<INSERT LOCAL LETTERHEAD>

CONSENT FOR A CHILD TO ACT AS SUBJECT IN A RESEARCH STUDY
(Subjects 4 months to 4 years old)

Protocol Title: The Phase III Multicenter, Randomized, Controlled Inhibitor Prevention Trial, comparing *Eloctate* (rFVIIIFc) vs. *Emicizumab* (Hemlibra) to Prevent 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: v3.0 08 June 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 inhibitor formation in severe hemophilia A patients.
- **Randomization:** There is a 3 in 4 chance of being randomized to Emicizumab and 1 in 4 chance of being randomized to Eloctate.
- **Specimen Collection and storage:** Blood draws will be collected at 6 time points: baseline, 4, 12, 24, 36, and 48 weeks; samples will be frozen and stored indefinitely.
- **Collection of Medical Record Information and subject diary:** Data collected will include demographics, hemophilia diagnosis, bleeding history, and medication used for bleeds. A diary will record the date and time of bleeds, and the medication used for bleeds and other medications, including date, time, and amount. A stool sample will be collected at baseline.
- **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:** You may benefit from participating in this study, as these study drugs may reduce bleeds; however, there is no guarantee.
- **Alternate Procedures:** If you/your child decide not to participate, there are other choices for 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 prevent 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 stops bleeding by making a blood clot, is missing or does not work properly. Individuals with severe hemophilia A have less than 1% of the normal clotting FVIII and have bleeds 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, doctors recommend regularly scheduled doses of FVIII called "prophylaxis". 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 against infused factor VIII because it looks "foreign" or different from your own FVIII. These inhibitor antibodies prevent standard clotting factor VIII from working properly. If an inhibitor occurs, treatment is by "bypass therapy" (VIIa or activated IX (aPCC)), 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* inhibitors. *Thus, a major goal of hemophilia treatment is to prevent inhibitors.*

Two FDA-approved drugs will be studied in the proposed trials. 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 induction, i.e. inhibitor eradication) in inhibitor patients, even those resistant to ITI. *Eloctate* is safe and effective in preventing bleeds in adults, adolescents, and children. The bispecific monoclonal antibody, *Emicizumab,* is a FVIII mimic, substituting for 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 Prevention Trial** is a 48-week phase III trial. We will enroll children with severe hemophilia A who have not been previously treated (except for circumcision). We will compare *Emicizumab with Eloctate* in the prevention of inhibitors in children *before* they have a bleed or surgery or trauma *(preemptive)* and continued weekly to prevent bleeds (*prophylaxis)*.

Who is being asked to take part in this research study?
Children with severe hemophilia A, 4 months of age or older, who have received three or fewer FVIII treatments for a bleed cared for at the <INSERT LOCAL SITE> will be recruited for this study.

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 FDA-approved 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, he will be screened for eligibility. If he is eligible, he will receive one of two treatment. Blood draws will be performed at 6 timepoints: baseline, 4, 12, 24, 36, and 48 weeks. Follow-up visits will be conducted monthly to the end of the study.

SCREENING VISIT & ENROLLMENT

Study Visit 1: *Screening*

If you agree for your child to participate in this study and sign the informed consent, the study staff will complete the following screening procedures (below) 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, and past circumcision and bleeding.
- Hemophilia history and previous FVIII treatment.
- Medication in the last 4 weeks.
- Brief physical exam with vital signs, height (cm) and weight (kg).
- Blood draw: Your child will have a ¾ tsp sample drawn for FVIII, inhibitor, immunity, genotype, and a sample stored for future related studies.
- 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

After the doctor determines your child can participate, he will begin the study drug. He will take it *preferably* between 7 am and 9 am weekly during the study.

Your child will receive one of two drugs: either *Eloctate* at 65 IU/kg IVweekly or *Emicizumab* 1.5 mg/kg SQ (after a 4-week induction at 3 mg/kg/week SQ*)* as part of his regular care. The drug will begin *before* the first bleed and continue weekly during the 48-week study. Your child will have a 3 out of 4 chance of receiving *Emicizumab* or 1 out of 4 chance receiving *Eloctate*. Which drug your child receives is determined by randomization process, like rolling dice. Subjects will use their own supply of *Eloctate* or *Emicizumab*. The dose used in this study is the same dose used in standard care.

- Your child will use his own supply of study drug. Your child will be assigned to receive either Eloctate or Emicizumab. If he receives Eloctate, it will be given IV (through a vein) using an infusion needle (butterfly) or by central line. If he receives Emicizumab, it will be given SQ (under the skin injection), depending on the study drug to which your child is assigned. You will decided with the nurse at the Hemophilia Center where your child's study drug will be given. If you have learned infusion or injection techniques and are certified by your <INSERT LOCAL SITE>, you may give the drug at home. If your child has breakthrough bleeds, your child's physician will discuss treatment and if a central line is needed, but it should not change where your child receives the study drug.

