Informed Consent to Participate in Research

BMT CTN 2001

A Multi-Center, Phase 2 Gene Transfer Study Inducing Fetal Hemoglobin in Sickle Cell Disease

Your Name: _____

Principal Investigator:

Insert local PI information

Sponsor: This study is co-sponsored by the National Heart, Lung and Blood Institute, a part of the National Institutes of Health, and the California Institute of Regenerative Medicine.

The ethics of this study have been reviewed and approved by the National Marrow Donor Program Institutional Review Board.

Your study doctor or nurse will review this **Consent Form** with you, including:

- ✓ The purpose of the research
- ✓ Possible risks and benefits
- ✓ Other options available to you
- ✓ Your rights if you join the study

The word "you" throughout this form refers to you or your child.

1. Study Overview

We are inviting you to participate in a research study. Before deciding to participate in this study, it is important that you read and understand the following explanation. It describes the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. It also describes the alternatives available and the fact that you have the right to withdraw from the study at any time. No guarantee or assurance can be made as to the results of the study. Participation in the research study is completely voluntary, and refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

You're being asked to join because you have sickle cell disease (SCD).

SCD is usually treated with medicines to manage the symptoms of SCD. Currently, the only treatment that has the potential to cure SCD is hematopoietic stem cell transplantation (HSCT), also called bone marrow transplant. HSCT uses blood-forming cells/stem cells retrieved from different sources (i.e., bone marrow cells) from a matched donor, but not every patient with SCD has a matched donor. In this study, we want to test whether a new treatment using the patients' own blood-forming cells called gene therapy can be used instead of donor HSCT to safely reduce SCD symptoms. We want to learn whether it can be used safely, and whether it improves or eliminates the symptoms of SCD.

If you join, you'll:

- Have your blood-forming (hematopoietic) cells/stem cells collected, receive medicines used for chemotherapy during HSCT procedures and receive an infusion of gene modified blood forming cells.

- Be in the study for 24 months post-infusion and will be offered enrollment in a long-term follow-up study for another 13 years for a total of 15 years of follow-up.

Some possible risks and benefits of joining the study include:

Possible Risks: Most of the risks you may experience are from the conditioning regimen you will receive and the gene modified cell infusion. More details can be found within this consent.

Possible Benefits: Participation in this study does not guarantee any benefit to you. A possible benefit is that you may have fewer symptoms of SCD after the gene modified stem cells are infused. Information from this study may help doctors learn more about a new treatment option for sickle cell patients in the future.

If you do **not** join the study, you have other treatment options, such as:

- HSCT from an unrelated or haplo-identical donor
- FDA-approved medications and/or supportive care measures for sickle cell disease
- Continue with your current treatment regimen
- Joining another clinical trial

Key points:

- Being in any research study is your choice.
- You may or may not benefit from being in the study. Knowledge gained from this study may help others.
- If you join the study, you can quit at any time. If you decide to quit the study, it will not affect your care at [name of facility or institution].
- Ask the study staff questions about anything you do not understand, or if you would like more information. You can ask questions now or any time.
- Take time to talk about the study with your doctor, study staff, and your family and friends. It is **your** choice to be in the study. If you decide to join, please sign the end of this Consent Form. You'll get a copy to keep. No one can force you to join this study.

2. Study Purpose

The goal of this research study is to test a new possible treatment for SCD. We want to learn whether gene therapy can be used safely, and whether it improves or eliminates the symptoms of SCD. We do not know yet if this treatment will have any benefit to patients. This is a phase 2 study. Studies in this phase test how well a new treatment will work to treat a disease after a phase 1 study showed that it is safe. Gene therapy has been performed in limited numbers of people so far, including a small number with SCD.

Gene Therapy for SCD has not been approved by the U.S. Food and Drug Administration (FDA) or other regulatory authorities. This research study is registered with the FDA, and they will monitor it.

Many patients with SCD cannot have a HSCT because they don't have a genetically matched donor. We would like to treat SCD by gene therapy, using the patient's own cells, without needing

to find a matched donor. Patients' own cells can be used for treatment of SCD because researchers have developed a way to make these cells able to produce **hemoglobin that doesn't cause the red blood cells to sickle.** This is done by inserting genetic material (DNA) into the patient's own cells, a process called gene transfer. To get the DNA inside the patient's blood-forming cells, we use a virus found in nature that is specialized to carry DNA into human cells. Although a virus is an infectious agent the virus that is used in this study cannot infect you. The virus has been changed in the laboratory so it has become unable to grow and infect people, but is able to carry a gene or genes of interest and deliver them to SCD blood-forming stem cells to treat the disease. We call this virus a "vector." To allow the gene changes to be done in the right cells, patients first receive a medicine (plerixafor) that causes blood-forming cells to be released from their bone marrow into their bloodstream. These blood-forming cells will be grown in the laboratory in a manner that will allow the blood-forming cells to take up the vector and increase fetal hemoglobin in the cell. The modified blood-forming cells will then be given back to the patient through an intravenous infusion (IV) like a blood transfusion.

Importantly, using the patient's own cells avoids or reduces some of the more serious risks of donor HSCT. These risks include a severe condition known as graft versus host disease (GVHD), in which the donor cells react against and damage the patient's body, and graft rejection, in which the donor cells are eliminated by the patient's cells.

How will the gene therapy treat sickle cell disease?
Sometimes gene therapy works by putting in a normal version of the exact same gene that is broken. This has been done successfully in other diseases, and there are other SCD research trials now that transfer a normal version of adult hemoglobin gene into the patient's cells, without reducing the sickling hemoglobin, but instead diluting it with the newly produced normal hemoglobin. **In this study, we are using a different and unique strategy from these other gene therapy trials for SCD patients.** Instead of adding a globin gene, our strategy is to add "genetic instructions" that tell the red blood cell what kind of hemoglobin to make. Our goal is to "switch" the red blood cells from making sickle hemoglobin to making a non-sickling hemoglobin, called **fetal hemoglobin**. Fetal hemoglobin is the type of hemoglobin everyone's body makes in the womb and in young babies. We already know that increasing the amount of fetal hemoglobin and, at the same time, reducing the sickling hemoglobin helps to make SCD less severe. We have discovered a gene that is very important in controlling the amount of fetal hemoglobin the body makes. The gene is called BCL11A. BCL11A keeps down how much fetal hemoglobin your body's red blood cells make. Turning down the function of BCL11A by gene therapy in SCD patients will increase the amount of fetal hemoglobin, and at the same time also reduce the amount of sickle hemoglobin. So in this study, we will use a vector to add genetic material/DNA (the "hemoglobin control" DNA) to your blood forming cells that will cause your cells to make less sickling hemoglobin and more fetal hemoglobin by turning down the activity of BCL11A.

