<INSERT LOCAL LETTERHEAD>

CONSENT FOR AN ADULT TO ACT AS SUBJECT IN A RESEARCH STUDY
(Subjects ≥ 18 years old)

Protocol Title: The Phase III Multicenter, Randomized Controlled Inhibitor Eradication Trial comparing *Eloctate* Immune Tolerance Induction (ITI) plus *Emicizumab* vs. *Eloctate* ITI alone to Eradicate Inhibitor Formation in Severe Hemophilia A.

PRINCIPAL INVESTIGATOR: <INSERT LOCAL PI>

CO-INVESTIGATORS: <INSERT LOCAL CO-INVESTIGATORS>

SOURCE OF SUPPORT: HRSA, Health Resources Services Administration

Consent Version: v3.1 14 Oct 2021

Key Information: You are being asked to take part in a research study. Your participation is voluntary. The study team members will explain the study to you and answer any questions you may have. You should take time to make your decision.

- **Purpose of Research:** The purpose of this research is to eradicate (destroy) inhibitor formation in severe hemophilia A patients: two FDA-approved drugs will be compared.
- **Randomization:** There is an equal chance of *Eloctate* ITI (immune tolerance induction or eradication) with *Emicizumab* or *Eloctate* ITI alone like the flip of a coin.
- **Specimen Collection:** Blood draws will be collected at 6 time points: baseline, 4, 12, 24, 36, and 48 weeks; samples will be frozen and stored indefinitely. A stool sample will be collected at baseline.
- **Collection of Medical Record Information and Subject Diary:** Data collected will include age, date of birth, race, hemophilia diagnosis, bleeding history, and medication used for bleeds. The subject diary will record the date and time of bleeds, and the medication used for bleeds and other medications, including date, time, and amount.
- **Risks of Study:** The likely risks associated with this study include lightheadedness, bruising or bleeding from a blood draw, risk of minor pain, bleeding, or bruising following drug administration, allergic reaction to a study drug(s), risk of inhibitor formation, risk of blood clots, and the risk of breach of confidentiality of your health information.
- **Benefit of Study:** Currently there are no agents to eradicate inhibitors. You could benefit if any of the drugs eradicate inhibitors in severe hemophilia A.
- **Alternate Procedures:** If you decide not to participate, other choices include getting care and treatment without being in a study.

Why is this research being done?
You are being asked to participate in this research study to eradicate inhibitors (antibodies to infused factor VIII) in severe hemophilia A. Hemophilia A is an inherited (genetic) disease in which a protein (factor VIII, FVIII) that promotes blood clotting is missing or does not work properly. Individuals with severe hemophilia A have less than 1% of the normal clotting FVIII. As you are already aware, patients with severe hemophilia A have spontaneous bleeding (without trauma). Current treatment is by infusing FVIII into a vein. To prevent spontaneous bleeding in patients with severe hemophilia A, doctors recommend regularly scheduled doses of FVIII called "prophylaxis." Up to 30% of patients who receive factor VIII, may develop an "inhibitor." Inhibitors are proteins antibodies made by the immune system to fight against foreign (not made in the body) proteins, but in this case the infused factor VIII. Because inhibitors prevent clotting factor VIII from working properly, bypass therapy (that is VIIa or activated IX (aPCC) is required, but it controls bleeds poorly. As a result, they have more hospitalizations and complications than patients without inhibitors. At this time, it is not known how to *eradicate* inhibitors. *Thus, a major goal of hemophilia treatment is to eradicate inhibitors.*

Two FDA-approved drugs will be studied in this trial. These include 1) **Eloctate (rFVIIIFc)** or recombinant factor VIII Fc fusion protein, and 2) **Emicizumab (Hemlibra),** the bispecific monoclonal antibody that is a FVIII mimic. *Eloctate* increases the half-life (duration) of FVIII in the circulation, and, in small studies, may reduce the rate of inhibitor formation and shorten ITI in inhibitor patients, even those refractory to ITI. *Eloctate* is safe and effective in preventing bleeds in adults, adolescents, and children with hemophilia A. *Emicizumab* substitutes for missing or inhibited FVIII, and in clinical trials has been safe and effective in preventing bleeds in adults, adolescents, and children with severe hemophilia A with and without inhibitors.

This **Inhibitor Eradication Trial** is a 48-week phase III trial in children or adults with severe hemophilia A and inhibitors. We will compare *Eloctate* ITI with or without *Emicizumab* in the eradication of inhibitors. Children and adults with inhibitors who are refractory or were never tolerized are eligible, and also children who developed an inhibitor during the linked Prevention Trial. This Eradication Trial is expected to last a total of up to 7 years, or up to 48-weeks per subject. The <INSERT LOCAL SITE> is one of up to 41+ sites in the U.S. where this study will be conducted.

Who is being asked to take part in this research study?
Children or adults with severe hemophilia A and an inhibitor, anti-FVIII $\geq$ 5.0 B.U., who either are refractory to or were never tolerized (ITI) or who developed an inhibitor during the Prevention Trial and who are cared for at the <INSERT LOCAL SITE> will be recruited for this study. The total enrollment for this study will be up to 90 subjects including 2-4 subjects from this site.

What procedures will be performed for research purposes?
This is a 48-week outpatient study with approximately 13 study visits which include screening, follow-up, and end of study visits. The study involves two drugs; one is given IV (intravenously – injection directly into the vein) and one given SQ (subcutaneously – injection under the skin).

If you agree to participate in this study, you will be screened for eligibility. Should you be eligible, you would be randomized into one of two treatment types. Blood draws will be performed at 6 time points: baseline, 4, 12, 24, 36, and 48 weeks. Follow-up visits will be conducted throughout the duration of the study between screening and the end of study visit.

SCREENING VISIT

Study Visit 1: *Screening*
If you agree to participate in this study and have signed the informed consent, the study staff will complete the following tests and procedures during the screening period to determine if you can participate in the study. The screening procedures (listed below) will be completed within 24 hours of enrollment.

- Study staff will collect age, date of birth, race, and hemophilia genotype.
- Study staff will ask about your medical history, height, weight, past factor treatment, dose and frequency, circumcision and bleeding.
- Hemophilia history and previous exposure to FVIII.
- Medication history including medications within 4 weeks of starting the study drug(s).
- Brief physical exam including vital signs, height (cm) and weight (kg).
- Blood draw: You will have ¾ tsp sample for FVIII, inhibitor, immunity, genotype, trough FVIII activity, and a sample will be stored for future studies in hemophilia.
- A stool sample will be collected at baseline (may be collected at home and mailed back into the Hemophilia Center of Western Pennsylvania {Coordinating Center}) to assess genes and bacteria in the gut (microbiome).

Enrollment
If you are currently receiving *Emicizumab*, you will be asked to discontinue the drug prior to randomization. No washout period is required. If you are unwilling to discontinue *Emicizumab* prior to randomization, you will no longer be eligible to participate in the study.

After the doctor determines you are eligible, you will begin the study drug(s). Screening may occur on the same day, or this may be on a second visit, if necessary, to collect your information or records. You will receive the study drug to which you are assigned and take it *preferably* between 7 am and 9 am on the assigned schedule for 48 weeks.

