Informed Consent Cover Page for FDAAA consent posting:

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STUDY TITLE: Addition of JSP191 (c-kit antibody) to Non-myeloablative Hematopoietic Cell Transplantation for Sickle Cell Disease and Beta-Thalassemia

STUDY SITE: NIH Clinical Center (CC), National Heart, Lung, and Blood Institute (NHLBI)

Cohort: Adult Recipient (or Minor 13-17 years of age)

Consent Version: 20 AUG 2024

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

Transplantation in your sickle cell disease (SCD) or β-thalassemia has been shown to be curative. A transplant is a procedure where blood "stem cells" from a donor are given to you through a plastic tube in the veins. The cells may grow into the different cells that make up your blood and immune system. Your pre-transplant testing shows that the disease is serious enough to justify a transplant; additionally, a family member who is a proper tissue match has been identified as a possible donor.

We would like to find out if transplantation that involves a c-kit antibody medication, briquilimab (also known as JSP191), combined with another antibody medication, alemtuzumab, and radiation, is less toxic (compared to a standard hematopoietic cell transplant).

Also, not all patients with SCD and beta-thalassemia who receive a hematopoietic cell transplant are cured. We cannot predict whether you will benefit from taking part in this study and you may prefer to receive standard sickle cell treatments instead, or to receive a transplant at another hospital without enrolling on this study.

If you agree to participate in this study, the length of time for your involvement during the treatment portion is about 36 months.

During study participation, here are some of the significant events that will happen:

Pre-transplantation evaluation: We will perform many tests to find out how sickle cell has affected your organ function. You will also have a bone marrow collection (about a tablespoon) from the pelvic bone to check the condition of your marrow for research. Lastly, you will speak with our social worker to discuss related issues to the transplant. It is necessary that a family member or friend stay with you once discharged from the hospital to assist with day-to-day activities.

Transplantation: To prepare your body to receive donor blood stem cells, you will undergo treatment called "conditioning". Over 7-13 days, you will receive briquilimab and alemtuzumab antibodies, radiation, and sirolimus. The donor blood stem cells are then infused, which may take 8 or more hours. You may need medicine to manage complications, such as nausea, diarrhea, fever, or pain. You may also need periodic transfusions of red blood cells and platelets until the bone marrow begins producing enough of those cells on its own.

Leaving the hospital: Usually the average length of hospital stay after transplant is 30 days. Full recovery to normal physical fitness takes at least several months.

Follow-up after transplant (post-transplant):

Up to 2-3 months post-transplant: Day 100 post-transplant is a significant time point when we perform a comprehensive evaluation, similar to the pre-transplant testing.

After 3 months post-transplant: If you are stable at day 100 or soon thereafter, you can return home if you temporarily relocate to the Bethesda area. We will see you as needed but will schedule follow up visits at: Months 6, 12, 24, and 36 post-transplant.

Costs: We will cover the cost for some of your expenses, such as travel, lodging, and/or meals. Someone will work with you to review the costs of taking part and what we will support.

You are free to stop participating in the trial at any time. However, because patients need to be followed closely for several months to years after transplant for their safety, we recommend everyone to fully understand the requirements to undergo transplant and the extent and length of commitment before deciding to take part.

If you receive conditioning, you should not withdraw from the study without receiving donor cells to minimize the risk of having low blood counts (aplasia). After you receive the donor cells, you should try not to withdraw without receiving the medications to ensure donor stem cells take hold (engraft) and prevent possible donor immune cells causing injury to organs such as GI tract, skin, or liver (graft-versus-host disease) and/or infection. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

Compensation: If you choose to participate in the quality of life (QoL) and reproductive health assessment portion, you may receive up to $60 each year you complete the optional surveys and assessments during specific follow-up visits.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you

about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being enrolled is a minor then the term "you" refers to "you and/or your child" throughout the remainder of this document.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative (LAR), will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

You have sickle cell disease (SCD) or β-thalassemia in which transplantation has been shown to be curative. Hematopoietic (blood) cell transplantation is the same as bone marrow transplant or stem cell transplant. Stem cell transplant involves the use of high dose chemotherapy and often radiation to destroy bone marrow cells, and replacing them with a donor's normal marrow stem cells. The donor cells (graft) find their way to the bone marrow where they generate normal functioning red blood cells. You have a family member who is a proper tissue match and your pre-transplant testing shows that the disease is severe enough to warrant a transplant.

In this study, a new c-kit antibody medication, briquilimab, will be used. This medication is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat SCD. We are testing it in this research study to see if briquilimab, alemtuzumab, and low dose radiation might be better than alemtuzumab and radiation to prepare you for hematopoietic cell transplant.

