Informed Consent Cover Page for FDAAA consent posting:

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STUDY TITLE: Non-myeloablative Phase I/II Haploidentical HCT Study for Patients with Sickle Cell Disease, Including Compromised Organ Function

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

Cohort: Adult Recipient

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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.

Transplant may cure patients with sickle cell disease (SCD). A hematopoietic cell transplant (HCT) is a procedure where blood "stem cells" from a donor are given to you through a plastic tube in your veins. These cells may grow into the different cells that make up your blood and your immune system. Your pre-transplant testing shows that the disease is serious enough to justify a transplant; and, you have a family member who is a possible donor.

We ask that you participate in our research study to find out if transplant with a new combination of drugs and radiation, including an investigational drug called briquilimab, is less toxic and better tolerated in patients with SCD, including those with organ damage (compared to a standard hematopoietic cell transplant).

Briquilimab is considered investigational because it has not been approved by the Food and Drug Administration (FDA).

Also, not everyone with SCD who gets a HCT is cured. We cannot predict whether you will benefit from taking part in this study. You may prefer to have standard sickle cell treatments instead, or to have a transplant at another hospital without enrolling in this study.

If you join this study, we will follow you on this study for 5 years after the transplant.

If you join this study, here are some significant things that will happen:

Screening and Pre-transplant evaluation: You will have tests and evaluations to determine if you are a suitable candidate for this study. We will do many tests to find out how sickle cell

disease has affected your organ function. We will also take about 2 tablespoons of your bone marrow from your pelvic bone. We will check the condition of your marrow for research. We will also collect your own stem cells as a back-up in case the transplant does not work. Last, our social worker will speak with you to discuss related issues to the transplant. A family member or friend must stay with you after you are discharged from the hospital to assist with day-to-day activities.

Transplant: To prepare your body to receive donor blood stem cells, you will undergo treatment called "conditioning". Over 6-13 days, you will get briquilimab, alemtuzumab and abatacept; these are drugs that will help your body to accept the cells along with a dose of total body radiation. The donor's blood stem cells are then infused into your body, which may take 8 or more hours. After receiving cells from your donor you will receive 1-2 days of cyclophosphamide, and start sirolimus, and you will continue to receive abatacept at regular intervals until 6 months after your transplant.

In the days and weeks after the transplant, you may need medicine(s) to manage complications, such as nausea, diarrhea, fever, or pain. You may also need periodic transfusions of red blood cells and platelets until your bone marrow begins making enough of those cells on its own.

Leaving the hospital: The average hospital stay after transplant is 30 days, but may be shorter or longer. Full recovery to your normal physical fitness takes at least several months.

Follow-up after transplant (post-transplant):

> ***Day 100 post-transplant:*** In the first 100 days after transplant we will monitor your health closely and will have you come in for frequent visits. 100 days after the day you receive your cells (Day 100) is a significant time point when we will do a thorough evaluation, much like the pre-transplant testing.
>
> ***After 3 months post-transplant***: If you are stable at day 100 or soon after, you can return home if you temporarily relocated to be close to the NIH hospital. We will schedule follow-up visits at: 6, 12, and 18 months, as well as at 2, 3, 4, and 5 years post-transplant. We may also schedule other visits as needed.

Costs: Some of your expenses, such as travel and part of your lodging, and/or meals may be covered. NIH staff will work with you to review the costs of taking part in our study and what we are able to support.

You are free to stop participating in the trial at any time. However, once you start the conditioning and/or get the cells, these things cannot be undone. And you will need to be followed closely for months or years after transplant for safety reasons. Thus, we want you to fully understand the requirements to have a transplant. You need to understand the extent and length of your commitment before deciding to take part. We will discuss these with you and answer your questions.

Once you receive conditioning, you should not withdraw from the study:

- Without receiving donor cells to minimize the risk of having dangerously 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 your gut, 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.

The remaining document describes 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, 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. However, once you receive the conditioning and the cells this is highly discouraged for your own safety. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. 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?

The purpose of this research study is to find out if transplant that involves an antibody medication, briquilimab, combined with a drug to help re-educate your immune system, abatacept, another antibody medication, alemtuzumab, and radiation, is less toxic and better tolerated than standard stem cell transplant in people with sickle cell disease (SCD), including those with organ damage (compared to a standard hematopoietic cell transplant).

We are asking you to join this research study because you have SCD in which transplant has been shown to be curative. Hematopoietic (blood) cell transplant is the same as bone marrow transplant or stem cell transplant. Traditional stem cell transplant involves the use of high-dose chemotherapy and often radiation to destroy bone marrow cells, and replace them with a donor's normal marrow stem cells. The donor cells (graft) find their way to the bone marrow where they make normal functioning red blood cells. You have a family member who is a proper tissue match and your pre-transplant testing shows that your disease is severe enough that you need a transplant.