Gene therapy is still experimental for several reasons. First, although gene therapy has been used

successfully in other diseases, including another hemoglobin disease called thalassemia, it has only recently been used in SCD for the first time in other clinical trials. Second, some of the children who had gene therapy for other diseases had very serious complications (discussed in more detail below), so any gene therapy trial must be done carefully as a research study to look out for potential complications. Third, this is the first large research study using our strategy to regulate BCL11A activity and make more fetal hemoglobin, although we have recently completed a pilot (smaller) study using this same approach and vector, and the results of this pilot study are encouraging.

3. Study Treatment and Tests

The procedure is very similar to HSCT except that no other donor is needed, and your own blood-forming cells are used. These cells are also known as hematopoietic stem cells (HSCs). The HSCs used for gene therapy will be collected using a medicine called plerixafor, which causes the bone marrow to "release" the HSCs into the bloodstream, and then the HSCs can be collected directly from a vein. This is called peripheral blood mobilization. We will collect enough HSCs to use for two purposes: 1) to save and freeze as a back up in case there is a problem with the gene transfer procedure, and 2) for the gene transfer procedure itself. In order to make sure we have enough of these cells, we would need to do peripheral blood mobilization at least once (and possibly more times). There are three phases to the research study, the pre-gene transfer phase, the gene transfer phase, and the post-gene transfer monitoring phase.

Phase 1: Pre gene transfer

After you consent, but before the main part of the study begins, we will do tests to make sure that you are eligible for the study. This can take 1 to 2 months. This testing includes physical exam, blood tests to evaluate the status of your sickle cell disease and the genetic type of your sickle cell disease, if unknown (using a test called comprehensive globin sequencing), and other standard testing performed before all autologous bone marrow stem cells transplants including blood sampling and organ function studies.

Depending on the results of the pre-treatment testing we may need to remove you from the study prior to gene transfer. If you are eligible, you will continue on to receive pre-gene therapy work up. If you are not already following a transfusion regimen you will receive blood transfusions during the three months prior to gene therapy in order to reduce the amount of sickle hemoglobin in your blood. We will then proceed to collect your HSCs by the method mentioned above and described in more detail below.

Peripheral blood mobilization to collect HSCs using plerixafor

Plerixafor will be administered by subcutaneous injection (an injection into the soft tissue just under your skin, typically in your arm). Starting at least 2 hours after the plerixafor administration,

you will undergo a procedure called apheresis to collect your HSCs. Prior to apheresis, if you do not already have an apheresis compatible central line in place, a temporary apheresis catheter will be placed for the duration of the stem cell collection. In the apheresis procedure, blood is withdrawn through a catheter and mixed with an anticoagulant (medication to prevent blood from clotting) as it is drawn into a machine called a cell separator. The blood is pumped through the cell separator and the HSCs are collected in a sterile plastic container. Most of the blood in the cell separator is then returned to your body. All equipment used is commercially available, and all materials coming in contact with your blood are sterile, only used once and then destroyed. During the apheresis a nurse will be monitoring you closely, checking your vital signs at least every 15 minutes. You will have labs drawn again during the procedure. If the first mobilization procedure does not yield enough cells to use both for back up and for gene therapy, a second and/or third dose of plerixafor may be given the subsequent days, with an additional apheresis procedures. If necessary, another round of mobilization may be pursued at a later date.

If we are unable to collect adequate numbers of blood stem cells to successfully complete the gene transfer and for the back up supply of cells, you may need to undergo additional peripheral blood mobilizations cycles (as described above). These would be done no sooner than 2 weeks after each previous HSC collection to allow adequate time for the bone marrow to recover from the previous collection. It is possible that multiple mobilizations would be required to obtain enough cells, and you would have a choice after each one about whether to undergo another repeat collection. The maximum number of mobilization rounds will be one for back-up cells and no more than three additional mobilization rounds for the gene therapy cell product. The purpose of a back-up stem cell collection is for rescue in the event that the transplant has not taken (graft failure).

Your collected cells will be sent to a special cell manufacturing laboratory at Dana-Farber Cancer Institute where the stem cells will be purified and then mixed with the gene transfer vector containing the "hemoglobin control" DNA (transduction). After that the cells carrying the "hemoglobin control" DNA (called gene modified cells) will be counted and tested to make sure there are enough and that they are safe to give back. The cells will be frozen and stored until the time of infusion. The gene transfer is an experimental procedure. A private company is also supplying materials for the gene transfer part of the study. Miltenyi (Germany) makes a product (CliniMACS) that will be used to purify the blood stem cells.

Storage of Stem Cells:

Your back up stem cell product collected by apheresis will be frozen and kept for up to 10 years. This product will only be used in case of treatment related complications, as outlined below. Your back-up cells will be frozen in the Cell Processing Laboratory at the hospital in which the cells were collected and stored for 10 years for your use only. After 10 years, the laboratory will discard any remaining stored cells if your doctor determines that you have no clinical need for these cells. Alternatively, you may request in writing that we transfer this product to another facility of your

choice.

Phase 2: Gene transfer administration

Before your gene transfer, you will have more blood tests to be sure nothing has changed. Either then or at the time you are admitted for gene transfer you will have a special intravenous catheter (also known as a "central line") placed in your chest by a surgeon. The catheter will be used to ensure rapid delivery of the gene transfer cells, to help draw blood, and to give you medicines. The exact kind of line placed will be determined together with the doctors caring for you to provide the safest care.