WHAT WILL HAPPEN DURING THE STUDY?

If you decide to take part in this study, you will be asked to participate in study procedures and take the following drugs:

A. Pre-transplantation evaluation

On this visit to the outpatient clinic, the transplant team will take medical histories, perform physical examination, and explain the transplant procedure. About 6 tablespoons of blood will be drawn to confirm the diagnosis, to check previous exposures to common viruses, and determine the level of liver and kidney function and about 4 tablespoons for research. Tissue (human leukocyte antigen, or HLA) and blood (group A, B, O, or AB, short for ABO) typing will be repeated between you and the donor, even if the typing was done elsewhere.

Breathing tests, tests of heart function, chest x-rays, are done to make sure these organs are in ready shape for transplantation. The teeth and eyes are checked and any problems treated that could cause complications during the transplant. Also, you may see an endocrine doctor to assess fertility and other hormone producing glands such as your thyroid. Bone marrow sampling of approximately a tablespoon from the pelvic bone will be done to check the status of your marrow and for research.

You will meet with our social worker who will discuss the psychological issues related to the transplant, explain the potential costs, and provide information and resources so that you can find an appropriate place to stay during the transplant period. The social worker will also provide you with education and assistance with advanced directives and assigning a durable power of attorney. It is mandatory that a family member or friend stays with you once discharged from the hospital to help with chores, cooking, and transporting back and forth from the clinic.

B. Line placement

There are several situations where a different and larger intravenous line is needed for infusing donor blood stem cells. The line is placed in under local anesthetics, sedative medication, or general anesthesia in the radiology department, or even more rarely in the operating room. It enters the body in the upper part of the arm or chest and may be tunneled under the skin into a vein in the chest or neck.

C. Collection of your own blood stem cells

In the earlier transplant study with alemtuzumab and low dose radiation, there were a few patients whose transplant were not successful, and it took nearly two months for blood counts to recover. We are adding briquilimab antibody to alemtuzumab and radiation; this combination may change how fast blood counts recover after transplant. To minimize your time of having low blood counts, we plan to collect your own blood stem cells as a 'back-up.' We will give these back to you if your blood counts have remained very low for more than a month.

For this collection, you typically stay in the hospital for about a week. A special intravenous line is inserted. For SCD patients, red cell exchange and 1-2 days of plerixafor are planned. For beta-thalassemia patients, we monitor your blood counts and use 3 to 6 days of filgrastim and 1-2 days of plerixafor. If we are unable to collect enough cells during 1 cycle of collection, we may ask you to return after about 4 weeks later for repeat collection.

- HIV Testing: As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will still be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

D. Bone marrow suppression and immunosuppression

- **Hydroxyurea:** Is commonly given to reduce the complications of SCD, or to boost hemoglobin levels in those with beta-thalassemia. If you are taking hydroxyurea, we will continue this medication until the time of transplant. If you are not taking hydroxyurea, we

will start and keep you on this for about 1-3 months to help prepare your bone marrow for the transplant.

- **Briquilimab (also known as JSP191c-kit antibody):** Is an antibody given intravenously for 1 dose. It binds to the immature cells in the bone marrow and makes radiation more effective in making space in your bone marrow for donor cells.
- **Alemtuzumab (Campath-1H):** Is both an antibody drug and an immunosuppressant. It will be given for 5 days to lower your immune system so that donor cells can take hold (or engraft).

E. Graft versus host disease prevention with sirolimus (rapamycin)

One day before donor stem cells are infused, you will begin taking an oral medication called sirolimus. Sirolimus works by eliminating and decreasing the activity of immune cells called T-lymphocytes, and helps to re-educate the maturing transplanted immune cells to tolerate the residual recipient immune cells.

F. Transplantation

One day after radiation and sirolimus, the donor blood stem cells are infused. This process takes about 8 hours, sometimes longer. Blood stem cells circulate throughout the body, naturally lodge in the bone marrow spaces, and slowly begin to make blood cells. Initially the blood counts fall because some of your own marrow cells have been killed by the antibodies and radiation. After about 2-3 weeks, the first signs of the growth or "engraftment" of the donor's stem cells should be seen, with a gradual rise of white cells, platelets, and red cells. Before full recovery, you may need transfusions of red cells to prevent anemia, and platelets to prevent bleeding if necessary.

In the first few weeks following the transplant, you may develop a fever due to infection, transfusion reactions, reactions to drugs, or graft versus host disease. Because the most serious cause of fever is bacterial infection, we will automatically start intravenous antibiotics if the fever rises above a certain temperature. There may be other unpleasant symptoms including nausea, diarrhea, and mouth or belly pain. You may receive these treatments when your counts are low: other types of antibiotics, blood or platelets transfusions, intravenous feeding, and other medications to treat symptoms. This is a normal part of the transplant process.