In this study, an investigational antibody drug, briquilimab, will be used. This study drug 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,

abatacept, alemtuzumab, and low-dose radiation used together might be better than just 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. Screening and Pre-Transplant Evaluation

On your initial visit, we will run tests to see if you are eligible. About 6 tablespoons of blood will be drawn to confirm your diagnosis, to check previous exposures to common viruses, and check your liver and kidney function. 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.

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 be 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 who are at possible risk because of your HIV infection.

If you are eligible to join the study, some of the tests may be repeated when you are ready for transplant. During those visits, the transplant team will record your medical history and do a physical exam. About 9 tablespoons of your blood will be taken for research.

The following tests and procedures may be done at screening and/or shortly before your transplant:

Pulmonary Function Tests (Breathing Tests): This test involves blowing into a machine and measuring your breathing and lung function.

6-Minute Walk Test: The six-minute walk test is performed by asking you to walk laps over a level walkway over a period of 6 minutes while your heart rate and oxygen saturation are monitored. Maximal distance walked over 6 minutes is recorded; this provides a rough estimate of your heart and lung function.

Electrocardiogram (ECG): An electrocardiogram (ECG or EKG for short) is a test that looks at electrical activity of your heart. You will need to lie still for about 5 minutes. We will place electrodes on your chest, arms, and legs. Electrodes are small stickers that are attached to wires that go to the machine. Your heart's signals are recorded by the machine.

Holter Monitor: We will ask you to wear a holter monitor. This is a type of portable ECG to record your heart rate for 24 – 48 hours.

Echocardiogram: You will have an echocardiogram done as part of this study. An echocardiogram is a painless test using sound waves to take a picture of your heart. During this test, we will put some gel on your chest. We will then put the ultrasound probe on your chest and take the picture. We may ask you to lay on your side to get a better picture. The scan takes about 30 minutes to complete.

Brain MRI: An MRI makes pictures of the inside of your body using strong magnets instead of x-ray energy. At the time of each scan, you will be asked to fill out a screening

form to verify that it is safe for you to have the scan. You will also be asked to remove any metallic objects you are wearing (for example, watches, earrings, or piercings). We may ask you to change into a hospital gown.

Then you'll be asked to lie on a narrow bed that will move into the MRI scanner. The scanner is a long, narrow tube that is open at each end. Once you are comfortable, the table will be moved into the scanner. You will need to lie still on the table during the scan. The scan will take about 30 minutes to complete. You will hear normal "hammering" or clicking and squealing noises during the scan. We will give you earplugs or earmuffs to muffle the sound. You will be able to communicate with the technician running the scan the entire time. We will also give you an emergency button to squeeze at any time if you want the scan to stop.

Medical Consults: As needed, you may also be evaluated by disease specialists. For example, you may have your teeth and eyes checked. You also may see an endocrine doctor to assess fertility and or other hormone-producing glands such as your thyroid. Any results from tests done by these specialists may be used for this study and become part of the research data.

Visit with Social Worker: 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 help with assigning a durable power of attorney. In order to proceed with the transplant, we will first make sure that there is a person identified to be your "caregiver." Your caregiver will need to be with you at all times especially after you are discharged from the hospital. They will help make sure that you are taking your medications appropriately, that you come to your follow-up appointments, watch for new symptoms, and to be available to assist you as necessary. Your caregiver will require specific training about how to help you when you leave the hospital.

B. Pregnancy Issues

Females

Sirolimus, one of the drugs you will receive post-transplant, is known to increase the risk of birth defects and miscarriage in humans when taken during pregnancy and may have risks for breastfed infants. Therefore, people who are pregnant, planning a pregnancy, or breastfeeding are not allowed to participate in this study.

If you are a person who could possibly become pregnant (you have not completed menopause, had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who is able to father children, a blood or urine pregnancy test will be performed, and it must be negative to continue in the study.

Blood pregnancy tests may sometimes give a false positive or "indeterminate" result and additional testing may be required to confirm your eligibility for the study.

If you are eligible for transplant and are interested, we will discuss fertility preservation options that may be available such as freezing of your eggs.

You and your partner must agree to either abstain completely from vaginal intercourse for the duration of the study and for 12 months after your last dose of briquilimab, or use a highly effective method of contraception for the same length of time For example, these methods may include (a) partner vasectomy, (b) bilateral tubal ligation, (c) intrauterine devices (IUDs), (d) hormonal implants (such as etonogestrel (e.g., Implanon)), or (e) other hormonal methods (birth control pills, injections, patches, vaginal rings). If you and your partner are not currently using one of these methods your study doctor will discuss options with you, given your medical condition, your personal preferences, and the level of effectiveness required for this study. Because no birth control method is 100% effective, you should notify your study doctor immediately if you think there is any chance you could be pregnant even if you have had a recent negative pregnancy test.

If you do become pregnant during the study, your study doctor will stop sirolimus (if you are still taking it) or any other drug that might affect pregnancy. You will be followed for the duration of the pregnancy to better understand the potential effects of the study drug on safety and pregnancy outcomes.