If you are eligible, you will receive *Eloctate ITI* at 100 IU/kg every other day plus *Emicizumab* 1.5/ mg/kg (after a 4-week induction at 3 mg/kg/week); or *Eloctate ITI* at 100 IU/kg alone every other day during the 48-week study. Which drug you receive is determined by randomization, like a roll of dice. Subjects will use their own supply of *Eloctate* and/or *Emicizumab*. The dose used in this study is similar to the dose used in standard care.

- Eloctate will be given by IV (intravenously into a vein) by an infusion needle (butterfly) or by central line, if required. Emicizumab will be given by SQ (subcutaneous, under the skin) injection. It is anticipated that study drug(s) will be administered by the nurse at the Hemophilia Center. If you have learned infusion or injection techniques, you may give

the study drug(s) at home. If you have bleeds, your physician will discuss if dose frequency should be increased or if a central line is needed, which is anticipated in less than 1% of participants, but this will not change where the study drug(s) is/are given.

- All doses of study drug(s) will be given either by venipuncture, using a butterfly or central line, if required, or by subcutaneous injection. The study drug(s) will be given over about 5-10 minutes.
- You will record all doses of study drug(s) that you take, including day, date, time, dose in a patient diary which will be given to you by the study nurse. You will bring this back at all study visits to review with the study nurse.

The nurse will discuss the study visits with you. The entire visit will last about 1 hour.

In the event of a new bleed, *bypass therapy* (rFVIIa) may be given at the discretion of the hemophilia physician caring for you, similar to what is done in standard care. Activated factor IX (aPCCs) will not be allowed in this trial, as it may cause complications when used with *Emicizumab*. (Note, at most hemophilia centers, the treating physician will be the study physician.) The trough factor VIII levels obtained during study will be for information only and not the basis for dose change. Only *Eloctate* and/or *Emicizumab* may be used during the study, and only *rFVIIa* may be used for breakthrough bleeds, as directed by your physician. It is expected that the response of bleeds to *rFVIIa* will be the same as when this drug is used in clinical practice.

If a bleeding episode occurs during study, your physician will decide with you the best dose and frequency to treat that bleed. During the study, you should only use the study drug(s) to which you are assigned unless the inhibitor resolves (see below). You will be asked to record all your bleeds and all study drug(s) use in a Subject Diary. You will be responsible for assuring you have study drug(s) to allow for the prescribed dosing frequency, per the treating hemophilia physician at all times. Bleeding which occurs during the study will be managed as described above: if an inhibitor is present, rFVIIa will be given for bleeds, but if the inhibitor has resolved, *Eloctate* will be given for bleeds, as determined by your physician. The Study nurse will work with you and review this information during this visit and throughout the study.

If the inhibitor resolves, it will be confirmed by a repeat blood test within 4 weeks. If the two tests confirm the inhibitor is no longer detected, then your physician will decide with you the best treatment. Additional testing for factor peak and half-life, just as routinely done in ITI, may be drawn to determine when full tolerization has occurred and when it is safe to switch medications. Even if you stop the study drug(s), you will remain on study for collection of information and follow up until the end of the study (48 weeks). If you have no bleeding, then there will be no change in treatment until the second blood test confirms absence of the inhibitor: at that time the treating physician will decide with you the best treatment approach. If an inhibitor resolves and bleeding occurs not responding to study drug, even before the inhibitor is confirmed, you may stop study drug and receive treatment at the discretion of your physician but will continue to be followed on study until week 48. At no time will activated FIX (aPCCs) be allowed on this trial because of potential thrombosis (see above). The entire study schedule and procedures are outlined and in the Appendix of this consent form.

FOLLOW-UP VISITS:
At follow-up visits, you will review your supply of study drug(s) with the hemophilia center nurse who will assist you in ordering additional doses to assure you have enough for the study (or more, if prescribed by your physician) until the next visit. You will need to record all your bleeds and medication on the Subject Diary. For subjects who already have a supply of *Eloctate* and/or *Emicizumab*, the first dose may be given on the day of screening. For all other subjects, the first dose may be given as soon as the prescription is filled. Follow up visits will be monthly at <INSERT LOCAL SITE> at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 weeks.

Study Visit 2: Week 4, Follow-up Visit

- Your diary will be reviewed for frequency, type and site of bleeds, and for date, time, and dose of study drug(s).
- Study drug use will be reviewed and more ordered as needed.
- All medications will be recorded and reviewed.
- Assessment for adverse events (complications) will be completed.
- Vital signs and weight (kg) will be obtained.
- A ¾ tsp blood sample will be drawn for FVIII, inhibitor, immune studies, and a sample will be stored storage for future studies. All samples must be drawn prior to the study drug(s) dose.

Study Visits 3, 5, 6, 8, 9, 11, 12: Monthly Follow-up Visits (Can be done remotely or in person)

- Your diary will be reviewed for frequency, type and site of bleeds, and for date, time, and dose of study drug(s).
- Study drug use will be reviewed and more ordered as needed.
- All medications will be recorded and reviewed.
- Assessment for adverse events (complications) will be completed.

Study Visit 4, 7, 10: Quarterly Follow-up Visit

- Your diary will be reviewed for frequency, type and site of bleeds, and for date, time, and dose of study drug(s).
- Study drug use will be reviewed and more ordered as needed.
- All medications will be recorded and reviewed.
- Assessment for adverse events (complications) will be completed.
- Vital signs and weight (kg) will be obtained.
- A ¾ tsp blood sample will be drawn for FVIII, inhibitor, immune studies, and a sample will be stored storage for future studies. All samples must be drawn prior to the study drug(s) dose.

END-OF-STUDY VISIT:

Study Visit 13: Week 48, End-of-Study Visit

- Your diary will be reviewed for frequency, type and site of bleeds, and for date, time, and dose of study drug(s).

- All medications will be recorded and reviewed.
- Assessment for adverse events (complications) will be completed.
- Vital signs and weight (kg) will be obtained.
- A ¾ tsp blood sample will be drawn for FVIII, inhibitor, immune studies, and a sample will be stored storage for future studies. All samples must be drawn prior to the study drug(s) dose.

The total blood volume for all tests is 4½ tsp during the 48-week study. The blood samples will be de-identified and sent to the Hemostasis Laboratory, Puget Sound Blood Center, Seattle WA, and to the Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD.

What are the possible risks, side effects, and discomforts of this research study?
As with any study drug(s), there may be side effects that are currently unknown, and it is possible these could be permanent, serious, or life threatening. This study involves FDA-approved study drug(s) *Eloctate* or *Emicizumab*. Each drug has been shown safe and effective in adults and children and are used as part of standard care. It is not known whether the study drug(s) will eradicate inhibitor formation in individuals with severe hemophilia A.

You should talk to the study doctor or your regular doctor about these risks. Every effort will be made to reduce these risks. There are risks associated with receiving the study drug(s) and having blood drawn. You will be asked to report any safety problems or side effects associated with administration of study drug(s), whether given at <INSERT LOCAL SITE>, infusion center, or at home.

Discontinuing Emicizumab Prior to Randomization
There are no known risks associated with discontinuing *Emicizumab*. It is possible that your bleed frequency could increase if prophylaxis (eg. factor VIIa) is not given or infrequently given due to the more difficult intravenous route than *Emicizumab*. If a bleed occurs, factor VIIa will be given until it resolves and monitored by your treatment records and physician.