Following the transplant, your mood/depression, anxiety, self-image, or other pre-existing medical or mental condition(s) may worsen. If you have a history of these problems or believe you experience any of these problems following the transplant, please contact the research team immediately.

G. Leaving the hospital

The average length of stay after transplant is 30 days. You will be able to leave the hospital when you are eating normally, have no fever, and the blood count has risen to a minimum of 500 neutrophils (these are the white cells that fight bacterial or fungal infection). We will discontinue some of the antibiotics, but continue antiviral medications (such as acyclovir), other antibiotics (Bactrim and penicillin VK or equivalent), and antifungal medications (nystatin). At this stage, you may still feel weak and short of stamina. Full recovery to normal physical fitness takes at

least several months and the initial process may seem slow. Foods may not taste normal and it may be an effort to take in enough calories to maintain your weight.

H. Follow-up after transplant

Up to 2 to 3 months after transplant: you will come weekly or twice weekly to the outpatient clinic. Even if you are feeling well, there are serious complications that we look for, and treat immediately even before they cause symptoms. For this reason, we require you to stay within one hour of the NIH for the first 3 months after transplant. At each visit we ask about symptoms, carry out a physical examination, and check blood tests to monitor blood counts, immune function, organ function, and blood mineral levels. We may also draw about 3-4 tablespoons of extra blood for research. We will monitor for the development of a serious viral infection called cytomegalovirus (CMV) by blood testing. If we see signs of the virus in your body, we start treatment immediately. We will also look for signs of graft versus host disease. Day 100 post-transplant is a significant time point when we perform a comprehensive evaluation, similar to the pre-transplant testing.

After 3 months: If you are stable at day 100 or soon thereafter, you can return home if you temporarily relocated to the Bethesda area. You will be followed by your primary doctor, who will receive a summary of your care, a list of blood tests that should be checked, and will be encouraged to communicate any problems to us so that we can advise on the best approach. We will continue to see you as needed but will schedule follow up visits at 6, 12, 24, and 36 months after transplant. After that time, we would like to see you or hear from you on a yearly basis. During these visits, we will be monitoring transplant outcomes with blood tests, possibly bone marrow aspiration and biopsy and extra blood (3-4 tablespoons) for research.

Most patients have engraftment of donor cells but still have some of their own residual bone marrow cells following the transplant. This is called mixed chimerism. A test will be performed on some of your blood and/or bone marrow after the transplant to confirm donor engraftment. At 1 year following the transplant, we may start to taper off the sirolimus.

I. Neuropsychological and quality of life testing

Neuropsychological testing involves answering questions to see how you learn, solve problems, pay attention, and remember things. Depending on your age, testing will take 3.25 or more hours, and will take place prior to transplant, at 12 and 24 months following transplant.

A brain MRI scan will take place at 12 and 24 months post-transplant as part of neuropsychological testing. We will review the test results with you.

You may be asked to complete questionnaires about pain and quality of life (everyday functioning) before your transplant, 100 days, and then 12 and 24 months after transplant. These questionnaires will take about 10-30 minutes to complete at each visit.

J. Reproductive health testing

You will be asked to complete a questionnaire assessing reproductive health before your transplant and at approximately 12 months and 24 months after transplant. You can choose not to take this questionnaire; this will not affect the care that you will receive.

K. Brain, liver and heart MRI

MRI is a technique using magnetism, not x-ray, to detect abnormal structures in the body. A MRI of your heart may be performed at baseline and post-transplant to assess your heart function. These scans are performed initially with no gadolinium (contrast), but if an abnormality is detected, an additional MRI may be performed with gadolinium.

The MRI scanner is a large hollow tube. You will lie flat on a table that can slide in and out of the tube. While the scanner makes pictures, you will hear a knocking sound. Headphones or earplugs will be provided to you to muffle the noise. We will ask you to hold your breath intermittently for about 5-20 seconds. You will be in the MRI scanner for about 45-90 minutes. There are microphones so you can talk with the technicians. At any time, you may request to stop the study and will be removed from the MRI unit. Please tell the investigators if you suffer from claustrophobia (fear of enclosed spaces).