Males

If you are eligible for transplant and are interested, we will discuss opportunities for evaluation of your sperm and sperm storage.

An increased risk of certain birth defects has been observed in pregnancies where the father was taking sirolimus (medication given after transplant) at the time of conception (start of pregnancy). Therefore, men who are currently trying to become fathers cannot participate in this study.

If you have a partner who could possibly become pregnant (she has not completed menopause, or has not had a hysterectomy and/or both tubes and/or both ovaries removed), you and your partner must agree to either abstain completely from vaginal intercourse during transplant conditioning and for 12 months after your transplant, or use a highly effective method of contraception for the same length of time. Examples of highly effective methods include (a) vasectomy, (b) bilateral tubal ligation, (c) intrauterine devices (IUDs), (d) hormonal implants (such as etonogestrel (e.g., Implanon)), or (e) other hormonal methods (birth control pills, injections, patches, vaginal rings). If you and your partner are not currently using one of these methods your study doctor will discuss options with you, given your medical condition, your personal preferences, and the level of effectiveness required for this study.

You should not donate sperm once you receive the transplant and for at least 1 month after your last dose of sirolimus.

You should notify your partner about your participation in this study, and the potential risks to pregnancies that begin while you are taking sirolimus. If your partner becomes pregnant during the study, you should notify your study doctor, and your partner should notify their doctor. Your partner will be asked for permission to collect information about the pregnancy to better understand the potential effects of the study drug on safety and pregnancy outcomes.

C. Line Placement

Before your transplant we will arrange placement of a large intravenous line that can stay in your body for the entire duration of transplant and recovery period. This will be your "lifeline" for transfusions of red cells and platelets, antibiotics, intravenous feeding, other intravenous

medications, and will even be used to give you the cells from your donor. This line can also be used for blood drawing.

The line is put in under local or rarely general anesthesia in the radiology department or, even more rarely, the operating room. It enters the body most commonly in the upper part of the chest and is then tunneled under the skin to feed into a vein in the chest or neck. You may feel some discomfort and stiffness in your chest and shoulder for a few days after the line has been placed. We will leave the line in for as long as necessary, which may be up to 1-2 months.

If the line becomes clogged or infected, it would have to be replaced by a new line. The line will need to be flushed once a day to try and prevent clogging. Once you leave the hospital after the transplant you will be taught how to do this yourself. While you are in the hospital we will provide you with special wipes to help keep the line clean and prevent infection.

D. Collection of Your Own Blood Stem Cells

In earlier transplant studies with alemtuzumab and low-dose radiation with or without cyclophosphamide given after the transplant, there were a few participants whose transplant was not successful, and it took nearly two months for blood counts to recover. Briquilimab antibody and abatacept added to alemtuzumab and radiation may change how fast blood counts recover after transplant. To minimize the risk of having low blood counts for a prolonged period of time, we plan to collect your own blood stem cells as a 'back-up.' We would give these back to you if your blood counts have remained very low for more than a month.

For this collection, you will typically stay in the hospital for up to a week. A special intravenous line is inserted and a red cell exchange and 1-2 days of plerixafor (a drug used to move the blood stem cells from your bone marrow into the peripheral blood) are planned. 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.

Therefore, prior to transplant, we will collect stem cells and freeze them either by plerixafor-induced mobilization or bone marrow harvest. If your cells were already collected on another protocol, we may be able to use these instead of you having another stem cell collection.

E. Bone Marrow Suppression and Immunosuppression

- **Hydroxyurea:** Is commonly given to reduce the complications of SCD. If you are taking hydroxyurea, we may attempt to increase your dose for optimal effect. 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. We will continue this medication until the time of transplant.
- **Briquilimab:** 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 an antibody that acts as an immunosuppressant. It will be given for 5 days to lower your immune system so that donor cells can take hold (or engraft).

- **Abatacept:** Is a drug that also acts as an immunosuppressant. You will receive 6 doses, with the first dose being the day before transplant and the last dose being 6 months after transplant, to decrease the chance that you will reject the donor cells.

F. Transplant

One day after radiation, 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 may 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. You may receive filgrastim (G-CSF) after transplant to stimulate the initial growth of the new donor cells as they engraft in your bone marrow.

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 platelet 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 inform the research team immediately.

G. Graft versus Host Disease (GVHD) Prevention with Sirolimus (Rapamycin)

One day after the cyclophosphamide is given, you will begin taking an oral medication called sirolimus. Sirolimus works by eliminating and decreasing the activity of white blood cells that make up your immune system called T-lymphocytes, and helps to re-educate the maturing transplanted immune cells to tolerate any remaining immune cells in your body. You will take this medicine for at least the first year and may continue afterwards depending on the amount of donor cells in your blood.

H. Graft versus Host Disease (GVHD) Prevention with Cyclophosphamide (Cytoxan)

Cyclophosphamide is another powerful immunosuppressant. It will be given through your central line over one hour 3 days after your transplant or 3 and 4 days after your transplant.