SCD patients getting HSCT are normally treated with medicines to suppress or destroy the existing abnormal cells in the marrow, which allows the donor bone marrow to grow in the bone marrow cavity. These medicines are also used for the treatment of cancer (chemotherapy). After the HSCs have been gene modified, we will give you chemotherapy to prepare your body for the gene modified cells, see Table 2 below for timing. Without this treatment we believe that it would be difficult for enough gene modified cells to survive because they would be in competition with the cells already there in the bone marrow. The chemotherapy we will use and its side effects are listed in the section below regarding risks.

After the chemotherapy is complete and the gene modified cells have been counted and checked, you will receive the gene modified cells as an infusion through the central line into your bloodstream. Because the chemotherapy kills your blood-forming stem cells that are producing the sickled red cells as well as all your mature blood cells, and it takes time for the new gene modified cells to grow, your blood cell counts will all become temporarily very low and this is expected. Following the infusion of cells, it usually takes 2 to 4 weeks to see a rise in white blood counts indicating that the transplant has taken (called "engraftment"). Just like after a HSCT, you will remain in the hospital restricted to the transplant floor until there is evidence of engraftment. If the number of gene modified cells is lower than we expected, we will give the back up cells (the cells that have not been changed) after the gene modified cells to be sure that your blood counts will recover. This may occur many weeks after you receive the gene modified cells and only in the case of the gene modified cells not engrafting correctly.

Phase 3: Post gene transfer Monitoring

A. Immediately after receiving gene modified cells

   For approximately 12 hours after receiving gene modified cells, you will be observed closely for any side effects from the procedure.

B. You will remain in hospital until your white blood cell count has come up and you have recovered from the procedure. This may take up to 6-8 weeks but is likely to be less. In addition to blood draws and physical examinations in the hospital and in the outpatient clinic for clinical care, we will also monitor you with additional blood tests for research, to test for the level of gene modified cells and development and recovery of the white blood cells and platelets. These additional blood tests will be done at months 1, 3, 6, 9, 12, 18 and 2 years after the gene therapy treatment. This will be done at the same time as blood draws for clinical purposes where possible but may need to be done separately. The amount of blood is several teaspoons and will be limited according to your weight to prevent you from becoming anemic (low hemoglobin level). You will also be asked to complete a questionnaire about your quality of life at the beginning of the study and periodically during the follow-up period. You will be followed on this study for 2 years. In order to better understand gene therapy beyond 2 years, you will be invited to participate in a long-term study after you have completed this study.

Before Your Treatment

You'll need to have several tests to see if you are eligible to be in the study. These tests are part of your regular care. The tests include:

Table 1: Schedule for Health Evaluations Pre-Gene Transfer

	Pre-gene transfer			Admission to HSCT/ GT
	Screening/ Eligibility	Baseline	Collection for back-up and gene therapy product	
History and Physical	X	X		X
Growth (height and weight) and Vital Signs	X	X		
Pre-Transplant Studies		X[1]	X[1]	
Performance Status	X			
Pulmonary Function Tests (PFTs)	X			
Echocardiogram (ECHO)	X			
Transcranial Doppler Ultrasound (if less than or equal to 14 years at enrollment)		X		
Urine albumin, serum cystatin C		X		
Brain MRI/MRA		X		
Complete Blood Count with differential + reticulocyte count+ iron studies	X			X
Bone Marrow Aspirate/Biopsy	X			
High Performance Liquid Chromatography ("Hb electrophoresis") to measure Hemoglobin F		X		X
Chem-10 panel, LDH, Liver Function Tests	X			X
PT/PTT	X			
T/B/NK cell subsets and IgG, IgM, IgA		X		
B cell memory panel and gamma/delta T cell assay		X		
Comprehensive globin sequencing		X		
Peripheral CD34 cell count and C-reactive Protein		X	X	
Vector copy number (Peripheral Blood sorted lineages)		X		
Flow cytometry of Peripheral Blood to measure F cells and exploratory testing		X		
PROMIS and HMH surveys		X		
Replication Competent Lentivirus		X		
Save serum, cells and DNA		X		
Safety Monitoring	X	X	X	X

[1]List of studies typically performed prior to standard autologous transplant or for patients receiving transplant for SCD: **i**nfectious disease testing, ECHO/EKG, PFTs, Brain MRI/MRA, Chest X-ray, Dental consult, Ophthalmology consult, Audiology consult, GFR/creatinine clearance, Chemistries, G6PD, ABO/Rh

During the Study

If you join the study, here's what will happen:

Table 2: Timeline

	Day – 54 or earlier	Days -53 to -50 or earlier	Days -49 to -7	Day -6	Days -5 to -2	Day 0
CD34+* collection (including back-up)	X					
CD34 transduction and cryopreservation		X				
Release testing			X			
Subject admitted to transplant unit				X		
Conditioning (busulfan administration)					X	
Infusion of gene-modified cells						X

*Blood-forming stem cells

Table 3: Schedule for Health Evaluations Post-Gene Transfer

	1 month	3 months	6 months	9 months	12 months	18 months	2 years
Medical history, physical exam & weight	X	X	X	X	X	X	X
CBC, chemistries, LDH, LFTs, RETIC, iron studies, HPLC	X	X	X	X	X	X	X
Pulmonary Function Tests							X
Echocardiogram							X
Transcranial Doppler Ultrasound (if less than or equal to 14 years at enrollment)							X
Urine albumin, serum cystatin C							X
Brain MRI/MRA					X		X
T/B/NK cell subsets and IgG, IgM, IgA			X		X		X
B cell memory panel and gamma/delta T cell assay							X

	1 month	3 months	6 months	9 months	12 months	18 months	2 years
Vector copy number (Peripheral Blood sorted lineages)	X	X	X	X	X	X	X
Flow cytometry of Peripheral Blood to measure F cells and exploratory testing	X	X	X	X	X	X	X
PROMIS and HMH surveys							X
Integration site analysis*			X		X	X	X
Replication Competent Lentivirus		X	X		X	X	X
Safety Monitoring	X	X	X	X	X	X	X

*= The amount of blood drawn will follow institutional guidelines of your treating hospital. Children ages 14 or younger may have less volume drawn.