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement during the treatment portion of the study is expected to last for 36 months.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 90 people (donors and recipients) participate in this study at the NIH Clinical Center.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

There is a possibility that you may continue to experience symptoms related to your prior disease, such as bone or joint pain. Although there are risks associated with any procedure or treatment, many of the risks in this section are expected for any stem cell transplant.

a. Hydroxyurea

The common (more than 30%) side effects are lowering of the white blood cell count, and at higher doses can also lower both red blood cell and platelet counts. Your blood counts are monitored regularly to make sure it is properly dosed. Less common (10% - 30%) side effects include fatigue, stomach pain, skin and nail bed changes. Rare (less than 10%) side effects include infections and bleeding from low blood counts.

b. Line placement

The risks from this procedure are low, including lightheadedness, bleeding, bruising or infection at the site of insertion or rarely, fainting due to temporary lowering of blood pressure. You may feel some discomfort and stiffness in your arm, chest, or shoulder for a few days after the line has been placed. Very rarely, there may be collapse of one lung during line insertion. If the lung collapses, another tube may have to be inserted through the skin into the chest and remain in place until the lung re-expands. Because of this a chest x-ray following the procedure will be done to make sure the line is in the correct place and that the lung is not collapsed. We will leave the line in for as long as necessary, which may be from one week to 3 months. If the line becomes clogged or infected, it may have to be replaced by a new line. The line may need to be flushed once a day to prevent clogging and you will be taught by the nursing staff how to do this yourself.

c. Plerixafor

In general, plerixafor has been well tolerated in healthy volunteers or individuals with sickle cell or beta-thalassemia but has been associated with side effects. Common (more than 30%) ones are gastrointestinal-related: nausea, vomiting, diarrhea, passing gas, decreased appetite, and pain and/or swelling of the abdomen; injection related: redness, burning, bruising, pain, itching, or swelling. Less common (10% - 30%) symptoms are neurologic-related: dizziness, headache, disorientation, tingling, or ringing in the ears. Rare (less than 10%) symptoms include: chest tightness, heart racing, pain, or enlargement of spleen.

d. Filgrastim (G-CSF)

Filgrastim (G-CSF) commonly (more than 30%) cause bone pain (usually mild), muscle aches, headache, fatigue, insomnia, and increases in white cell counts. Less commonly (10% - 30%), it causes fever, worsening of pre-existing skin rash, brief decrease in platelet count (usually mild without increased risk for bleeding), and transient and reversible elevation of liver enzymes (possibly brief inflammation of the liver). Pain can be treated with acetaminophen (Tylenol) and will decrease once G-CSF is discontinued. Very rarely (less than 1%), G-CSF has caused a rupture of the spleen requiring urgent surgery, chest pain or heart attacks in those with serious heart disease, bleeding into the lungs in those who smoke cigarettes, blood clots, or stroke.

e. Apheresis and collection of stem cells

It is a standard procedure that includes placing a temporary plastic tube (intravenous line) into a vein in each arm or a central line. Blood flows from one vein to the apheresis machine, where the white blood cell fraction containing stem cells is collected and saved. The remaining blood is infused back through the vein in the other arm. This procedure takes about 4-6 hours and is performed by trained nurses who are supervised by Blood Bank staff.

Apheresis is less burdensome and avoids the need for an operation under general anesthesia to take the bone marrow cells from your hip bones (also called marrow harvesting). The cells obtained by apheresis have the same or greater capacity to restore normal bone marrow function as cells collected directly from the bone marrow.

f. Briquilimab (also known as JSP191 c-kit antibody)

Briquilimab is given as an intravenous drug. The common (more than 30%) side effects include respiratory symptoms such as cough and temporary decrease in the number of blood cells where you may need transfusions. Less common (10% - 30%) side effects include respiratory or other infection, allergic reaction (rash/hives, swelling of throat, mouth, or tongue), sores/pain in mouth or throat. Rare (less than 10%) side effects include life-threatening anaphylactic reaction (blood pressure changes, trouble breathing, irregular heartbeats), changes in liver or kidney function, or blood counts remaining low.

Briquilimab and alemtuzumab have been shown to decrease sperm production in mice and/or humans. Therefore, in the first few months after transplant, we expect temporary or little to no sperm production. We do not know if or when normal sperm production will return to levels before transplant. There are also unknown long-term effects to fertility or sex hormone production. These risks are estimated to be low at this time.

g. Alemtuzumab (Campath-1H)

This medication is given subcutaneously. The common (more than 30%) side effects are infusion-related: fever, chills, nausea, and changes in blood pressure. Less common (10% - 30%) side effects include diarrhea, rash, shortness of breath, fatigue, headache, and bone pain. We give medications before starting alemtuzumab to minimize these effects and monitor closely.

There are also infection-related effects, which are related to low white cell count, when your body is less able to fight off infections for a number of months after receiving this antibody. These infections can be very severe and even result in death. These infection risks are also true of patients who undergo transplant without using alemtuzumab.