I. Graft versus Host Disease Prevention with Abatacept

Abatacept is an antibody used to prevent certain interactions between your immune cells. You will receive 6 doses of this antibody starting 1 day before you receive your donor cells to about 6 months after. This will further help your new immune system by preventing your white blood cells from activating and further decreasing the risk of graft rejection and /or GVHD.

J. Leaving the Hospital

Most people stay in the hospital after transplant about 30 days. You will be able to leave the hospital when you are eating normally, have no fever, and your white blood count has risen to a minimum of 500 neutrophils (these are the white cells that fight bacterial or fungal infection). We will stop some of the antibiotics, but continue giving you antiviral medications (such as acyclovir), other antibiotics (Bactrim and penicillin VK or equivalent), and antifungal medications (nystatin). Your intravenous (IV) line will also be removed.

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 hard to eat enough calories to maintain your weight. You and your caregiver will receive additional education before leaving the hospital.

K. 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 you for development of serious viral infections called cytomegalovirus (CMV), adenovirus, Epstein-Barr virus (EBV), and human herpesvirus 6 (HHV6), by testing samples of blood. If we see signs of the virus in your body, we may start treatment immediately. We will also look for signs of graft versus host disease. Some participants have engraftment of donor cells but will still have some of their own residual bone marrow cells following the transplant. This is called mixed chimerism. We will test some of your blood and/or bone marrow after the transplant to confirm donor engraftment.

Day 100 - Starting at 100 days after transplant, the risk of serious transplant complications decreases enormously. If you are doing well at day 100, or soon thereafter, you will be allowed to return to your home if you had to temporarily relocate to the Bethesda area for the transplant. You will be followed by your primary doctor, who will receive a detailed summary of your case, a list of blood tests that should be checked, and they will be encouraged to communicate any problems to us so that we can advise on the best approach. Day 100 post-transplant is a significant time point when we perform a comprehensive evaluation, similar to the pre-transplant testing and a bone marrow aspiration and biopsy

After 3 months- We will continue to see you as needed but your next scheduled follow-up will be 6 months after transplant when you will receive your final dose of abatacept to decrease the risk of late graft rejection and GVHD. We will also schedule follow-up visits at 6, 12 and 18 months and 2, 3, 4, and 5 years after transplant. These visits are key to evaluate long-term effects of the transplant on your organs. After that time, we would like to continue to see you or hear from you on a yearly basis. During these visits, we will be monitoring transplant outcomes with blood tests, organ assessments, possibly bone marrow aspiration and biopsy, and extra blood (3-4 tablespoons) for research. At 1 year after the transplant, we may consider stopping the sirolimus if your percentage of donor cells is high enough.

The following tests may done during these follow-up visits:

Quality of Life -

You will be asked to complete the questionnaire one month, two months, at 100 days and six months after your transplant, and then once yearly after your transplant.

Neuropsychologic Testing -

You will be asked to undergo testing with our psychologists to assess your mental status 100 days (+/- 3 months) and two years (+/- 6 months) after your transplant.

Reproductive/Fertility Surveys -

You will be asked to complete some surveys that ask about your fertility and sexual function as part of this study yearly after your transplant.

Bone Marrow Evaluation -

This procedure will be done 100 days after transplant, 1 year after transplant and after this only if your doctor thinks it is needed.

Brain, Liver and Heart MRI -

An MRI of your brain and heart will be performed 2 years post-transplant. The brain MRI will also be repeated 5 years after your transplant. A liver MRI may be repeated after transplant if your baseline test was abnormal, most commonly if you are found to have too much iron in your liver.

Bone density scans (Dual-energy X-ray Absorptiometry or DEXA) -

You will have a DEXA (Dual Energy X-Ray Absorptiometry) scan to measure your bone density. This procedure will take place at the NIH Clinical Center and will take about 20 minutes to complete. During that time, you will need to lie still on a padded table while the instrument scans your body.

We will do a scan at baseline and repeat every 1 to 2 years so that we can study the bone effects from sickle cell disease and monitor the effect of transplant on bone disease.

Occasionally, one or two of the DEXA scans may need to be repeated.

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 5 years.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Up to 30 recipients will be transplanted 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. 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 up to 1-2 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. You will be taught how to prevent infection from your line and while you are in the hospital, the nursing staff may ask you to use special wipes to help prevent infection.

b. Hydroxyurea

Hydroxyurea is a drug used to reduce the risk of sickle cell crisis. 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 the hydroxyurea 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 ulcers, nausea, infections and bleeding from low blood counts.

c. Plerixafor

Plerixafor is a molecule that causes the stem cells in the bone marrow to move into the peripheral blood. In general, plerixafor has been well tolerated in healthy volunteers or individuals with sickle cell disease 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 the spleen.

d. Filgrastim (G-CSF)

Filgrastim (G-CSF) may be given after transplant to help your donor's white blood cells engraft more quickly. G-CSF commonly (more than 30%) causes 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; we may also give a medication to help prevent pain with G-CSF. 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

The method of collecting stem cells from the peripheral blood is called apheresis. During this procedure your blood is circulated in a closed system where the cells that are needed are removed, and the rest of the cells are returned back to you.