Patient Reported Outcomes

If you agree to take part in this study, we will ask questions about your health and how well you can do your normal everyday activities (Patient Reported Outcomes (PRO) surveys, as well as household material hardships (HMH)). The CIBMTR Survey Research Group will contact you by email, phone or mail to collect PRO and HMH surveys online or on paper. Your transplant center will provide your name and contact information to the CIBMTR Survey Research Group when you enroll in the study, so that they may administer the survey to you. You will take the surveys before your conditioning regimen and at 2-years post gene therapy

Seeing your Research Results

Your doctor may share with you your research results. Your doctor will share any results with you if they show that you need new treatment or need to change your treatment. If you'd like to see specific results, tell your doctor.

Timeline and Participants

This study will take about 4 years to complete and will include 27-30 people.

4. Risks and Benefits

Possible Benefits

If you agree to take part in this research study, there may not be a direct medical benefit to you. There may be no improvement in the amount of sickle hemoglobin in your blood, or in the symptoms of your SCD, and you would then continue to require ongoing treatment for SCD, which may include your current medications, or an unrelated donor stem cell transplant.

It is possible that the gene modified cells will give rise to red blood cells that are healthier and function better than the abnormal SCD cells. In this case, your anemia, pain, and other SCD-related organ problems may improve as a result of this study.

You may learn new genetic information about your disease phenotype during this study. This may be helpful for you and for your family by providing you with more knowledge about the specification of your disease type. These results will help doctors to better understand about specific types of SCD, and the best treatment for any particular patient with SCD.

Regardless, the results of this study will give the investigators important information that could benefit other people with SCD. Results arising from research may improve how doctors prevent, diagnose, and treat SCD as well as other diseases and will be of benefit to patients in the future.

Possible Risks

You may have side effects during the study. Side effects can range from mild to severe. Your health care team may give you medicine to help with certain side effects, like an upset stomach. In some cases, side effects can last a long time or may never go away.

What are the risks of this research study? What could go wrong?

There are risks of this research study that are specific to the experimental gene transfer part, and other risks that are similar to the risks associated with going through a donor HSCT. All of these are explained below and are listed with the more severe or serious risks first. As with any very new therapy, there is also a chance of unknown risks or complications occurring. Please note that once the gene transfer has happened, the genetic changes will have occurred and thus will not be reversible.

The form will go over these risks in detail. They can be broadly placed in two categories: those that are specific to the gene transfer experimental treatment, and those that are part of any stem cell transplant. Overall, this can include the risk of death or serious disability.

- Risks associated with gene transfer
  - Blood Cancer or other cancer.
  - Failure of the new cells to stay in you (failure to engraft).
  - Other cells (not blood cell producing cells) being affected.
- Risks associated with any stem cell therapy
  - Extreme anemia requiring blood transfusions.
  - Decreased immune system and decreased white cells permitting life threatening infections.
  - Mouth ulcers.

- Bleeding.
- Discomfort and infection from the bone marrow aspirates.
- Side effects from the procedures and medications that are required to perform a stem cell transplant.
- Psychologic and emotional consequences of combinations of procedures, long hospital stays and coping with the side effects.
- Medication may compromise the ability for both men and women to have children in the future.

Risks of Gene Transfer Causing Cancer Due to Insertion of the "Hemoglobin Control" gene

The most important possible side effect of gene transfer is cancer in blood cells. We explain below why this is a possible side effect, why we believe the risk to be small in this trial, and how we will monitor for it.

In some previous gene transfer trials for children with rare deficiencies of the immune system using a different vector, there have been serious complications, including leukemia, a type of blood cancer. The leukemia was caused by a component of the gene transfer vector and its effect in the place where it lands in the patient's cell DNA. In at least one instance, the leukemia has led to the death of a subject, while in other cases the leukemia has been successfully treated. There are also other blood and bone marrow problems that have been seen in gene transfer trials. In Germany, two young adults who had gene transfer for an immunodeficiency called chronic granulomatous disease (CGD) developed a blood disease called myelodysplastic syndrome (MDS). MDS is a condition in which the bone marrow is damaged, does not produce enough healthy blood cells, and may develop into leukemia.

The vector we are proposing to use in the current trial is different from the vectors that cause leukemias or MDS and contains many safety improvements. This vector has not caused leukemia in animal studies. Moreover, none of many patients treated with similar vectors for other diseases, some now 10 years ago, have developed leukemia. However, we will not know for sure that it is safe in humans until we use it in many more people.

It is important that you understand that leukemia or MDS or other blood diseases could occur as a result of participating in this trial; any of these diseases could be serious or even fatal. As described above, we believe the gene transfer vector being used for this study is safer for several reasons. Nevertheless, some of the additional blood draws that are part of this protocol are being used to look for cancer-causing changes in the DNA. We will alert you to any concerning findings and do further testing if we suspect that leukemia or MDS might be developing. You will also be kept up to date throughout your participation in this study regarding any new developments in this gene transfer trial or in others like this one.

Other Risks Associated With the Gene Transfer

A goal of the gene transfer is to change the amount of the gene BCL11A in the red blood cells. BCL11A is a gene that, when suppressed in red blood cells might reduce or eliminate the symptoms or complications of SCD by making more fetal Hb (the Hb variant present during early stages of life) that is not contributing to sickling. Our gene therapy vector is designed so that it decreases BCL11A only in red blood cells and we do not expect any change of the amount of this BCL11A in any other blood cells nor in other part of the body. Based on the experiments that have been done in the lab (in cells and in animals), and in our pilot study there has been no sign of problems caused by decreasing the amount of BCL11A in the red blood cells and their precursors. However, we will be monitoring this closely. Besides the red blood cells, there is a small risk that the amount of BCL11A could slightly change in other blood cells, such as the infection-fighting cells. This may cause problems, such as infections, for young children. We will be monitoring carefully to make sure if any changes occur that we are aware of these and provide appropriate treatment as indicated.