Emicizumab
Common risks include injection site reactions, headache, and arthralgia (joint pain).

Eloctate
Common risks include chest pain, feeling cold, feeling hot, dizziness, dysgeusia (altered taste), headache, joint swelling, myalgia (muscle pain), abdominal pain – lower and upper, angiopathy (vascular pain after injection of study drug), hypertension, bradycardia (slowed heart rate), procedural hypotension, cough, and rash.

Inhibitor Development
Inhibitor development occurs in 28-30% of individuals with severe hemophilia A (factor VIII deficiency). Among those who develop inhibitors 95% or more occur within 50 exposure days, usually in childhood after 10-20 exposure days, by the age of 2. Currently there is no known way to prevent inhibitor formation. You will be followed closely to monitor this risk, and samples to detect inhibitors will be taken at several time points in the study to monitor for this possibility.

Should an inhibitor occur, treatment with factor VIIa (rFVIIa) will be determined at the discretion of your physician.

Allergic or Anaphylactic Reaction
Allergic type reactions including anaphylaxis have only rarely, <0.001%, or less than 1 per 100,000 people, been reported for factor VIII and other hemostatic drugs. Symptoms could include hives, rash, swelling, chest tightness, shortness of breath, wheezing, faintness, low blood pressure, rapid heartbeat, and anaphylaxis (a life-threatening condition). If this occurs, the infusion should be stopped, and you should contact us immediately. If your symptoms are severe, call 911. You should receive immediate treatment. Should these symptoms occur, Benadryl, a medication which reduces inflammation, or an epi-pen, which improves vessel tone and lung function, may be given, with close monitoring of symptoms. Benadryl may cause drowsiness, dizziness or low blood pressure; an epi-pen may cause rapid heart rate, sweating, nausea, or anxiety. You will be monitored for these symptoms after receiving this drug. No one with a history of allergy to FVIII will be enrolled in these trials.

Thromboembolism/Thrombogenicity
Historically factor VIII products and other hemostatic agents are rarely, if ever, associated with the development of thromboembolic complications (blood clots). None have been detected in any of the studies of *Emicizumab*, or *Eloctate*, in adults or children, except rarely when activated factor IX (aPCCs) are taken with Emicizumab, < 0.01% or less than 1 per 100 people. For that reason, aPCCs will not be allowed on this trial. There is the unlikely possibility, < 0.001%, or less than 1 per 100,000 people, that these drugs (in the absence of aPCCs) could cause a clot, swelling, or inflammation in a vein. This risk will be very carefully monitored clinically. Should these symptoms occur in you, you should contact us immediately, or if the symptoms are severe, measures considered standard of care, including stopping the study treatment and/or removing the line in which it was given, if that is the source of the clot, should be done as soon as possible.

Bleeding Events
Because you have hemophilia, there is an additional risk of bleeding at the infusion site. Contact us if this occurs and seek medical attention. In the event that bleeding at the infusion site cannot be stopped with pressure, it may be necessary to use a stitch or an adhesive material to stop the bleeding. The devices used to administer the stitch or adhesive may cause the following negative side effects: bleeding, a build-up of blood known as a hematoma, infection, allergic reaction, nerve injury, and swelling.

Venipuncture
There may be discomfort with drawing your blood, which is common, occurring in up to 25%, or 25 in 100 people: this may include pain, lightheadedness, fainting, bruising, or bleeding or infection in the tissue around the vein. This may be alleviated or reduced by applying pressure to the blood draw site for 5 minutes and having you lie on your back. The risk of repeated blood draws is anemia, or a low blood count, but this will be carefully monitored. Injections may rarely, in less than 1%, or less than 1 in 100 people, cause pain, soreness, redness, warmth, itching, numbness, tenderness, swelling, skin changes (discoloration, breakdown, or thickening), or swelling or lymph nodes near the injection site.

IV Placement
There may be discomfort during IV placement. Insertion of an IV line is typically a minimal risk procedure. However, taking blood or putting and intravenous catheter in people with hemophilia may increase chance of pain, bleeding or bruising at the spot where the needle enters your body, lightheadedness or fainting, swelling and redness at needle site, infection, or inflammation of vein. Emla cream (a skin-numbing medicine) may be used to minimize this discomfort.

Subcutaneous Injection
Subjects could develop a reaction at the site of the injection, which could include pain, tenderness, redness, swelling, itching, sores, skin color changes, or other reactions around the injection site.

Central Line Placement
In young children, difficulty obtaining venous access due to small veins may require the placement of a central line. The insertion of a central line may reduce the discomfort of needle sticks and will be suggested at the discretion of the treating physician. Placement of central lines may cause bleeding, and thus additional factor treatment may be necessary. There is also the risk of anesthesia required for the line placement procedure. In addition, central lines may be complicated by infections that require hospitalization, antibiotics, and/or removal and replacement of the line. The insertion of a central line is part of clinical care and not required for this study. Placement of a central line could lead to an infection or pneumothorax (collapsed lung).

Stool Collection
There are no known risks of stool sample collection

Collection of Medical Information and Subject Diary
Study participation and related data will be protected to maintain confidentiality. There is a possibility that your personal information could become generally known. In order to reduce risks of disclosure or breach of confidentiality, the research related documents, blood samples and clinical information stored in your research files will be assigned an alphanumeric (letters and numbers) identifier (that do not contain personal identifiers). A linkage key for linking this number and your name will be kept at <INSERT LOCAL SITE> under lock and key by the research staff. Any publication arising from this study will not contain names or other identification unless you give permission in another signed consent.

Future Genetic Testing of Stored Samples
There is the possibility that if the results of the research studies involving your genetic material were to become generally known, this information could affect your ability to be insured, employed, or influence plans for children or have a negative impact on family relationships, and/or result in paternity suits or stigmatization. . Your biological sample or genetic material may lead, in the future to new inventions or products. If the research investigators are able to develop new products form the use of your biological sample or genetic material, there are currently no plans to share with you any money or other rewards that may result from the

development of the new product. Since the genetic testing for this study is done by a research laboratory, results from this study laboratory cannot be released.

In addition, there is a Federal law, called the Genetic Information Nondiscrimination Act (GINA), that generally makes it illegal for health insurance companies and group health plans to use genetic information in making decisions regarding your eligibility or premiums. GINA also makes it illegal for employers with 15 or more employees to use your genetic information when making decisions regarding hiring, promoting, firing, or setting the terms of employment. This new Federal law does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

Your research data/samples may be shared with investigators conducting other research; this information will be shared without identifiable information. These research data/samples may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

The data, samples, and genetic data generated from samples may be shared with other researchers and with federal repositories, in a de-identified manner without additional informed consent.

What are possible benefits from taking part in this study?
Currently there are no agents to eradicate inhibitors. You could benefit if the study finds that any of the study drug(s) will eradicate inhibitors in severe hemophilia A subjects. This could improve quality of life and decrease or prevent costs associated with inhibitor development or eradication. However, it is important to note that you may not receive direct benefit from taking part in this research study and the only benefit may be that information obtained from your participation may help others in the future.