Alemtuzumab also cause other blood related changes, where the number of red cells and platelets remain low. Other rare (less than 10%) side effects are cardiac-related: palpitations, irregular heartbeat, difficulty breathing, dizziness, swelling in your ankles, chest discomfort, or pain. Another is liver-related: changes in blood test results that may indicate liver injury, pain the abdomen, swelling of legs and torso, bleeding, fatigue, yellow skin or eyes, or loss of appetite. These changes tend to occur within a week of receiving alemtuzumab . We have also seen thyroid-related changes in blood testing that may indicate over- or under-active function. Symptoms of an abnormal thyroid gland may include fatigue, weight gain, tremor, change in energy level, or hair loss. These changes could occur one or more years after transplant. We may ask specialist doctor to confirm diagnosis and help with treatment. Other side effects can be found in the prescribing information.

h. Sirolimus

The side effects of sirolimus are usually mild and are reversible when you stop the drug. They can be found in the prescribing information.

The common (more than 30%) ones include: higher amount of cholesterol and fat in blood, pain in joints and/or muscles, muscle injury, swelling in your hands, arms or legs, decrease in blood counts, and changes in the levels of some of the salts or minerals in your blood. These levels will be monitored and may need to be replaced. We will also follow blood levels of the drug to make sure that you are getting the right dose, which reduces the likelihood of the complications listed above. Because sirolimus is an immunosuppressant, you may be at higher risk for developing infections, especially it is given in combination with alemtuzumab and other transplant related drugs. These infections can be mild to life threatening and you will need to be monitored for at least 6 months after the transplant even if the transplant does not take. Less common (10% - 30%) complications include headaches, mouth ulcers, fluid build-up elsewhere, difficulty breathing, inflammation around the heart, protein spilling in the urine, and kidney injury. Sirolimus also has been rarely (less than 10%) reported to cause PRES (posterior reversible encephalopathy syndrome which is a presentation of confusion and/or seizures), slow wound healing after surgery and a severe form of red cell destruction.

i. Stem cell infusion, red cell or platelet transfusion

Some temporary side effects that may occur during the infusion of blood stem cells include: nausea, headache, increased pressure in your blood or lungs, abnormal heart rhythm, or decrease in kidney function. These abnormalities generally return to normal after the infusion is complete.

Transfusions of red cells, platelets, including the infusion of donor blood stem cells, can cause fevers or allergic reactions. We will monitor carefully during the first hour after any administration of blood or blood stem cells and give medications to counteract side effects if they occur.

Because stem cell transplantation affects the whole body, damages can occur to the brain, heart, kidney, liver, and lung from causes other than those mentioned. Infections from very rare organisms can occur which are unpredictable. Damages can occur to the brain, heart, kidney, liver, and lung from causes other than those mentioned. Full allogeneic transplant carries about 5% chance of death from complications of the transplant. Although we have good reason to believe this low intensity transplant has a low death rate, the procedure still carries some risk. Your actual estimated risk will depend on your age and the amount of damage you may have from the anemia and/or iron overload on your organs.

j. Graft versus host disease (GVHD)

GVHD is when donor T-lymphocytes attack your own cells, causing serious damage to your vital organs. Although we believe that this treatment decreases the risk of serious GVHD, it may still occur. You will be monitored regularly for GVHD and treated with appropriate medications (see below).

- **Acute GVHD** in the gastrointestinal (GI) tract can cause nausea, abdominal pain or cramps, diarrhea, loss of weight, and loss of appetite. Sometimes you may need intravenous feeding temporarily until your gut has had time to heal. Furthermore, a special test called an endoscopy may be performed, where a flexible tube will be inserted into the GI tract and a small sample of tissue removed to help with diagnosis. We will ask for a separate consent before performing this procedure. Occasionally (in less than 5% of cases), it can be fatal. When GVHD affects the skin, rash with itching or skin peeling can occur. When GVHD affects the liver, abdominal pain, changes in liver function blood test, and/or skin yellowing can occur.
- **Chronic GVHD:** A delayed form of GVHD may also occur. It can be mild to severe and can take the form of hardening of the skin and soft tissues, dry mouth from failed saliva production, gritty eyes from reduced tear production, digestive problems leading to weight loss, liver damage leading to yellowing of the skin, and lung damage leading to progressive shortness of breath and chronic cough. Patients with chronic GVHD are also more at risk from infection.
- **Treatment of GVHD:** Treatment of GVHD will depend on the severity of the symptoms. Mild GVHD causing skin rash only may not require treatment. If the symptoms are easily controlled, we may treat as an outpatient. More severe GVHD often requires re-admission to the hospital and treatment with steroids starting at a high dose, decreasing rapidly to a low dose to reduce serious side effects. Other treatment may include limiting your diet, providing fluids through an intravenous line, and providing medications to treat the GVHD or control the risk of infection. Most GVHD respond to treatment. However, some GVHD

may be unresponsive to treatment, leading to major changes in your daily activities and/or death.