Risks Associated With the Transplantation Procedure

We use a chemotherapy drug called busulfan before gene therapy to allow the transplanted blood stem cells to find enough space in the patient's body and grow. Busulfan is often used in HSCT for a number of conditions and for treatment of some types of cancer and have some of the same expected side effects. It may cause your hair to fall out, but it almost always grows back again. You may feel nauseated, may have some abdominal pain and diarrhea, may develop temporary painful sores in the mouth and intestines, and may stop eating for 1-3 weeks. It is also very possible that busulfan will cause infertility (the inability to produce sperm or eggs needed to have a child). It may be possible to store sperm cells (if you are a man) for future use (depending on your stage of development) or undergo other procedures (if you are a woman) to try to preserve fertility; these options will be discussed with you. There is a risk that chemotherapy could cause secondary leukemia or cancer, although previous experience in HSCT for conditions like SCD suggest the risk is low.

Of note, for a sickle cell bone marrow transplant using another person as the donor (rather than gene therapy), a common chemotherapy regimen includes busulfan. The amount of busulfan used for this gene therapy trial will be similar to the top end of the range of what would be given with for a HSCT.

The risks of the specific chemotherapy drug used in this trial is listed below:

Drug Risk Table. What it means for a side effect to be "likely", "less likely" and "rare, but serious"

Likely	This side effect is expected to happen in **more than** 20% of patients.
Less Likely	This side effect is expected to happen in 20% of patients **or fewer**.
Rare, but Serious	This side effect does not happen often – in **fewer than** 2% of patients – but is serious when it happens.

Busulfan

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in 20% or fewer patients, but more than 2%)	**Rare, but Serious** (May happen in 2% or fewer patients)
• Abnormal or fast heartbeat • Abnormal salt and/or vitamin levels that may require IV fluids • Anemia (low red blood cells) which may require blood transfusions • Chills, fever • Constipation, diarrhea, heartburn, nausea, vomiting, loss of appetite, stomach pain • Cough, stuffy nose • Damage to the liver or kidneys • Difficulty sleeping • Dizziness, headache • Feeling tired • High blood pressure • Infection, especially when white blood cell count is low • Infertility (inability to produce sperm or eggs needed to have a child)	• Blood in the urine • Coughing up blood • Damage to or scarring of the lungs • Loss or absence of sperm • Seizure • Visual disturbances	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Fluid around the heart • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Leukemia and other cancers • Low blood pressure which may cause feeling faint

• Low platelet counts which may cause bruising or bleeding • Pain • Rash • Sadness, worry • Sores in mouth which may cause difficulty swallowing • Swelling of the body		

After the chemotherapy is given and the gene-modified cells have been returned, there are many different kinds of risks that can occur. During this period, you will be at very high risk of bleeding and or infection because of very low blood counts. You will remain in the protected environment of the transplant floor and will be treated with oral and intravenous antibiotics, antiviral and antifungal agents, and transfusions of red blood cells and platelets to protect you from infection or bleeding. Despite the fact that all of the transfused blood products are specially screened, there is a very small risk of acquiring a blood borne infection such as hepatitis or HIV.

Some patients can have veno-occlusive disease of the liver (VOD). This complication usually results from high doses of chemotherapy. Patients with VOD become jaundiced (yellowish skin), have liver function abnormalities, fluid retention, abdominal swelling, and abdominal pain. If organ damage symptoms are severe, you may have to stay in the hospital longer or be re-hospitalized after transplant. Although many patients recover completely, these complications may cause permanent damage or even death.

While we have tried to design the trial to ensure that engraftment of the blood stem cells in the bone marrow will occur promptly, the stem cells may not grow. The busulfan is intended to destroy or suppress the SCD cells and give room for the transplanted cells to grow. If there is no sign of engraftment by 7 weeks after gene transfer (no increase in white blood cell counts), we will infuse your own unchanged back-up blood stem cells. If we need to do this, however, it may take an additional several weeks for the blood counts to improve, which makes the likelihood of life-threatening infection or bleeding higher.

There are significant risks, including the possibility of death, with this treatment program. It is important to weigh the risks and benefits for you as an individual carefully before agreeing to participate in this study.

Since this is a research study and the treatment is new and experimental, there may be additional side effects that are not known or predictable at this time.

Some people with SCD die despite attempts at treatment. In the event of your death, investigators will ask permission to do an autopsy, even though this may be years after gene transfer. This may

help investigators learn more about the effects of gene transfer. By signing this consent, you are not agreeing to an autopsy. You should, however, talk about this request among your family members.

Other Risks Associated with Gene Transfer

Risk of Infection

There is a small risk that your cells could become infected with human viruses or bacteria during the time the cells are being worked on in the laboratory. The researchers will check the cells for bacterial infection before they are given back. If the cells are found to be infected with bacteria, we would cancel the infusion and give the frozen backup bone marrow instead. There is a small chance that even though the tests show no infection, one might be present and upon infusion could produce a serious or even fatal infection in your blood.

The cells are grown in liquid that contains human blood products. The liquid has been checked for a wide range of well-known infectious viruses, including HIV, and found to be negative. It is not possible, however, to check for the presence of all possible viruses.

Risk of an Immune Reaction

With any type of infusion of blood cells there is a possibility of a reaction resulting from clumping of cells that stick to blood vessels in the lungs. Because the infused cells are your own stem cells the probability of this type of reaction is very low.

Risk of a Graft-Versus Host Disease-Like Rash

A graft-versus host disease-like rash may develop when the new cells grow and expand. This is most likely to occur between 6 and 12 weeks after infusion of the cells. This rash can be treated with topical and/or a short course of medication, such as corticosteroids. If necessary, a treatment plan will be recommended after you have been examined by the investigator. Additional blood tests and a skin biopsy may be requested by the investigator to confirm diagnosis.

Bone Marrow Aspiration/Biopsy

You may have a bone marrow aspiration biopsy so the doctor can further investigate your stem cells.