Will I receive any results from taking part in this study?
The results of inhibitor testing will be provided to you during the study.

What treatments or procedures are available if I should not take part in this research study?
There are no known cures for those with hemophilia and inhibitors. Other alternative factor treatments (e.g. rFVIIa for inhibitors) are available to you to treat or prevent bleeds.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?

Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study (i.e., the Screening Procedures, Monitoring, and End of Study visits described above). Neither the study nor the sponsor of the study will provide the *Eloctate* or *Emicizumab* as you will be using your own supply of drug. Should your clinical physician recommend central line placement, the costs will not be covered by this research study.

Will I be paid if I take part in this research study?
<INSERT LOCAL COMPENSATION>
Who will pay if I am injured as a result of taking part in this study?
<INSERT LOCAL COMPENSATION FOR INJURY LANGUAGE>

Who will know about my participation in this research study?
Any information about your obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. De-identified information will also be stored in a secure database. The web-based data base is located at the Data Coordinating Center, Graduate School of Public Health, University of Pittsburgh. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

In addition to the investigators listed and their research staff, the following individuals may have access to your information related to your participation in this research study:

- Authorized representatives of the study sponsor, federal regulatory agencies, Data Safety and Monitoring Board (DSMB) and the University of Pittsburgh Office of Research Protections may review your identifiable research information for purposes of monitoring the conduct of this research study.
- Information collected from this study may be shared with federal repositories and/or other investigators; however, this information will be shared in a de-identified manner (i.e., without identifiers).
- De-identified blood samples in this study will be sent to the Hemostasis Laboratory, Puget Sound Blood Center, Seattle WA, and to the Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD.
- If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by <INSERT LOCAL STATE> law, the appropriate agencies.
- <INSERT ANY LOCAL ENTITIES>

<INSERT LOCAL DATA RETENTION PERIOD LANGUAGE>

HIPAA Authorization for Disclosure of Protected Health Information (PHI)
<INSERT LOCAL HIPAA AUTHORIZATION LANGUAGE OR USE THE FOLLOWING>
As part of this research study, we are requesting your authorization or permission to review your medical records to determine eligibility criteria for this study and any adverse events associated

with testing. This information will be used for the purpose of determining the effectiveness and safety of the study drug(s) in individuals with hemophilia A. This authorization is valid for an indefinite period of time. We will obtain the following information: your diagnosis, age, past medical history, diagnostic procedures, and results of any blood tests, including results of genetic tests that were already done as part of your standard medical care.

As part of this research study, some information that we obtain from you will be placed into your medical records held at <INSERT LOCAL SITE>, including the results of tests related to effectiveness, safety, and information related to any adverse events your child may suffer during these tests.

This identifiable medical record information will be made available to members of the research team for an indefinite period of time.

Your medical information, as well as information obtained during this research study, may be shared with other groups, possibly including authorized officials from the study sponsor, federal regulatory agencies, and the University of Pittsburgh Office of Research Protections, for the purpose of monitoring the study. Authorized representatives of <INSERT LOCAL SITE> or affiliated health care providers may also have access to this information to provide services and addressing billing and operational issues.

We will protect your privacy and the confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information obtained from your medical records, once your personal information is disclosed to others outside <INSERT LOCAL SITE> or the University.

You can always withdraw your authorization to allow the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing. If you do so, you will no longer be permitted to participate in this study. Any information obtained from you up that point will continue to be used by the research team.

Is my participation in this research study voluntary?

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. Whether or not you provide your consent for your participation in this research study will have no effect on your current or future relationship with the <INSERT LOCAL SITE>. Whether or not you provide your consent for your participation in this research study will have no effect on your current or future medical care at <INSERT LOCAL SITE> or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before you agree to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this

research study. You are not under any obligation to participate in any research study offered by your doctor.

May I later withdraw my permission for me to participate in this research study?
You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the <INSERT LOCAL SITE>. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at <INSERT LOCAL SITE> or affiliated health care provider or your current or future relationship with a health care insurance provider.

If you withdraw, or the study doctor decides to discontinue, your study drug treatment, you may be asked to return for a follow-up visit. If you leave this study, you will not lose any benefits to which you may be entitled.

If I agree to take part in this research study, can I be removed from the study without my consent?
You may be withdrawn from this study by the study doctor or they may take you out of the study if there is a reason. Some of the reasons the doctor may take you out of the study include: your condition worsens; the study is stopped; you cannot meet all the requirements of the study; new information suggests taking part in the study may not be in your best interests; you decide to take back your permission for us to collect, use or share your health information. If you are unwilling to discontinue *Emicizumab* prior to randomization, you will no longer be eligible to participate in this study. You may also choose for you to leave the study at any time. Your participation in this study may be stopped by the study doctor at any time.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

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VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given.

I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I consent to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____
Printed Name of Participant

_____ _____
Participant's Signature Date and Time

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no component of this protocol was begun until after consent was signed.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____	_____
Signature of Person Obtaining Consent	Date and Time

Table 1: Schedule of Events

Table 1	Schedule of Events												
Study Week	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Screening, consent	**X**												
Initiate study arms	**X**												
Initiate study diary	**X**												
Clinical monitoring		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
End-of-study visit													**X**
Laboratory tests													
Anti-FVIII NBU chromogenic	**X**	**X**		**X**			**X**			**X**			**X**
Hemophilia genotype*	**X**												
HLA type*	**X**												
FVIII chromogenic (trough)*	**X**	**X**		**X**			**X**			**X**			**X**
T cell (ELISPOT,Ig, RNA)**	**X**	**X**		**X****			**X****			**X**			**X**
Microbiome	**X**												
Sample for storage	**X**	**X**		**X**			**X**			**X**			**X**

*Genotype, HLA are on buffy coat; **FVIII chromogenic is on aliquot of anti-FVIII; **ELISPOT is after 5 exposure days, in lieu of wk 12 or 24, if closer.

<INSERT LOCAL LETTERHEAD>

CONSENT FOR A CHILD TO ACT AS SUBJECT IN A RESEARCH STUDY
(Subjects < 18 years old)

Protocol Title: The Phase III Multicenter, Randomized Controlled Inhibitor Eradication Trial comparing *Eloctate* Immune Tolerance Induction (ITI) plus *Emicizumab* vs. *Eloctate* ITI alone to Eradicate Inhibitor Formation in Severe Hemophilia A.

PRINCIPAL INVESTIGATOR: <INSERT LOCAL PI>

CO-INVESTIGATORS: <INSERT LOCAL CO-INVESTIGATORS>

SOURCE OF SUPPORT: HRSA, Health Resources Services Administration

Consent Version: v3.1 14 Oct 2021

Key Information: Your child is being asked to take part in a research study. Your child's participation is voluntary. The study team members will explain the study to you/ your child and answer any questions you/ your child may have. You/your child should take time to make your decision.