The risks of apheresis include pain, bruising, lightheadedness or dizziness, nausea, vomiting and chills. Bruising may last up to 72 hours.

Tingling around the mouth, fingers, or toes and mild muscle cramps may develop from slight lowering of the blood calcium by the blood thinner used during the procedure. These symptoms can be treated by either temporarily stopping the procedure or by giving a calcium pill. Apheresis uses a completely closed sterile system. The risk of infection is minimized by cleaning the skin before the needle stick. No infections from apheresis have been noted in thousands of such procedures performed over the last 10 years at the NIH.

Rarely, there can be a malfunction of the apheresis machinery that might prevent the return of your blood being processed in the machine. The amount of blood lost would be very small and not harmful. It is also rare for people to faint, have seizures, or have air trapped in the bloodstream.

Temporary or permanent nerve damage may occur at the needle placement sites. This is very rare. At the NIH, to this point, there have been no cases of permanent nerve damage with apheresis.

During the apheresis procedure, your platelet count may decrease because platelets are collected with the white blood cells. Platelets are cells that help your blood to clot. Taking aspirin in combination with a lowered platelet count may increase your chance of developing bleeding. Therefore, you should not take aspirin or aspirin-containing drugs for 2 weeks after the procedure without physician approval.

f. Briquilimab

Briquilimab is an antibody that helps to create space in the bone marrow by binding temporarily to the stem cells. It 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), nausea, dizziness, back pain, decreased energy, and 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. 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 pre-transplant levels. Also, there are unknown long-term effects to fertility or sex hormone production. These risks are estimated to be low at this time.

g. Alemtuzumab (Campath-1H)

Alemtuzumab is an antibody that binds to cells that are responsible for some of the immune responses in infections as well as graft versus host disease. This medication is given subcutaneously (under the skin). 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 you 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 people who undergo transplant without using alemtuzumab.

Alemtuzumab may 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 in 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 a specialist doctor to confirm the diagnosis and help with treatment. Other side effects can be found in the prescribing information.

Rare instances of stroke (clot in the brain/bleeding in the brain) in people who have multiple sclerosis when they received alemtuzumab has also been reported.

Alemtuzumab can temporarily lower the number of red cells, white cells, and platelets in the blood (1-10%), which can in rare instances cause death

h. Sirolimus

Sirolimus is a drug that helps prevent graft versus host disease. The side effects of sirolimus are usually mild and are reversible when you stop the drug. Most commonly (>10%) you may experience anemia, a decrease in the platelet count, mouth ulcers, increase in your cholesterol levels, pain in joints or muscles, swelling in your hands or lower legs, headache, and changes in the levels of some of the salts and minerals in your blood.

These levels will be monitored and in some cases, we may need to use a different drug. We will also follow blood levels of the drug sirolimus to make sure that you are getting exactly the right dose, which prevents many of the above listed complications.

Since sirolimus decreases your immune system, you will also be at higher risk for developing infections, especially as it is given in combination with abatacept, alemtuzumab, cyclophosphamide, and transplant, all of which also make you more susceptible to infections. 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 commonly (1-10%), you could experience difficulty breathing, an allergic reaction, muscle injury, damage to your kidneys and/or protein release into your urine, and fluid buildup such as in your face, stomach, legs, lungs, and heart. Sirolimus also has been rarely reported (<1%) to cause confusion, seizures, stroke, blood clots in your legs or lungs, and bleeding in the lungs.

Also, because it depresses the immune system, sirolimus, like other immunosuppressants, may rarely cause a cancer, most commonly of the glands (lymphoma in <10%) or skin. We will monitor

you after transplant, and we will ask you to wear sunscreen with a high protection factor and wear protective clothing after transplant to decrease your risk of skin cancer. You may also experience a numbness and tingling sensation (pins and needles) while taking sirolimus.

While taking sirolimus you will need to avoid taking medication with grapefruit juice and not take St. John's wort. if you are a woman of childbearing potential, effective birth control should be used before starting this drug because of the potential risks to the unborn child.