In this procedure you will be placed on your abdomen. A special needle is placed through the skin into the marrow cavity of the hipbone where stem cells and blood are collected. Two or three skin punctures are made on each hipbone. Although the punctures will not show, there are bone punctures underneath the skin. Once the procedure is finished, a bandage is placed over the needle marks to protect them.

You will be sedated or have anesthesia for this procedure, and it may require an overnight stay at the hospital. You may be asked to sign a separate hospital consent form for this procedure.

Risk from Bone Marrow Aspiration/Biopsy

Bone marrow biopsies are associated with discomfort and minor bleeding. Rarely, they are associated with infection.

Risks associated with Central Venous Line Placement

Placement of a central venous catheter (CVL) is done by a surgeon and may require sedation or anesthesia. The surgeon placing the CVL will obtain a separate informed consent from you prior to placement. The general risks associated with vascular access devices include bruising or bleeding around the catheter insertion site. There is a risk of infection which may require antibiotics or catheter removal. Central line-associated venous thromboembolism (blood clots) may require treatment with anti-coagulation (blood thinners) and/or catheter removal. Every effort will be made to minimize the risks associated with the central venous access.

Risks Associated with Plerixafor Administration

Adverse effects associated with plerixafor have been mild and transient, including headache, erythema and stinging at injection site, numbness/tingling around the mouth, nausea, and sensation of abdominal distention. Effects in the blood cells have included high white blood cell count and low platelet count. Enlargement of the spleen was observed following prolonged (2-4 weeks) daily plerixafor administrations in rats at doses approximately 4 time higher than the recommended human dose. The most common adverse reactions (greater than or equal to 10%) reported in patients who received plerixafor together with G-CSF, and more frequent with plerixafor than placebo during stem cells mobilization and apheresis were diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting.

Administration of the stem cell mobilizing drugs leads to an increase in the white blood cells (WBC) count. When WBC count is high in individuals with sickle cell disease, there may be a risk of sickle cell disease-related complications, including vaso-occlusive crisis, acute chest syndrome, splenic sequestration, or stroke. Problems like these have occurred when SCD patients were given G-CSF. According to our experience we have observed that administration of plerixafor has minimal/less chance of causing these problems, because it does have a moderate increase in the WBC count and the length of time with a high WBC count is much shorter when compare to G-CSF administration. These risks will be minimized by close monitoring and pre-plerixafor transfusion.

Risks Associated with Blood Transfusions

Some patients will receive blood transfusions prior to gene therapy that are not part of routine clinical management. The risks of transfusion include infection; transfusion reactions, including allergic reactions, febrile reactions, hemolytic reactions, or other rare reactions; alloimmunization; and other risks, including local tenderness, local infection, loss of red blood cells, anticoagulant discomfort, or air infusion.

Risks Associated with Blood Draws

Risks associated with a blood draw may include minor discomfort, bruising, fainting, and infection. When possible, we will draw blood at the time of a clinically-indicated procedure to reduce the number of needle sticks.

Risks Related to Potential Pregnancy

Being in this study while pregnant may expose the unborn child to risks, so pregnant females will not be included in the study. Routine pregnancy testing will be done on all female subjects at the beginning and every 12 weeks during the study. Males should not father a child while taking this medication. The effects of the drug being studied on the reproductive system (sperm, eggs) or to the developing fetus are unknown. For this reason, patients participating in the study should not become pregnant for 2 years following the gene therapy. **If you or your partner become pregnant during this study, the study staff must be informed immediately.** If you report a pregnancy of your partner, your study doctor will first need to obtain permission (consent) from your partner about sharing data before asking any questions about the pregnancy. If your partner consents to provide this information, your study doctor will follow up directly with your partner.

For entry into this study, we require that all participants agree to either abstain from sexual intercourse or use a reliable, effective contraception for 2 years following gene therapy. Before you start on this research study, pregnancy testing will be performed. The results of the pregnancy test are confidential. Results will be given to you by one of the study nurses or doctors in private. Every effort will be made to maintain confidentiality regarding positive pregnancy test results.

For patients who are minors, our policy is that we would not tell parent(s) or guardian(s) without the child's permission. However, under certain circumstances, we might be compelled to reveal this information. For example, if a child's life or someone else's life was at risk, or if abuse was suspected, it may be necessary to inform parent(s) or guardian(s) of a positive pregnancy test. If we believe it's necessary to tell a parent or guardian of a positive pregnancy test without the child's permission, we would meet with the child first in private to discuss our concerns before divulging any information regarding pregnancy. If a patient on the trial becomes pregnant, she will be required to stop the treatment plan as outlined by the study. She will continue to be followed on the study until the six-month off-treatment evaluation.

This means that even if we do not reveal the results, parent(s) or guardian(s) may suspect that their

child is pregnant despite our best efforts to maintain confidentiality. If a child becomes pregnant or if there is any chance that a child is pregnant (late menstrual period), please contact the study personnel immediately so that we may provide medical assistance and counseling.

Other Risks

Unanticipated medical information: During this study, it is possible that we will learn new information about your health or genetic background of your disease. If this information is thought to be important to your health care, we will notify you. At your request, we will explain the results to you, and with your permission, to your personal physician.

Going through HSCT or gene transfer is an intensive process and can lead to psychological difficulties, stress, depression, anxiety and other symptoms.

One subject in a prior trial was diagnosed with type 1 diabetes mellitus within a few weeks after receiving bone marrow conditioning and the gene modified cells. Sometimes new diseases such as type 1 diabetes mellitus or other serious disorders can first become evident when the person's body is under stress, caused for example by an infection or by the stress of the stem cell transplant. Thus, it is possible that the stem cell transplant and/or the known possible complications after transplant (such as infection) could be a trigger for a new disease process to develop. There have been no other reported cases of patients developing type 1 diabetes mellitus in the short-term follow-up period after receiving gene therapy (for sickle cell disease or for other diseases), but that does not rule out the possibility of a connection.