- **Purpose of Research:** The purpose of this research is to prevent and eradicate (destroy) inhibitor formation in severe hemophilia A patients through two linked studies.
- **Randomization:** There is an equal chance of being randomized to one of two treatments like the flip of a coin. The two treatments are *Eloctate* ITI (immune tolerance induction) with *Emicizumab* vs. *Eloctate* ITI alone.
- **Specimen Collection:** Blood draws will be collected at 6 time points: baseline, 4, 12, 24, 36, and 48 weeks; samples will be frozen and stored indefinitely. A stool sample will be collected at baseline.
- **Collection of Medical Record Information and Subject Diary:** Data collected will include hemophilia diagnosis, bleeding history, and medication used for bleeds. The subject diary will record the date and time of bleeds, and the medication used for bleeds and other medications, including date, time, and amount.
- **Risks of Study:** The likely risks associated with this study include lightheadedness, bruising or bleeding from a blood draw, risk of minor pain, bleeding, or bruising following drug administration, allergic reaction to a study drug(s), risk of inhibitor formation, risk of blood clots, and the risk of breach of confidentiality of your/your child's health information.
- **Benefit of Study:** You may benefit from participation in this study, as the use of the study drugs may lead to fewer bleeding events; however, there is no guarantee.
- **Alternate Procedures:** If you/your child decide not to participate, other choices include getting care and treatment without being in a study.

Why is this research being done?

Your child is being asked to participate in this research study to eradicate inhibitors (antibodies to infused factor VIII) in severe hemophilia A. Hemophilia A is an inherited (genetic) disease in which a protein (factor VIII, FVIII) is missing or does not work properly, which results in bleeding with trauma or without trauma (spontaneous). Current treatment for hemophilia A is by infusing the missing clotting FVIII into a vein. To prevent spontaneous bleeding in patients with severe hemophilia A, regularly scheduled doses of FVIII called "prophylaxis" is recommended. However, in up to 30% of patients who receive factor VIII, an "inhibitor" can form. Inhibitors are proteins or antibodies made by the immune system to fight against foreign (not made in the body) proteins, but in this case the "inhibitor" is against infused factor VIII. These inhibitor antibodies prevent clotting factor VIII from working properly, so standard FVIII treatment is less effective. For this reason, bypass therapy (that is VIIa or activated IX (aPCC) is required, but bleeds are poorly controlled with these agents. As a result, patients with inhibitors have more hospitalizations and complications than those without inhibitors. At this time, it is not known how to *prevent* or *eradicate* inhibitors. *Thus, a major goal of hemophilia treatment is to prevent and eradicate inhibitors.*

Two FDA-approved drugs will be studied in the proposed trial. These include 1) **Eloctate (rFVIIIFc)** or recombinant factor VIII Fc fusion protein, and 2) **Emicizumab (Hemlibra),** the bispecific monoclonal antibody that is a FVIII mimic. *Eloctate* increases the half-life (duration) of FVIII in the circulation, and, in small studies, may reduce the rate of inhibitor formation and shorten ITI (immune tolerance inhibition, i.e. inhibitor eradication) in inhibitor patients, even those refractory to ITI. *Eloctate* is safe and effective in preventing bleeds in adults, adolescents, and children. *Emicizumab* is a bispecific monoclonal antibody and FVIII mimic that substitutes for the missing or inhibited FVIII in the coagulation pathway, and in clinical trials has been safe and effective in preventing bleeds in adults, adolescents, and children with severe hemophilia A with and without inhibitors.

This **Inhibitor Eradication Trial** is a 48-week phase III trial. Children and adults with severe hemophilia A and inhibitors will be enrolled. We will compare *Eloctate* ITI with or without *Emicizumab* in the eradication of inhibitors in children and adults with inhibitors, who may be either refractory or never tolerized, or whose inhibitors arise during the linked Prevention Trial. This Eradication Trial is expected to last a total of up to 7 years, or up to 48-weeks per subject. Procedures and visits are outlined below. The <INSERT LOCAL SITE> is one of up to 41+ sites in the U.S. where this study will be conducted.

Who is being asked to take part in this research study?

Children or adults with severe hemophilia A and an inhibitor, anti-FVIII $\geq$ 5.0 B.U., who either are refractory to or were never tolerized (ITI) or who developed an inhibitor during the Prevention Trial and who are cared for at the <INSERT LOCAL SITE> will be recruited for this study. The total enrollment for this study will be up to 90 subjects including 2-4 subjects from this site.

What procedures will be performed for research purposes?
This is a 48-week outpatient study with approximately 13 study visits which include screening, follow-up, and end of study visits. The study involves two drugs; one is given IV (intravenously – injection directly into the vein) and one given SQ (subcutaneously – injection under the skin).

If you agree for your child to participate in this study, your child will be screened for eligibility. Should your child be eligible, your child would be randomized into one of two treatment types. Blood draws will be performed at 6 time points: baseline, 4, 12, 24, 36, and 48 weeks. Follow-up visits will be conducted throughout the duration of the study between screening and the end of study visit.

SCREENING VISIT
Study Visit 1: *Screening*
If you agree for your child to participate in this study and have signed the informed consent, the study staff will complete the following tests and procedures during the screening period to determine if your child can participate in the study. The screening procedures (listed below) will be completed within 24 hours of enrollment.

- Study staff will collect age, date of birth, race, and hemophilia genotype.
- Study staff will ask about your child's medical history, height, weight, past factor treatment, dose and frequency, circumcision and bleeding.
- Hemophilia history and previous exposure to FVIII.
- Medication history including medications within 4 weeks of starting study drug(s).
- Brief physical exam including vital signs, height (cm) and weight (kg).
- Blood draw: Your child will have ¾ tsp sample for FVIII, inhibitor, immunity, genotype, trough FVIII, and a sample will be stored for future studies in hemophilia.
- A stool sample will be collected at baseline (may be collected at home and mailed back into the Hemophilia Center of Western Pennsylvania {Coordinating Center}) to assess genes and bacteria in the gut (microbiome).

Enrollment
If your child is currently receiving *Emicizumab*, you will be asked to discontinue the drug prior to randomization. No washout period is required. If you are unwilling to discontinue *Emicizumab* prior to randomization, you will no longer be eligible to participate in the study.

After the doctor determines your child is eligible, your child will begin the study drug(s). Screening may occur on the same day, or this may be on a second visit, if necessary, to collect your child's information or records. Your child will receive the study drug to which he is assigned and take it *preferably* between 7 am and 9 am on the assigned schedule for 48 weeks.

If your child is eligible, your child will receive *Eloctate ITI* at 100 IU/kg every other day plus *Emicizumab* 1.5/ mg/kg (after a 4-week induction at 3 mg/kg/week); or Eloctate ITI alone every other day during the 48-week study. Which drug your child receive is determined by

randomization, like a roll of dice. Subjects will use their own supply of *Eloctate* and/or *Emicizumab*. The dose used in this study is similar to the dose used in standard care.

- Eloctate will be given by IV (intravenously into a vein) by venipuncture using an infusion needle (butterfly) or by central line, if required; Emicizumab will be given by SQ (subcutaneous, under the skin) injection. It is anticipated that most if not all of your child's study drug(s) will be administered by the nurse at the Hemophilia Center. If you have learned infusion or injection techniques, you may give the study drug(s) at home. If your child has bleeds, your child's physician will discuss if dose frequency should be increased or if a central line is needed, which is anticipated in less than 1% of participant, but this will not change where the study drug(s) is/are given.
- All doses of study drug(s) will be given either by venipuncture, using a butterfly or central line, if required, or by subcutaneous injection. The study drug(s) will be given over about 5-10 minutes.
- Your child will record all doses of study drug(s) that you take, including day, date, time, dose in a patient diary which will be given to your child by the study nurse. Your child will bring this back at all study visits to review with the study nurse.