As of July 26, 2022, three participants with SCD transplanted at the NIH experienced a drug interaction that happens when sirolimus is taken with a group of medications to lower your blood pressure/decrease protein in your urine. These medications are in a group called angiotensin receptor blockers (ARB, i.e., losartan) or angiotensin-converting enzyme (ACE)-inhibitors (ACEI, i.e., lisinopril). The reaction can be severe, causing trouble breathing and lip or face swelling. One of the participants developed this complication and required support in the intensive care unit. The ARB medicine was stopped and the participant recovered. The participant restarted sirolimus without any problems. Your transplant team will review your medication list before transplant and determine if you are on any of these medications. In addition, after transplant, when you return home to your local doctors, it will be important to notify your transplant team before starting a medication in this ARB or ACE-I group if you continue to take sirolimus.

i. Abatacept

Abatacept is an antibody used to prevent certain interactions between your immune cells. Most common side effects (>10%) include nausea, headache, and infections. More rarely (<10%), you may develop a rash, or during the infusion your blood pressure may be low or you may experience trouble breathing. Very rarely (<1%), a severe allergic reaction (i.e., anaphylaxis) may occur. Lastly, abatacept may increase the risk of viral reactivation of EBV. We will monitor you closely for EBV infection and start treatment early if necessary.

j. Cyclophosphamide

Cyclophosphamide is an alkylator that blocks the production of DNA in cells. It is particularly effective against activated T cells and thus prevents the development of Graft versus Host Disease.

Cyclophosphamide is typically well tolerated but can cause some side effects as follows:

- Most commonly (>10%), people may have nausea, vomiting, diarrhea, mouth sores, and hair loss. There is also an increased risk of infection. Cyclophosphamide also can temporarily decrease the number of red cells and platelets, and you will receive transfusions as needed. Cyclophosphamide may affect your gonads' (ovaries or testes) ability to produce hormones such that you may require hormone replacement therapy long-term after transplant.
- Less commonly (1-10%), you may develop irritation of the lining of your bladder wall which could lead to serious bleeding. To help protect your bladder from the toxic effects of cyclophosphamide, we will infuse a drug called mesna to minimize this risk. You may also have stuffiness of your nose, rash, flushing (redness of your face), an abnormality of one of the salts in your blood, or kidney damage, which usually resolves once the drug is stopped. Cyclophosphamide can also lead to the development of a cancer or

myelodysplastic syndrome, which is a form of pre-leukemia which may progress to leukemia, in the future.

- Rarely (<1%) you may have blurry vision, abnormal heart rhythm or decreased heart function, darkening of your skin or nails, liver irritation, or difficulty breathing.

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 400 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 400 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, hair loss, 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, fluoroscopy, and nuclear medicine scans in which radioactive materials were injected into your body.

k. 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, and the infusion of donor blood stem cells, can cause fevers or allergic reactions. We will monitor you 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 transplant affects the whole body, damage 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. Traditional 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 SCD and/or iron overload on your organs.

l. 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 tests, and/or eye/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, pain during sexual intercourse due to dryness of the vaginal mucosa, and lung damage leading to progressive shortness of breath and chronic cough. People 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 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 responds to treatment. However, some GVHD may be unresponsive to treatment, leading to major changes in your daily activities and/or death.

m. Possible Transplant Outcomes

Although we added briquilimab and abatacept to alemtuzumab, radiation, cyclophosphamide, 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 could be less. We may discuss restarting sickle cell 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 people 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 disease, previous use of hydroxyurea, radiation, infection, or immunosuppression. Treatment for acute leukemia usually involves leukemia-specific chemotherapy, leukemia-specific antibody or immune therapy, or another hematopoietic cell transplant.

n. Graft Rejection

In order to engraft with your donor's stem cells, it is important that you be immunosuppressed before have transplant. This is why you will get strong immunosuppressive therapy before you receive your donor's cells. If you fail to engraft, your blood counts should return within six weeks. In the rare event that your blood counts do not recover, we will give you the "back up" cells that we collected before transplant. A test will be done on some of your blood and bone marrow after the transplant to confirm donor engraftment. Some participants may have engraftment of donor cells but still have some of their own residual bone marrow cells too after the transplant. This is called mixed chimerism.

Participants who have stable mixed chimerism may continue sirolimus for more than 1 year after the transplant. If the engraftment by donor cells is decreasing, your Sirolimus may be increased or restarted. Unfortunately, you may fail to engraft with donor cells, and it is not possible to predict beforehand whether you will or will not engraft.

Also, with the emphasis being on safety in this regimen, it is possible that more participants will not engraft because the goal of this type of transplant is to limit the toxicity as much as possible. Participants who fail to engraft with donor marrow will either be considered for repeat transplant or will be referred back to their primary doctor after they have recovered from the transplant. We will also want to continue to follow you to evaluate the impact of transplant on your organs.

o. Autoimmune Cytopenia

Even after successful transplant patients can develop autoimmune cytopenias; this is when the immune system attacks blood cells and causes low platelets, low red blood cells, and/or low

neutrophils. Generally when this complication occurs after transplant it can be very difficult to treat and is associated with a higher risk of death. The exact cause of autoimmune cytopenias after transplant is unknown; it may be a side effect of medications used in conditioning, due to mixed chimerism, or due to some other aspect of transplant.

p. Hyperinflammatory Syndromes

Inflammatory reactions may occur after transplant which cause the body's defense system, the immune system, to malfunction. Certain white blood cells can attack other blood cells and organs which can lead to severe damage and even death. This complication has developed on this protocol as well as prior SCD transplant protocols at the NIH. If we see high rates of this complication it could lead to early termination of this protocol.