k. Possible transplant outcomes

Although we added briquilimab antibody to alemtuzumab, radiation, and sirolimus, this transplant is still a marrow sparing preparative (low intensity) transplant. The donor cells may first engraft, but appear to decrease near month 2 or later, sirolimus may be increased or restarted, and other medications (such as steroids and/or other immunosuppressants) may be added. We may also discuss a stem cell 'boost' from the original donor. If donor cells are no longer present, your own bone marrow and blood cells should return, but the severity of disease should be less. We may discuss restart sickle cell or beta-thalassemia specific treatments, or other ongoing clinical trials with your home providers.

Since briquilimab and alemtuzumab antibodies can last in your body for days or a few weeks after infusion, there is a small chance donor cells may fail to engraft within the first month after transplant. In the rare situation where your own bone marrow and blood counts do not return, we may infuse your own 'back-up' cells or discuss the possibility of another transplant.

Because this is not a full transplant, your remaining immune system (antibody to donor red cells) can persist and cause anemia (fatigue, less physical stamina, or even shortness of breath). These antibodies to red cells may last for months after transplant, and you may need red cell transfusions for a few to possibly many months. If the antibody remains a problem beyond 1 or 2 years, we may treat with corticosteroids and/or other medications. Sometimes your remaining immune system (antibodies or immune cells) can cause severe bleeding, not related to anemia, where you need different combination treatments to correct the condition.

To date, a few patients have developed acute leukemia, also known as cancer of the bone marrow white cells. This rate is higher than we expected. There is no clear pattern to why the leukemia occurred. The cause includes one or more of the following conditions: prior sickle cell, previous use of hydroxyurea, radiation, infection, or immunosuppression. Treatment for acute leukemia usually involve leukemia-specific chemotherapy, leukemia-specific antibody or immune therapy, or another hematopoietic cell transplant.

l. Cytomegalovirus (CMV) and other viral reactivation

Because of the immunosuppression from the transplant and sirolimus, you are at increased risk for dormant virus in your body to start multiplying and lead to symptoms or infections after transplantation. These viruses include CMV, adenovirus, Epstein-Barr virus, "chicken pox" virus, and others. Most adults may have been exposed to these viruses, and the viruses were inactive in the body, causing no problems. When your immune system has not had time to recover and work fully after a transplant, one or more viruses can "wake up" and cause severe damage to your body: fatal pneumonia, bladder irritation leading to blood in the urine, cancer in the lymph glands, rash, or abdominal pain. Part of the monitoring after transplant is to detect these viruses by one or more very sensitive tests. This monitoring will be weekly for the first 2-3 months and then periodically thereafter. If reactivation of a virus occurs, we will start an antiviral medication, which is usually effective when diagnosed early.

m. Veno-occlusive disease

In some patients, radiation followed by allogeneic transplantation results in damage to the liver causing blockage of its blood vessels and in severe cases liver failure and death. This complication occurs in less than 5% of patients undergoing full transplant and less frequently with low intensity transplants. Unfortunately, it is hard to predict who will develop this complication. Treatment is usually aimed at reducing symptoms, but up to half of patients with severe veno-occlusive disease dying.

n. Neuropsychological Testing

Talking about being ill or answering questions about your illness is difficult for some people. While neuropsychological testing may be interesting to many, some parts may be challenging, even to the point of becoming frustrated or tired. You may take a break if you become distressed or tired. You can stop the testing if you don't want to continue, and you don't have to answer every question. It is possible we may find problems that require the attention of a mental health care professional. We will let you know and make recommendations for follow-up if needed. A psychologist, psychology associate, or clinical social worker will be available if you would like to speak with a mental health professional.

o. MRI of the heart, liver, and brain

Magnetic Resonance Imaging (MRI): MRI is a technique using magnetism, not x-ray, to detect abnormal structures in the body. It does not cause physical pain. You should inform the doctors if there is any metal in your body. Patients are at risk for injury from MRI if they have: a cardiac pacemaker, neural pacemaker, aneurysmal clips, shrapnel fragments in brain, metallic ocular foreign body, or metallic cochlear implants. Please tell the investigators if you have any implanted or magnetically activated device (e.g., insulin pump or non-MRI compatible metallic ear implant), as you will not be able to have the MRI scan.