- All doses of study drug will be given either by venipuncture, using a butterfly or central line if required, or by subcutaneous injection and take about 5-10 minutes.
- You will record all doses of study drug that your child takes (date, time, dose) in a patient diary which the study nurse will give you. You should bring it to all study visits to review with the nurse.
- If your child is currently being treated with Emicizumab, you will be asked to discontinue the drug prior to randomization. If you are unwilling to discontinue Emicizumab treatment prior to randomization, you will no longer be eligible to participate in this study.

The nurse will discuss study visits with you. The visit will take 1 hour.

If your child has a bleed, *Eloctate* will be given, similar to standard care, and whether your child is assigned to receive *Eloctate or Emicizumab*. That is because *Emicizumab* prevents, but does not treat, bleeds. After the bleed resolves, your child's physician will discuss with you whether to treat more frequently with *Eloctate* for bleeds, similar to standard care. Only *Eloctate* or *Emicizumab* may be used during the study, and your child should only use the study drug to which he is assigned, unless an inhibitor develops (see below). You will be responsible to work with the nurse to assure your child has enough study drug(s) at all times.

If your child develops an inhibitor, a repeat blood testing must be drawn within 4 weeks to confirm it. If confirmed, your child's physician will decide with you the best treatment for your child. Even if your child stops the study drug, he will remain on study for collection of information and follow up until the end of the study (48 weeks). If at the time of inhibitor detection, your child has no bleeding, then there will be no change in study drug until the second blood test confirms the inhibitor (within 4 weeks): at that time your child's doctor will decide with you the best treatment for your child. If an inhibitor develops and bleeding does not respond to *study drug,* then even before the inhibitor is confirmed, your child may stop *study drug* and receive treatment, but he will be followed until week 48. At no time will activated FIX (aPCCs) be allowed on this trial because of potential thrombosis with recent emicizumab use. The schedule and procedures are outlined below and in the Appendix of this consent form. Please note: if your child develops an inhibitor on the trial, he may be invited to join the linked "Inhibitor Eradication Trial." Your child's doctor will discuss this with you.

FOLLOW-UP VISITS:
At follow-up visits, you will review your child's supply of study drug with the study nurse who will help order more doses to assure you have enough until the next visit. You will need to record all your child's bleeds and medicines on the Subject Diary. The first dose may be given on the day of screening, or 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 bleeds and the date, time and dose study drug was given, other medications given, and any complications.
- Study drug use will be reviewed and more ordered as needed.
- Vital signs will be taken, and weight will be obtained.
- A ¾ tsp blood sample will be drawn for inhibitor, FVIII, immune studies, and a sample stored for future studies. All samples must be drawn before the study drug is given.

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 bleeds and date, time and dose of study drug.
- More study drug will be 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 bleeds and date, time and dose of study drug.
- More study drug will be ordered as needed.
- All medications will be recorded and reviewed.
- Assessment for adverse events (complications) will be completed.
- Vital signs and weight will be obtained.
- A ¾ tsp blood sample will be drawn for for inhibitor, FVIII, immune studies, and a sample stored for future studies. All samples must be drawn before the study drug is given.

END-OF-STUDY VISIT:

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

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

The total blood draw during the study is 4½ tsp. The blood draw will be less for children weighing less than 14 pounds. (See the Appendix, last page). The blood samples will be de-identified (no name) 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, there may be side effects that are currently unknown, and it is possible these could be permanent, serious, or life threatening. This study involves study drug *Eloctate* or

Emicizumab, each approved by the FDA for the prevention of bleeds for hemophilia. 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 either study drug will prevent inhibitor formation in individuals with severe hemophilia A.

You should talk to the study doctor or your child's regular doctor about the potential risks. Every effort will be made to reduce these risks. There are risks associated with receiving the study drug and having blood drawn. You will be asked to report any safety problems or side effects associated with administration of study drug, 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*. If a bleed occurs, factor VIII will be given until it resolves and monitored by your child's doctor.

Eloctate
Common risks include malaise (feeling unwell) and joint aching in 2% (2 per 100 people); and in 1% (1 per 100 people) feeling hot or cold, dizziness, unusual taste, headache, joint swelling, muscle pain, abdominal discomfort, blood vessel disease, high blood pressure, slow heart rate, skin rash, and cough.

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

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. No children with a past history of bleeding or inhibitors will be enrolled on this study.

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 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 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 <INSERT LOCAL SITE> 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 prevent inhibitors. Your child could benefit if the study finds that any of the study drug(s) will prevent 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, the 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 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>.

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 treatment 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 child (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 participation in this research study and provide my authorization to share my child's 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

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
_____	_____
Name	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.