Risks of Genetic Research: It is possible this type of research may uncover information about your genetic factors that indicate that you or a relative are at risk for a genetic disorder in the future. Some people involved in genetic studies feel anxious about the possibility of carrying an altered gene that places them at risk or that may be passed on to children. If these feelings arise at any time during the study, you may contact us and we will arrange for you to speak with a genetic counselor.

You should also be aware that there might be social and economic disadvantages associated with the gathering of genetic information. For example, genetic information provided to the wrong source could affect you and your family. A U.S. law called the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and employers to discriminate against you based on your genetic information. Under this law, health insurance companies, group health plans, and most employers may not request your genetic information that we get from this research. For more information about GINA, please see: http://www.eeoc.gov/laws/types/genetic.cfm. This law does not protect information for being used when applying for life or long-term care insurance. We will do our best to keep all information confidential and only with your permission would we share this information with others. Thus, it

will be unlikely that an insurance company or employer would ever learn of such results.

Risk of Information Storage: We will keep the information secure and private by storing all of the data in password protected, secured databases. The study sponsor will protect your personal information in accordance with government regulations.

Other Treatments or Medicines

Some medicines react with each other, so it's important to tell the study doctor or staff about any other drugs, treatments, or medicines you're taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments.

It's also important that you tell the study staff about any changes to your medicines while you're in the study.

Surveys

There are very few risks with taking the study surveys. The main risk is that your confidentiality could be lost. The study team will do everything it can to keep your answers confidential.

Also, some of the questions or topics may upset you. If this happens, your doctor can connect you with a counselor or trained support specialist, if needed.

Your doctor will not be able to see your answers on the surveys. The answers will not be shared with anyone until after the study is done and you will not be able to be identified.

Unforeseen Risks

Other new risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. There may be some unknown or unanticipated side effects from this treatment. The study team will do everything they can to keep you safe and lower your risk of side effects.

For more information about risks and side effects, ask your study doctor.

5. Your Rights to Withdraw, Ask Questions, and Seek Other Treatment

Being in this study is your choice. You can choose **not** to be in this study or leave this study at any time. If you choose to not join or leave this study, it won't affect your regular medical care in any way. If at any time you are considering leaving the study, talk to your study doctor about your health and safety.

You have the right to ask questions about the study at any time. If you have questions about the study, please contact:

[Insert contact details for Principal Investigator or study team]

If you want to talk with someone not directly involved in the study, or have any complaints or questions about your rights as a research participant, you may contact:

NMDP Institutional Review Board Administrator at: 1 (800) 526-7809

You must tell [insert name of Principal Investigator] if you decide to leave the study.

If you choose not to join, other options are available. Your study doctor will talk with you about your options. If you decide not to join this study, your medical care will not be affected in any way. If you join this study, you cannot be in another clinical trial at the same time.

Your other choices may include:

- Allogeneic transplant from an unrelated or haplo-identical donor
- Continue with your current treatment regimen
- FDA-approved medications and/or supportive care measures for sickle cell disease
- Joining another clinical trial (check with your doctor)

Every treatment option has benefits and risks. Talk with your doctor about your choices before you decide if you will be in this study.

6. New Information Available During the Study

During this study, the study doctors may learn new information about gene therapy for SCD or the risks and benefits of taking part in the study. If they learn new information, they'll tell you as soon as it's available.

The new information may mean that you can no longer participate in the study, or you may not want to continue. If this happens, the study doctor will stop your participation and offer you all available care to meet your health care needs.

7. Privacy, Confidentiality, and Use of Information

Your privacy is very important to us. The study doctors, study sponsor, and other groups with access to your study-related medical information will do everything they can to protect it. The study doctors can protect your records if there is a court case. However, some of your medical information may be shared if required by law. If this happens, the study doctors will do their best to make sure that any information that goes out to others will not identify you.

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept confidential (private). However, we cannot promise total privacy.

To make sure the study is running ethically, some government agencies or other groups may need to access part of your medical records. For this study, those groups include:

- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP)/Be The Match registry and The Emmes Company, who are coordinating the studies of the BMT CTN
- The Food and Drug Administration (FDA) and National Institutes of Health (NIH), which includes the National Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI) – including the Recombinant DNA Advisory Committee (RAC)
- Office of Human Research Protection (OHRP)
- Data and Safety Monitoring Board (DSMB), not part of [Institution]
- Institutional Review Boards (IRBs) responsible for this study
- Connell & O'Reilly Families Cell Manipulation Core Facility, Dana-Farber Cancer Institute
- California Institute for Regenerative Medicine (CIRM)

- Study Investigators

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Study information may also be used for research in the future. These projects could be related to your disease or similar diseases, or development of the study investigational treatment.

We might use information from this study to get approval from the government, like the Food and Drug Administration (FDA).

Private information, blood, or tissue taken during the study may be used for future research. If the study team does this, the information, blood, or tissue will not be attached to you or your name in any way and results of the research done with it will not be given to you. To learn more, read section 8 on Blood Samples for Future Research.

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 website will include a summary of the results. You can search this website at any time.

You will not be able to access your study results before the study is done. This helps keep the study results accurate and trustworthy.

When the study is complete, you can ask your study doctor for your health information from the study**. By signing this Consent Form, you agree to ask for your results only after the study is done.** You will still have access to your regular medical records.

Data about your health, including follow up after 2 years may be obtained by the BMT CTN from the CIBMTR, which captures information on all US transplants.

Storage of Stem Cells:
If your back-up cells are not used, the Cell Manipulation Core Facility (CMCF), which is the center where cells are processed and stored, will store your cells in their freezers for 10 years. If after 10 years of storage your physician determines that the products are no longer useful to you, you will be contacted (e.g. by registered mail) and offered the option to request transfer of your products to another facility at your cost. If we do not receive a request to transfer your products, the products will be either discarded or de-identified and used for research, validation, or quality improvement projects. If after a time in storage, the product integrity or labeling no longer meets current standards for clinical use, the same notification process will be followed prior to product discard or de-identification and use by the lab.

Disposition of Gene-Modified Cells:
If some or all of your gene-modified cells are not infused into you, the sponsor may decide if the

cells will be discarded or used for research.

