteria	X								
Demographics	X								
Medical history review	X								
Vital signs	X		X			X			
Weight	X		X			X			
Physical examination	X								
Haem-A-QoL & EQ-5D-5L	X								
Clinical lab tests (6.6.1)	X								
Concomitant medications	X		X			X			
AE assessment	X		X	X	X	X	X	X	
Eligibility	X		X						
ADA Hemlibra (emicizumab)			X						
Drug administration (loading dose)				X			X		
Cease BPA prophylaxis		X							
Cease ITI			X						
Cease FVIII prophylaxis						X			
Activity monitoring device (data acquisition)	X								

* An adequate quantity of Hemlibra (emicizumab) will be dispensed during study visit 2 for the loading and maintenance doses. The quantity will be at the discretion of the Study Investigator and will depend on the storage capacity at the subject's home
† A minimum of 24 hours prior to first loading dose of Hemlibra (emicizumab)

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Evaluation *Visit Window:*	**Study Visit 2***					
	Day 14			Day 21		
	±2 days			*±2 days*		
	Pretreatment	Treatment	Post-treatment	Pretreatment	Treatment	Post-treatment
Informed consent						
I/E criteria						
Demographics						
Medical history review						
Vital signs	X			X		
Weight	X			X		
Physical examination						
Haem-A-QoL & EQ-5D-5L						
Clinical lab tests (6.6.1)						
Concomitant medications	X			X		
AE assessment	X	X	X	X	X	X
Eligibility						
ADA Hemlibra (emicizumab)						X
Drug administration (loading dose)		X			X	
Activity monitoring device (data acquisition)						X

* An adequate quantity of Hemlibra (emicizumab) will be dispensed during study visit 2 for the loading and maintenance doses. The quantity will be at the discretion of the Study Investigator and will depend on the storage capacity at the subject's home

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	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Visit Window:	*±2 weeks*	*±2 weeks*	*±2 weeks*	*±2 weeks*	*±2 weeks*	*±2 weeks*	*±2 weeks*	*±2 weeks*
Visit @ local provider	X	X	X		X	X	X	
Visit @ IHTC				X				X
Activity monitoring device (data acquisition)	X	X	X	X	X	X	X	X
Subject study documentation (transfer to IHTC)	X	X	X	X	X	X	X	X
CBC panel w/diff		X		X		X		X
Review of breakthrough BEs		X		X		X		X
Review of hospitalizations		X		X		X		X
Review of incidences of anemia		X		X		X		X
Haem-A-QoL & EQ-5D-5L				X				X
CT and/or MRI				X				X
ADA Hemlibra (emicizumab)				X				X
Hemlibra (emicizumab) dispensation*				X				X
Concomitant medications	X	X	X	X	X	X	X	X
Review of AEs	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Physical examination				X				X
Review of patient diary	X	X	X	X	X	X	X	X
Collection of used/empty vials				X				X

* Hemlibra (emicizumab) will be dispensed and shipped to the subject at various times of the year to ensure the subject has a continuous supply

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	Month 27*	Month 30*	Month 33*	Month 36*	Month 39*	Month 42*	Month 45*
Visit Window:	*±2 weeks*	*±2 weeks*	*±2 weeks*	*±2 weeks*	*±2 weeks*	*±2 weeks*	*±2 weeks*
Visit @ local provider	X	X	X		X	X	X
Visit @ IHTC				X			
Activity monitoring device (data acquisition)	X	X	X	X	X	X	X
Subject study documentation (transfer to IHTC)	X	X	X	X	X	X	X
CBC panel w/diff		X		X		X	
Review of breakthrough BEs		X		X		X	
Review of hospitalizations		X		X		X	
Review of incidences of anemia		X		X		X	
Haem-A-QoL & EQ-5D-5L				X			
CT and/or MRI				X			
ADA Hemlibra (emicizumab)				X			
Hemlibra (emicizumab) dispensation†				X			
Concomitant medications	X	X	X	X	X	X	X
Review of AEs	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Physical examination				X			
Review of patient diary	X	X	X	X	X	X	X
Collection of used/empty vials				X			

* Depending on when a subject enrolls and when the study ends, the subject might not participate in all study visits beyond month 24. Although the study is 48 months, a month 48 visit is not specified in the protocol as the study close-out visit will occur at approximately the same time and will comprise largely the same labs and procedures

† Hemlibra (emicizumab) will be dispensed and shipped to the subject at various times of the year to ensure the subject has a continuous supply

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	Study close-out visit*
Visit @ local provider†	
Visit @ IHTC	X
Activity monitoring device (data acquisition)	X
Subject study documentation (transfer to IHTC)	X
CBC panel w/diff	X
Review of breakthrough BEs	X
Review of hospitalizations	X
Review of incidences of anemia	X
Haem-A-QoL & EQ-5D-5L	X
CT and/or MRI	X
ADA Hemlibra (emicizumab)	X
Hemlibra (emicizumab) collection‡	X
Concomitant medications	X
Review of AEs	X
Vital signs	X
Weight	X
Physical examination	X
Review of patient diary	X

* Depending on the date of the most recent annual visit, the Study Investigator may decide that not all specified items are necessary at the close-out visit
† Following the close-out visit, the subject will be requested to meet with their local hemophilia physician to determine ongoing care
‡ Unused vials and empty vials of Hemlibra (emicizumab) will be returned to the IHTC

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