The nurse will discuss the study visits with you/your child. The entire visit will last about 1 hour.

In the event of a new bleed, *bypass therapy* (rFVIIa) may be given at the discretion of the hemophilia physician caring for your child, similar to what is done in standard care. Activated factor IX (aPCCs) will not be allowed in this trial, as it may cause complications when used with *Emicizumab*. (Note, at most hemophilia centers, the treating physician will be the study physician.) The trough factor VIII levels obtained during study will be for information only and not the basis for dose change. Only *Eloctate* and/or *Emicizumab* may be used during the study, and only *rFVIIa* may be used for breakthrough bleeds, as directed by your child's physician. It is expected that the response of bleeds to *rFVIIa* will be the same as when this drug is used in clinical practice.

If a bleeding episode occurs during study, your child's physician will decide with you/your child the best dose and frequency to treat that bleed. During the study, your child should only use the study drug(s) to which your child is assigned unless the inhibitor resolves (see below). Your child will be asked to record all your child's bleeds and all study drug(s) use in a Subject Diary. You will be responsible for assuring your child has study drug(s) to allow for the prescribed dosing frequency, per the treating hemophilia physician at all times. Bleeding which occurs during the study will be managed as described above: if an inhibitor is present, rFVIIa will be given for bleeds, but if the inhibitor has resolved, *Eloctate* will be given for bleeds, as determined by your child's physician. The study nurse will work closely with you/your child and review this information during this visit and throughout the study.

If the inhibitor resolves, it will be confirmed by a repeat blood test within 4 weeks. If the two tests confirm the inhibitor is no longer detected, then your child's physician will decide with you/your child the best treatment. Additional testing for factor peak and half-life, just as routinely done in ITI, may also be drawn to determine when it is safe to switch medications. Even if your child stops the study drug(s), your child will remain on study for collection of

information and follow up until the end of the study (48 weeks). If your child has no bleeding, then there will be no change in treatment until the second blood test confirms absence of the inhibitor: at that time your child's doctor will decide with you/your child the best treatment approach. If your child has bleeding not responding to study drug, even before the inhibitor, your child may stop study drug and receive treatment at the discretion of your child's physician but will continue to be followed on study until week 48. At no time will activated FIX (aPCCs) be allowed on this trial because of potential thrombosis (see above). The entire study schedule and procedures are outlined and in the Appendix of this consent form.

FOLLOW-UP VISITS:
At follow-up visits, you will review your child's supply of study drug(s) with the hemophilia center nurse who will assist you in ordering additional doses to assure your child has enough for the study (or more, if prescribed by your child's physician) until the next visit. Your child will need to record all your child's bleeds and medication on the Subject Diary. For subjects who already have a supply of *Eloctate* and/or *Emicizumab*, the first dose may be given on the day of screening. For all other subjects, the first dose may be given as soon as the prescription is filled. Follow up visits will be monthly at <INSERT LOCAL SITE> at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 weeks.

Study Visit 2: Week 4, Follow-up Visit

- Your child's diary will be reviewed for frequency, type and site of bleeds, and for date, time, and dose of study drug(s).
- Study drug use will be reviewed and more ordered as needed.
- All medications will be recorded and reviewed.
- Assessment for adverse events (complications) will be completed.
- Vital signs and weight (kg) will be obtained.
- A ¾ tsp blood sample will be drawn for FVIII, inhibitor, immune studies, and a sample will be stored for future studies. All samples must be drawn prior to the study drug(s) dose.

Study Visits 3, 5, 6, 8, 9, 11, 12: Monthly Follow-up Visits (Can be done remotely or in person)

- Your child's diary will be reviewed for frequency, type and site of bleeds, and for date, time, and dose of study drug(s).
- Study drug use will be reviewed and more ordered as needed.
- All medications will be recorded and reviewed.
- Assessment for adverse events (complications) will be completed.

Study Visit 4, 7, 10: Quarterly Follow-up Visit

- Your child's diary will be reviewed for frequency, type and site of bleeds, and for date, time, and dose of study drug(s).
- Study drug use will be reviewed and more ordered as needed.
- All medications will be recorded and reviewed.
- Assessment for adverse events (complications) will be completed.

- Vital signs and weight (kg) will be obtained.
- A ¾ tsp blood sample will be drawn for FVIII, inhibitor, immune studies, and a sample will be stored for future studies. All samples must be drawn prior to the study drug(s) dose.

END-OF-STUDY VISIT:
Study Visit 13: Week 48, End-of-Study Visit

- Your child's diary will be reviewed for frequency, type and site of bleeds, and for date, time, and dose of study drug(s).
- All medications will be recorded and reviewed.
- Assessment for adverse events (complications) will be completed.
- Vital signs and weight (kg) will be obtained.
- A ¾ tsp blood sample will be drawn for FVIII, inhibitor, immune studies, and a sample will be stored for future studies. All samples must be drawn prior to the study drug(s) dose.

The total blood volume for all tests is 4½ tsp during the 48-week study. The blood samples will be de-identified and sent to the Hemostasis Laboratory, Puget Sound Blood Center, Seattle WA, and to the Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD.

What are the possible risks, side effects, and discomforts of this research study?
As with any study drug(s), there may be side effects that are currently unknown, and it is possible these could be permanent, serious, or life threatening. This study involves FDA-approved study drug(s) *Eloctate* and/or *Emicizumab,* each approved by the FDA for the prevention of bleeds for hemophilia. Each drug has been shown to be safe and effective in adults and children and are used as part of standard care. It is not known whether the study drug(s) will prevent or eradicate inhibitor formation in individuals with severe hemophilia A.

You should talk to the study doctor or your child's regular doctor about these risks. Every effort will be made to reduce these risks. There are risks associated with receiving the study drug(s) and having blood drawn. You will be asked to report any safety problems or side effects associated with administration of study drug(s), whether given at <INSERT LOCAL SITE>, infusion center, emergency room, or at home.

Discontinuing Emicizumab Prior to Randomization
There are no known risks associated with discontinuing *Emicizumab*. It is possible that your child's bleed frequency could increase if prophylaxis (eg. factor VIIa) is not given or infrequently given due to the more difficult intravenous route than *Emicizumab*. If a bleed occurs, factor VIIa will be given until it resolves and monitored by your treatment records and physician.

Emicizumab
Common risks include injection site reactions, headache, and arthralgia (joint pain).

Eloctate
Common risks include chest pain, feeling cold, feeling hot, dizziness, dysgeusia (altered taste), headache, joint swelling, myalgia (muscle pain), abdominal pain – lower and upper, angiopathy (vascular pain after injection of study drug), hypertension, bradycardia (slowed heart rate), procedural hypotension, cough, and rash.

Inhibitor Development
Inhibitor development occurs in 28-30% of individuals with severe hemophilia A (factor VIII deficiency). Among those who develop inhibitors 95% or more occur within 50 exposure days, usually in childhood after 10-20 exposure days, by the age of 2. Currently there is no known way to prevent inhibitor formation. Your child will be followed closely to monitor this risk, and samples to detect inhibitors will be taken at several time points in the study to monitor for this possibility. Should an inhibitor occur, treatment with factor VIIa (rFVIIa) will be determined at the discretion of your child's physician.