Although rare, some pediatric patients may require oral or IV sedative medication for the MRI brain scan. In this case, a separate consent will be reviewed with the parents. Risks related to pediatric sedation include but are not limited to nausea and vomiting, gastritis, diarrhea, prolonged sedation, abnormal movements, agitation, and slow breathing.

p. Gadolinium

Gadolinium contrast is an injected medication used to improve MRI images. Most patients experience a metallic taste when gadolinium contrast is injected. Some (<2%) report mild symptoms such as headache, nausea or vomiting, or a rash near the injection site. Rarely (<0.1%) patients experience severe symptoms such as wheezing, shortness of breath, and low blood pressure as part of an allergic (anaphylactoid) reaction that may require emergency medical treatment.

In a few cases per million, usually in patients with severe kidney disease, gadolinium contrast can cause a rare, debilitating or even fatal, skin disease called Nephrogenic Systemic Fibrosis (NSF) that causes thickening of the skin and other organs. Since physicians became aware of the disease, began screening patients at risk of kidney disease, and switched to safer ("macrocyclic") forms of gadolinium contrast, new reports of NSF are much rarer.

There are also reports of gadolinium retained in the brain, bone, and skin. It is not known whether this is important to health. We use "macrocyclic" forms of gadolinium contrast, such as gadobutrol, that are thought to reduce this risk. We request that you report to us all gadolinium contrast exposure you have received over the previous year. We will also provide you with a gadolinium medication guide, per FDA guidance.

You may receive doses of gadobutrol (gadolinium contrast) higher than the U.S. Food and Drug Administration (FDA) has approved for MRI of the heart to optimize imaging.

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to use effective birth control methods and try not to become pregnant throughout the study and 12 months after transplant. You will have a pregnancy test prior to starting this study. If you become pregnant, there may be unknown risks to the fetus or unborn child that we did not anticipate. Also, there may be long-term effects of the treatment that could increase the risk of harm to a fetus. You must tell the study doctor if you think or know you have become pregnant while participating in this research study. If you plan to become pregnant in the future, please discuss this with the study team.

If you are a sexually active person with a partner who can become pregnant, you and your partner must agree to use acceptable birth control prior to enrolling in this study. It is important that your partner not become pregnant before, during, or within a few months after transplant. There may be unknown risks to a fetus or risks we did not anticipate. If your partner has become pregnant during your participation in this study, please contact the study team as soon as possible. If your partner plans to become pregnant, please also discuss this with the study team.

What are the risks of radiation from being in the study?

During your participation in this research study, your skin, bones, and bone marrow will be exposed to 300 cGy of radiation from Total Body Irradiation (TBI). You will also receive a much smaller amount of radiation from scans used to plan your treatment and measure your progress. Theses scans include DEXA and chest x-ray. The amount of radiation from these scans adds minimal additional risk to the higher radiation doses received in the course of treatment. This radiation has been reviewed by the NIH Radiation Safety Committee and deemed appropriate for this study.

The radiation exposure from bone density scans is not necessary for your medical care and is for research purposes only. The radiation exposure is very small compared to the 300 cGy of TBI used for transplant. Thus, most of the side effects and risk discussed here are mainly from TBI. The most common of other side effects include headaches, nausea, swelling of the salivary glands in your cheeks, mouth sores called mucositis, and skin darkening. A week after TBI, your marrow may temporarily stop making red blood cells, white cells, and platelets. From then on, you will initially rely on blood or platelet transfusions, then later your donor's stem cells to supply new blood cells. Less commonly, radiation can cause your thyroid to stop normal functioning, damage the lungs, and very rarely cause cancer. The risk of cancer (in organs, lymphoid system, or bone marrow) appears to be related to the dose of radiation given as well as to the degree of immunosuppression, and with the dose being given here, the risk is significant. There is also an

undetermined risk of becoming infertile as a result of radiation. Although infertility is uncommon with this dose of radiation, this cannot be entirely ruled out. Therefore, if you wish to have children after the procedure, discuss sperm or egg storage with the transplant doctors.

If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects.

Please tell your doctor if you have taken part in other research studies or received any medical care at the NIH or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization, fluoroscopy, and nuclear medicine scans in which radioactive materials were injected into your body.

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You may or may not benefit from being in this study. However, by enrolling in this study, there is a chance that your disease may be cured, but this cannot be guaranteed. The tests in this study are performed to diagnose or better understand how your organs have been affected by sickle cell or beta-thalassemia. The procedures are to ensure the main parts of the transplant can be carried out safely.

Are there any potential benefits to others that might result from the study?