8. Blood Samples for Future Research

Throughout your participation in this study, you will have blood draws at multiple timepoints. Some of these blood samples will be sent to Boston Children's Hospital and include samples that will be run in research labs and they are required to help determine that the gene transfer is safe and is working.

The section below describes additional blood samples that we would like your permission to draw at various timepoints throughout the study:

We will perform genomic analysis on your sample examining where the vector has inserted into your cells' DNA. In some cases, additional genomic studies may be needed to determine the contributions of other genetic sequences to these vector insertions called whole genome analysis (WGA). In WGA, all or most of your genes are studied and used by researchers to find alterations in a large number of genes that may contribute to understanding how your cells have been altered by the vector insertions. If the study doctors feels this type of study is needed on your cells, you will informed prior to these studies being undertaken.

We may collect blood samples and data including genetic and health data, clinical information from your medical record as well as other health information. We may continue to obtain updates on your health from your medical record or as long as you participate in this study. Data and samples may be linked for research purposes. There is no limit to the length of time we may keep your samples and data. If a previously or subsequently collected DNA, tissue, other biological sample, genomic sequence data, or other health data exists, we may obtain this instead of or in addition to the biological samples we are collecting as part of this research.

Your blood and cells have genetic information, called DNA. DNA from your stored blood samples and your health information might be used in future research / genome-wide association (GWA) studies.

- Your blood samples will not be attached to you or your name in any way. Results of the research done with this sample will **not** be given to you.

- The blood samples will be sent to the BMT CTN Research Sample Repository for processing and storage. The research sample will be given a bar code that **cannot** be linked to you.

- GWA studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may raise a person's risk of developing a certain disease.

- If your genetic information is used in a GWA study, the researcher will add the DNA test results and non-identifying information into a public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you or link you to your information or research samples.

9. Leaving the Study

You can choose to leave the study at any time.

You may also be told to leave the study for reasons such as:

- You don't meet the study requirements.
- There are not enough hematopoietic stem cells harvested for gene transfer.
- The gene modified cells are infected or otherwise unsafe to give to you.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You're having serious side effects.
- You become pregnant.
- You cannot keep appointments
- The study is stopped for any reason.

Even if you leave the study, the information already collected from you will be included in the study evaluation. If you don't want your information to be used, you must let your study doctor know.

Once gene transfer has occurred, the researchers will collect the results of follow-up exams and tests to determine if the gene transfer is safe. Once the gene transfer has happened, the genetic changes will have occurred and thus will not be reversible.

If the gene-modified cells have not been infused, the sponsor may decide if the cells will be discarded or used for research. If the back-up cells are not used, the sponsor may decide if the cells will be discarded or used for research.

10. Cost and Reimbursement

You will **not** be paid for joining this study. You will not be paid or reimbursed for any extra expenses (such as travel or meals) from your participation in this study.

A new drug or product may be developed from this study. [Institution] will **not** pay you if a commercial product is developed from blood or tissue taken from you during this study.

Most of the visits for this study are standard medical care for patients with SCD and will be billed to your health insurance company. You and/or your health insurance company will need to pay for some or all of the costs of standard medical treatment in this study.

Some health insurance plans will not pay for costs of care when you take part in a research study. Check with your health plan or insurance company to find out if they will pay.

You or your health insurance company will not be charged for extra tests or research costs for this study. Extra cost may include:

- Peripheral blood samples (correlatives)

For questions about your costs, financial responsibilities, and/or health insurance coverage for this study, please contact [Center/ Financial Counselor] at: [Number].

It is also possible that the data and samples we collect or what we learn or create from such data and samples, may be made available (with or without charge), for further research or use by such parties (e.g. other hospitals, universities, and businesses) to create commercial products, services, research tools, or inventions that have value. Participants will not receive any payments and no financial compensation will be provided for participation in the study, or for the development of any new products or services that result from the use of your data and/or samples.

Physical Injury as a Result of Participation

Tell your study doctor or staff if you think you've been hurt because of being in this study.

You'll get medical treatment if you're hurt as a result of this study. You and/or your health insurance company will be charged for this treatment. The study sponsor will not pay for medical treatment as a result of unintended injury.

In case of injury resulting from this study, you don't lose any of your legal rights to seek payment by signing this form.

11. Health Insurance Portability and Accountability Act 1 (HIPAA) Authorization to use health information for research

Your local study hospital will give you a separate form with information about the Health Insurance Portability and Accountability Act 1 (HIPAA).

TITLE: **BMT CTN 2001:** A Multi-Center, Phase 2 Gene Transfer Study Inducing Fetal Hemoglobin in Sickle Cell Disease

- I have read and understood this Consent Form. The purpose and description of the research study has been explained to me.
- I have had the chance to ask questions and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I have had the chance to discuss my participation in this research study with a family member or friend if I choose.

- I understand that…
  - I may not directly benefit from taking part in the study.
  - My name and personal information will not be identified even if information gained during the study is published.
  - I can leave this study at any time and doing so will not affect my current care or prevent me from receiving future treatment.
  - I will be given a copy of this signed consent form.
  - I do not give up any legal rights by signing this form.

_____

Printed Name of Participant

_____ _____

Participant Signature (if 18 years or older) Date (MM/DD/YYYY)

_____

Printed Name of Parent/Legal Guardian
(if participant is less than 18 years old)

_____ _____

Parent/Legal Guardian Signature Date (MM/DD/YYYY)
(if participant is less than 18 years old)

_____

Printed Name of Parent/Legal Guardian #2 (*Optional*)
(if participant is less than 18 years old)

Parent/Legal Guardian #2 Signature (*Optional*)
(if participant is less than 18 years old)

Date (MM/DD/YYYY)

Physician certification

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____

Printed Name of Counseling Physician

_____ _____

Counseling Physician Signature Date (MM/DD/YYYY)

Interpreter certification (if needed)

I certify that I have provided an accurate interpretation of this consent form. I believe the participant has understood the information provided.

_____

Printed Name of Interpreter

_____ _____

Interpreter Signature Date (MM/DD/YYYY)