Allergic or Anaphylactic Reaction
Allergic type reactions including anaphylaxis have only rarely, <0.001%, or less than 1 per 100,000 people, been reported for factor VIII and other hemostatic drugs. Symptoms could include hives, rash, swelling, chest tightness, shortness of breath, wheezing, faintness, low blood pressure, rapid heartbeat, and anaphylaxis (a life-threatening condition). If this occurs, the infusion should be stopped, and you should contact us immediately. If your child's symptoms are severe, call 911. Your child should receive immediate treatment. Should these symptoms occur, Benadryl, a medication which reduces inflammation, or an epi-pen, which improves vessel tone and lung function, may be given, with close monitoring of symptoms. Benadryl may cause drowsiness, dizziness or low blood pressure; an epi-pen may cause rapid heart rate, sweating, nausea, or anxiety. Your child will be monitored for these symptoms after receiving this drug. No one with a history of allergy to FVIII will be enrolled in these trials.

Thromboembolism/Thrombogenicity
Historically factor VIII products and other hemostatic agents are rarely, if ever, associated with the development of thromboembolic complications (blood clots). None have been detected in any of the studies of *Emicizumab*, or *Eloctate*, in adults or children, except when it is taken with activated factor IX (aPCCs) rarely, < 0.01% or less than 1 per 100 people. For that reason, aPCCs will not be allowed on this trial. There is the unlikely possibility, < 0.001%, or less than 1 per 100,000 people, that these drugs (in the absence of aPCCs) could cause a clot, swelling, or inflammation in a vein. This risk will be very carefully monitored clinically. Should these symptoms occur in your child, you should contact us immediately, or if the symptoms are severe, measures considered standard of care, including stopping the study treatment and/or removing the line in which it was given, if that is the source of the clot, should be done as soon as possible.

Bleeding Events
Because your child has hemophilia, there is an additional risk of bleeding at the infusion site. Contact us if this occurs and seek medical attention. In the event that bleeding at the infusion site

cannot be stopped with pressure, it may be necessary to use a stitch or an adhesive material to stop the bleeding. The devices used to administer the stitch or adhesive may cause the following negative side effects: bleeding, a build-up of blood known as a hematoma, infection, allergic reaction, nerve injury, and swelling.

Venipuncture
There may be discomfort with drawing your child's blood, which is common, occurring in up to 25%, or 25 in 100 people: this may include pain, lightheadedness, fainting, bruising, or bleeding or infection in the tissue around the vein. This may be alleviated or reduced by applying pressure to the blood draw site for 5 minutes and having your child lie on his back. The risk of repeated blood draws is anemia, or a low blood count, but this will be carefully monitored. Injections may rarely, in less than 1%, or less than 1 in 100 people, cause pain, soreness, redness, warmth, itching, numbness, tenderness, swelling, skin changes (discoloration, breakdown, or thickening), or swelling or lymph nodes near the injection site.

IV Placement
There may be discomfort during IV placement. Insertion of an IV line is typically a minimal risk procedure. However, taking blood or putting and intravenous catheter in people with hemophilia may increase chance of pain, bleeding or bruising at the spot where the needle enters your body, lightheadedness or fainting, swelling and redness at needle site, infection, or inflammation of vein. Emla cream (a skin-numbing medicine) may be used to minimize this discomfort.

Subcutaneous Injection
Subjects could develop a reaction at the site of the injection, which could include pain, tenderness, redness, swelling, itching, sores, skin color changes, or other reactions around the injection site.

Central Line Placement
In young children, difficulty obtaining venous access due to small veins may require the placement of a central line. The insertion of a central line may reduce the discomfort of needle sticks and will be suggested at the discretion of the treating physician. Placement of central lines may cause bleeding, and thus additional factor treatment may be necessary. There is also the risk of anesthesia required for the line placement procedure. In addition, central lines may be complicated by infections that require hospitalization, antibiotics, and/or removal and replacement of the line. The insertion of a central line is part of clinical care and not required for this study. Placement of a central line could lead to an infection or pneumothorax (collapsed lung).

Stool Collection
There are no known risks of stool sample collection

Collection of Medical Information and Subject Diary
Study participation and related data will be protected to maintain confidentiality. There is a possibility that your child's personal information could become generally known. In order to reduce risks of disclosure or breach of confidentiality, the research related documents, blood

samples and clinical information stored in your child's research files will be assigned an alphanumeric (letters and numbers) identifier (that do not contain personal identifiers). A linkage key for linking this number and your or your child's name will be kept at <INSERT LOCAL SITE> under lock and key by the research staff. Any publication arising from this study will not contain names or other identification unless you give permission in another signed consent.

Future Genetic Testing of Stored Samples
There is the possibility that if the results of the research studies involving your child's genetic material were to become generally known, this information could affect your or your child's ability to be insured, employed, or influence plans for children or have a negative impact on family relationships, and/or result in paternity suits or stigmatization.

In addition, there is a Federal law, called the Genetic Information Nondiscrimination Act (GINA), that generally makes it illegal for health insurance companies and group health plans to use genetic information in making decisions regarding your eligibility or premiums. GINA also makes it illegal for employers with 15 or more employees to use your genetic information when making decisions regarding hiring, promoting, firing, or setting the terms of employment. This new Federal law does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

Your research data/samples may be shared with investigators conducting other research; this information will be shared without identifiable information. These research data/samples may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

The data, samples, and genetic data generated from samples may be shared with other researchers and with federal repositories, in a de-identified manner without additional informed consent.

What are possible benefits from taking part in this study?
Currently there are no agents to eradicate inhibitors. Your child could benefit if the study finds that any of the study drug(s) will eradicate inhibitors in severe hemophilia A subjects. This could improve quality of life and decrease or prevent costs associated with inhibitor development or eradication. However, it is important to note that your child may not receive direct benefit from taking part in this research study and the only benefit may be that information obtained from your child's participation may help others in the future.

Will my child receive any results from taking part in this study?
The results of inhibitor testing will be provided to you during the study.

What treatments or procedures are available if my child should not take part in this research study?

There are no known cures for those with hemophilia and inhibitors. Other alternative factor treatments (recombinant factor VIII, rFVIII for hemophilia, or rFVIIa for inhibitors) are available to your child to treat or prevent bleeds.

If my child agrees to take part in this research study, will my child be told of any new risks that may be found during the course of the study?
You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?
Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study (i.e., the Screening Procedures, Monitoring, and End of Study visits described above). Neither the study nor the sponsor of the study will provide the *Eloctate* or *Emicizumab* as you will be using your own supply of drug. Should your child's physician recommend central line placement, the costs will not be covered by this research study.