q. Viral Reactivation

Because of the immunosuppressive drugs and the transplant procedure itself, you will be at an increased risk of developing serious viral infections. **CMV, EBV** and **adenovirus** are major infections patients are at risk for after transplant. They are common viruses that most adults have had without symptoms, and normally these viruses lie dormant in the body, causing no problems. But, when your immune system is not working properly after a transplant, the viruses can cause severe damage to your body, such as a fatal pneumonia, or severe bladder infection leading to blood in your urine. Part of the monitoring that we carry out after your transplant will be to detect, by sensitive techniques, the emergence of each of these viruses in your body. This monitoring will be at least weekly for the first 3 months and then spread out until at least 1 year after the transplant. If reactivation of a virus occurs, we will start either an antiviral drug or an immunosuppressive drug.

EBV can also cause a cancer in the lymph nodes (glands) after transplant. This type of cancer is called PTLD (post-transplant lymphoproliferative disease). Most of the time this cancer can be treated effectively with an antibody therapy. Rarely, it requires more aggressive treatment, such as with chemotherapy. Usually the risk of this cancer (PTLD) happening with this type of transplant is less than 10%. To try to decrease the risk of PTLD, patients will receive antibody therapy if EBV is detected at all after transplant.

Another virus that we will monitor you for, **HHV6**, can lead to an infection of the brain. If there is strong suspicion that the virus is leading to illness, we will start you on an antiviral medication.

One more virus, **BK virus**, can infect your bladder and kidneys and lead to kidney damage and/or blood in your urine. We will only check you for this virus if you have symptoms of infection and we will treat you with an antiviral medication if needed. If reactivation of a virus occurs, we will start an antiviral medication, which is usually effective when diagnosed early.

r. Veno-Occlusive Disease

In some patients, radiation followed by allogeneic transplant 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 may die.

s. 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. Some of the questions may be upsetting or make you feel uncomfortable. You can skip any of the questions you do not want to answer, and you can stop at any time.

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. Asking participants the questions included in the study instruments is not considered to cause significantly more discomfort or anxiety beyond the stresses that these patients are coping with on a day-to-day basis.

t. MRI of the Heart, Liver, and Brain

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during a MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

Patients may require sedative medication for the brain scan. These medications can be oral or IV, may need working with our Department of Anesthesia and Surgical Services (DASS), where a separate consent will be completed. You may need a responsible adult to be with if you plan to take the sedative medication. There are no known long-term risks from MRI scans.

u. Bone Marrow Aspiration and Biopsy

The bone marrow aspiration and biopsy may cause pain, bruising, bleeding and infection. Soreness near the site may last for a couple of days after the procedure. You may have more pain, risk of bleeding and bruising if you complete both aspiration and biopsy rather than just the aspiration. If your pain is severe or you develop a fever, please contact the study team immediately.

v. Surveys (Quality of Life, Reproductive and Fertility)

Some of survey questions may be upsetting or make you feel uncomfortable. You do not have to answer any questions you do not want to answer, and you can stop at any time.

w. 6-Minute Walk Test

The exercise test may cause muscle soreness, dizziness, shortness of breath, lightheadedness, abnormal heart rhythm, chest pain or you may feel faint. You will be monitored throughout the test by the study doctor.

x. ECG (Electrocardiogram)

Other than possibly experiencing some minor skin irritation from the electrodes, there are no anticipated risks related to complete the electrocardiogram and/or the echocardiogram

y. **Holter Monitor**

Similar to the ECG, possible minor skin irritation from the electrodes.

z. ECHO (Echocardiogram)

Other than the possibility of some mild discomfort during the test, there are no known risks to an echocardiogram.

aa. Invasion of Privacy/Breach in Confidentiality

Because this study involves collecting personal, identifiable information about you, there is a possibility that people who are not supposed to see this information might somehow gain access to it. We will take precautions to prevent this, but we cannot ever be certain that it won't happen. To minimize this chance, we will assign you a study number instead of labeling the information we collect from you with your name [or medical record number]. All of the information we collect will be stored in a secure manner, such as in a locked cabinets or password protected computer files.

bb. Discovery of Previously Unknown Condition(s)

As a result of the tests completed as part of this study, we may discover that you have a medical condition that you did not previously know about. If we discover something new as a result of these tests, you will be told about it. The study doctor/staff will talk with you about the findings and your options. You may be told to follow up with your regular doctor or other specialists for future care.

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 disease. 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 may have other treatment options. These treatment options vary depending on your age, treatment history, and complications. Before you decide to enroll in this study, we will discuss options such as continuing with hydroxyurea or sickle cell medications, red cell transfusions, and iron chelation. Other options with curative intent include a different half-matched (haploidentical) donor transplant study, the recently Food and Drug Administration (FDA)-Approved gene therapy (Lyfgenia) and gene editing (Casgevy) studies, other gene manipulation type of transplants, transplant using high intensity (myeloablative) or reduced intensity, and/or other experimental treatments. 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 get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned 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 very 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 by the study team for use in other studies?