In the future, other patients might benefit from this study because you contributed to new ways of making transplant procedures safer and more effective.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Patients with sickle cell disease and beta-thalassemia may have other treatment options. These treatment options vary depending on your age, treatment history, and complications. Before you decide to enroll, we will discuss options such as continuing with hydroxyurea or sickle cell medications, luspatercept or other thalassemia medications, red cell transfusions and iron chelation. Other options with curative intent include a different half-matched (haploidentical) donor transplant study, the Food and Drug Administration (FDA)-approved gene therapy (Lyfgenia) and gene editing (Casgevy) treatments, other gene manipulation type of transplants, transplant using high intensity (myeloablative) or reduced intensity, and/or other experimental therapies. We can assist with referrals.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will explain what we have learned. This may be information we learned from this study, or from other scientists doing similar research in other places.

Return of research results

We do not plan to give you any individual research results.

EARLY WITHDRAWAL FROM THE STUDY

You may withdraw from this study at any time. This decision will not affect your legal rights or the quality of health care that you will/may receive at NIH. At any time, the study doctor may tell you to stop taking part in the study. This may happen if you have a health-related event during the course of the study, you do not follow the instructions given by the study doctor, or if the study doctor believes it is in your best interest.

If you receive conditioning, you should not withdraw from the study without receiving donor cells to minimize the risk of having low blood counts (aplasia). After you receive the donor cells, you should try not to withdraw without receiving the medications to ensure donor stem cells take hold (engraft) and prevent possible donor immune cells causing injury to organs such as GI tract, skin, or liver (graft-versus-host disease) and/or infection. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding sickle cell disease, beta-thalassemia, or other related diseases or conditions. This could include studies to develop other research tests, treatments, drugs, devices, or that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data may be stored by the NIH possibly indefinitely or until they become irrelevant and are destroyed with the IRB approval.

Risks of Storage and Sharing of Specimens and Data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

PAYMENT

Will you receive any type of payment for taking part in this study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will be offered compensation for your time and inconvenience for participation and completion of questionnaires related to the research study as detailed below:

Financial Compensation Details				
Procedure	**Frequency**	**Compensation per Survey**	**Male Total**	**Female Total**
PROMIS QoL (male and female)	once / year, *Day 100	$20	*$20	*$20
Changes in Sexual Function Questionnaire (male and female)	once / year	$20	$20	$20
Fertility Survey (female only)	once / year	$20	N/A	$20
Priapism Impact Questionnaire (male only)	once / year	$10	$10	N/A
International Index of Erectile Function (male only)	once / year	$10	$10	N/A
Potential Total (USD)			$60	$60

*(*In the first year, subjects may receive up to $80 total if the Day 100 PROMIS survey is completed along with the other specified surveys for that timepoint.)*

If you are unable to finish the study, you will receive compensation for the questionnaires you completed.

We will need to collect your social security number to compensate you. You may withhold your social security number and still participate in the research study; however, you will not be able to receive compensation if you do.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

Will you receive reimbursement or direct payment by NIH as part of your participation?

This study offers reimbursement for, or payment of, travel, lodging and meals.

For the guardian, the protocol-specific standard rate for meals is $15.00 per day. For the patient, the protocol-specific standard rate for hotel lodging is $80.00 per night up to 7 nights, then the rate decreases to $30.00 per night for subsequent nights. If you live more than 30 miles away, we will reimburse you $0.40 per mile driven.

If your travel to the NIH Clinical Center (for example, flight and/or hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

Although we do not ask you to pay for your medical treatments and hospital costs, it is your responsibility to arrange for all the non-medical expenses (housing, meals, transportation, etc.) for yourself and your family before, during, and after the transplant procedure (about 4 months).

CONFLICT OF INTEREST

The NIH reviews NIH staff researchers at least yearly for conflicts of interest (COI). This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

The NIH and the research team for this study are using briquilimab developed by Jasper Therapeutics, Inc. through a collaboration between your study team and the company. The company also provides financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board (IRB)
- The study Sponsor National Heart Lung and Blood Institute or their agent, Jasper Therapeutics, Inc.

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy

Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the site Principal Investigator, John Tisdale, M.D., johntis@mail.nih.gov, (301) 402-6487. Other researchers you may call are: Matthew Hsieh, M.D. at (301) 402-7687 or Kelly Norris, RN at (301) 529-7104.

For questions about your rights while in this study, call the NIH Clinical Center Patient Representative at (301) 496-2626 or the NIH Office of IRB Operations at (301) 402-3713, If you have a research related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Parent/Guardian of a Minor Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I give permission for my child to take part in this study.

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date
Signature of Parent/Guardian	Print Name of Parent/Guardian	Date

Assent: I have had this study explained to me in a way that I understand, I have been given the opportunity to discuss it, and I have had the chance to ask questions. I agree to take part in this study.

Assent of Minor:

Signature of Minor	Print Name of Minor	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

_____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

_____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is:

_____.