Will I be paid if I or my child takes part in this research study?
<INSERT LOCAL COMPENSATION>

Who will pay if my child is injured as a result of taking part in this study?
<INSERT LOCAL COMPENSATION FOR INJURY LANGUAGE>

Who will know about my child's participation in this research study?
Any information about your child obtained from this research will be kept as confidential (private) as possible. All records related to your or your child's involvement in this research study will be stored in a locked file cabinet. Your child's identity on these records will be indicated by a case number rather than by your child's name, and the information linking these case numbers with your child's identity will be kept separate from the research records. De-identified information will also be stored in a secure database. The web-based data base is located at the Data Coordinating Center, Graduate School of Public Health, University of Pittsburgh. Your child will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

In addition to the investigators listed and their research staff, the following individuals may have access to your information related to your participation in this research study:

- Authorized representatives of the study sponsor, federal regulatory agencies, Data Safety and Monitoring Board (DSMB) and the University of Pittsburgh Office of Research Protections may review your identifiable research information for purposes of monitoring the conduct of this research study.
- Information collected from this study may be shared with federal repositories and/or other investigators; however, this information will be shared in a de-identified manner (i.e., without identifiers).

- De-identified blood samples in this study will be sent to the Hemostasis Laboratory, Puget Sound Blood Center, Seattle WA, and to the Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD.
- If the investigators learn that your child or someone with whom your child is involved is in serious danger or potential harm, they will need to inform, as required by <INSERT LOCAL STATE> law, the appropriate agencies.
- <INSERT ANY LOCAL ENTITIES>

<INSERT LOCAL DATA RETENTION PERIOD LANGUAGE>

HIPAA Authorization for Disclosure of Protected Health Information (PHI)
<INSERT LOCAL HIPAA AUTHORIZATION LANGUAGE OR USE THE FOLLOWING>
As part of this research study, we are requesting your authorization or permission to review your child's medical records to determine eligibility criteria for this study and any adverse events associated with testing. This information will be used for the purpose of determining the effectiveness and safety of the study drug(s) in individuals with hemophilia A. This authorization is valid for an indefinite period of time. We will obtain the following information: your child's diagnosis, age, past medical history, diagnostic procedures, and results of any blood tests, including results of genetic tests that were already done as part of your standard medical care.

As part of this research study, some information that we obtain from you will be placed into your child's medical records held at <INSERT LOCAL SITE>, including the results of tests related to effectiveness, safety, and information related to any adverse events your child may suffer during these tests.

This identifiable medical record information will be made available to members of the research team for an indefinite period of time.
Your child's medical information, as well as information obtained during this research study, may be shared with other groups, possibly including authorized officials from the study sponsor, federal regulatory agencies, and the University of Pittsburgh Office of Research Protections, for the purpose of monitoring the study. Authorized representatives of <INSERT LOCAL SITE> or affiliated health care providers may also have access to this information to provide services and addressing billing and operational issues.

We will protect your privacy and the confidentiality of your child's records, as described in this document, but cannot guarantee the confidentiality of your child's research records, including information obtained from your child's medical records, once your personal information is disclosed to others outside <INSERT LOCAL SITE> or the University.

You can always withdraw your child's authorization to allow the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing. If you do so, your child will no longer be permitted to participate in this study. Any information obtained from your child up that point will continue to be used by the research team.

Is my or my child's participation in this research study voluntary?
Your child's participation in this research study, to include the use and disclosure of your child's identifiable information for the purposes described above, is completely voluntary. Whether or not you provide your consent for your child's participation in this research study will have no effect on your child's current or future relationship with the <INSERT LOCAL SITE>. Whether or not you provide your consent for your child's participation in this research study will have no effect on your child's current or future medical care at <INSERT LOCAL SITE> or affiliated health care provider or your child's current or future relationship with a health care insurance provider.

Your child's doctor is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before your child agrees to participate in this research study, or at any time during your child's study participation, you may discuss your child's care with another doctor who is not associated with this research study. Your child is not under any obligation to participate in any research study offered by your child's doctor.

May I later withdraw my permission for my child to participate in this research study?
You may withdraw, at any time, your child's consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. Any identifiable research or medical information recorded for, or resulting from, your child's participation in this research study prior to the date that you formally withdrew your child's consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your child's consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your child's consent for participation in this research study will have no effect on your current or future relationship with the <INSERT LOCAL SITE>. Your decision to withdraw your child's consent for participation in this research study will have no effect on your child's current or future medical care at <INSERT LOCAL SITE> or affiliated health care provider or your or your child's current or future relationship with a health care insurance provider.

If you withdraw, or the study doctor decides to discontinue, your child's study drug treatment, your child may be asked to return for a follow-up visit. If your child leaves this study, you will not lose any benefits to which you or he may be entitled.

If my child agrees to take part in this research study, can he be removed from the study without our consent?
Your child may be withdrawn from this study by the study doctor or they may take your child out of the study if there is a reason. Some of the reasons the doctor may take your child out of the study include: your child's condition worsens; the study is stopped; your child cannot meet all

the requirements of the study; new information suggests taking part in the study may not be in your child's best interests; you decide to take back your permission for us to collect, use or share your child's health information. If you are unwilling to discontinue *Emicizumab* prior to randomization, your child will no longer be eligible to participate in this study. You may also choose for your child to leave the study at any time. Your child's participation in this study may be stopped by the study doctor at any time.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

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PARENTAL PERMISSION

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given.

I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

I understand that, as a minor (age less than 18 years), the below-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study and provide my authorization to share his/her medical records with the research team. A copy of this consent form will be given to me.

_____

Printed Name of Child-Subject

_____ _____

Parent's or Guardian's Name (Print) Relationship to Participant (Child)

_____ _____

Parent's or Guardian's Signature Date and Time

For children who are developmentally able to provide assent:

This research has been explained to me, and I agree to participate.

_____

Printed Name of Child-Subject

_____ _____
Signature of Child-Subject Date and Time

VERIFICATION OF EXPLANATION
I certify that I have carefully explained the purpose and nature of this research study to the above-named child in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e., assent) to participate in this study.

_____ _____
Investigator's Printed Name Date and Time

_____
Investigator's Signature

CERTIFICATION of INFORMED CONSENT:
I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date and Time

CONSENT FOR CONTINUED PARTICIPATION

I understand that I am currently participating in a research study. I further understand that consent for my participation in this research study was initially obtained from my parent because I was a minor at the time that this initial consent was requested. I have now turned 18 years old, and I am able to provide direct consent for continued participation in this research study.

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given.

I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing below, I agree to continue my participation in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date and Time

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____	_____
Signature of Child-Subject	Date and Time

Table 1: Schedule of Events

Table 1	Schedule of Events												
Study Week	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Screening, consent	**X**												
Initiate study arms	**X**												
Initiate study diary	**X**												
Clinical monitoring		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
End-of-study visit													**X**
Laboratory tests													
Anti-FVIII NBU chromogenic	**X**	**X**		**X**			**X**			**X**			**X**
Hemophilia genotype*	**X**												
HLA type*	**X**												
FVIII chromogenic (trough)*	**X**	**X**		**X**			**X**			**X**			**X**
T cell (ELISPOT,Ig, RNA)**	**X**	**X**		**X****			**X****			**X**			**X**
Microbiome	**X**												
Sample for storage	**X**	**X**		**X**			**X**			**X**			**X**

*Genotype, HLA are on buffy coat; **FVIII chromogenic is on aliquot of anti-FVIII; **ELISPOT is after 5 exposure days, in lieu of wk 12 or 24, if closer.