As part of this study, we are obtaining specimens and data from you. We plan to store and use these specimens and data for studies other than the one described in this consent form that are going on right now, as well as studies that may be conducted in the future. The specimens and data will be kept in a way that we will still know that they came from you (i.e., they will be identifiable to us). If we use your identifiable specimens or data for future research, our study will be reviewed and approved by an Institutional Review Board who will make sure that we are protecting your confidentiality. These future studies might help us better understand SCD and transplant or other diseases or conditions. This could include studies to develop other research

tests, treatments, drugs, or devices, 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 **identifiable** specimens and data to be stored and used by the study team for future studies as described above.

_____ Yes _____ No

Initial Initial

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

We may share your specimens and data with other researchers. The other researchers may be doing studies in similar areas to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or at commercial entities.

One way that we may share your data is by putting it into a large database called a repository, which is a way to make it widely available to the research community. If we do place your data in a repository, it will be labeled with a code, (not with your name or other information that could be used to easily identify you). Even though it will only be labeled with a code, some types of data, in particular data about your genes (called genetic or genomic data), can be used to figure out who you are, although this is difficult to do, and we think it is unlikely to happen.

The data in the repository will only be available to qualified researchers. These researchers must receive permission before they are allowed to access the data. Before receiving the data, the researchers must promise that they will not try to figure out the identity of the research participants. If we do share your specimens or data, we will know that the specimens and data came from you. However, the other researchers will not know that they came from you (i.e., they will be de-identified).

I give permission for my **de-identified** specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

In some cases, it may help other researchers to know that the specimens or data were collected from you (i.e., they will have your identifiers). If we share your identity with other researchers, their study will be reviewed and approved by an Institutional Review Board who will make sure that the study team is protecting your confidentiality.

I give permission for my **identifiable** specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

In addition to the planned use and sharing described above, we might remove any labels from your specimens and data that might identify you (i.e., anonymize them), and use them or share them with other researchers for future studies at the NIH or other places. When we or the other researchers use your anonymized specimens and data for these projects, there will be no way to know that they came from you. We want to make sure that you understand that this is a possibility if you participate in this study. Once we do this, we would not be able to remove your specimens or data from these studies or prevent their use in future studies because we would not be able to tell which specimens or data belong to you.

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 who 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 that no one will 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.

Can you change your mind about use and sharing for future research?

If you change your mind and do not want us to store and use your specimens and data for future studies, you should contact the study team. 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 is already complete, the information from that research may still be used. Also, if the specimens and data have been shared already, it might not be possible to withdraw them.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH possibly indefinitely.

PAYMENT

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

The amount of compensation given in this study 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 Test**	**Male Total**	**Female Total**
PROMIS Quality of Life Questionnaire	**once / year***		**$20**	

(male and female)		**$20**		**$20**
Changes in Sexual Function Questionnaire (male and female)	**once / year**	**$20**	**$20**	**$20**
Fertility Survey (females only)	**once /year**	**$20**	**N/A**	**$20**
Priapism Impact Questionnaire (males only)	**once / year**	**$10**	**$10**	**N/A**
International Index of Erectile Function (males only)	**once / year**	**$10**	**$10**	**N/A**
TOTAL (USD)			**$60**	**$60**

**Up to 5 PROMIS forms (up to $100) may be completed in the first year.*

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

REIMBURSEMENT

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

This study offers some reimbursement for participants who live out of state or internationally for both travel and lodging.

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.

Please note that although we do not ask you to pay for your medical treatments and hospital costs incurred on the protocol, it is your responsibility to make your own arrangements for all the nonmedical expenses (housing, meals, transportation, etc.) required for yourself and your family before, during and after the transplant procedure (a total of about 4 months). You will meet with our social worker who will discuss the psychological issues related to a peripheral blood stem

cell transplant, explain the potential costs to you, and provide you with information and resources, so that you can find an appropriate place to stay during the transplant period. The social worker will 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 stay with you once you are discharged from the hospital after the transplant, to help with chores, cooking, and transporting you back and forth from the clinic.

CONFLICT OF INTEREST (COI)

The NIH reviews NIH staff researchers at least yearly for conflicts of interest. 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.

Jasper Therapeutics is providing briquilimab for this study to NIH without charge. No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested. However, there are some research partners not associated with the NIH working on this study who may receive payments or benefits, limited by the rules of their workplace.

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
- The study Sponsor, the NHLBI

For the purposes of compensation, the research study team plans to collect social security numbers from research participants. You may withhold your social security number and still participate in the research study; however, if you do so, you may be unable to receive compensation.

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 and the Privacy Act.

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.

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, about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Courtney Fitzhugh, M.D. at (301)402-6496 or E-mail: Courtney.Fitzhugh@nih.gov. Another researcher you may contact is Jennifer Brooks, RN, at (301)318-2534. You may also 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**

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: _____.