INSTITUTE: National Institute of Allergy and Infectious Diseases

STUDY NUMBER: 14-I-0185 PRINCIPAL INVESTIGATOR: David H. McDermott, MD

STUDY TITLE: A Phase III, Double-blind, Randomized, Crossover Study of Plerixafor Versus G-CSF in the Treatment of Patients with WHIM Syndrome

Continuing Review Approved by the IRB on 05/21/18
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Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in at least one study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research staff before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

THE CONSENT PROCESS

You or your child are invited to take part in a study to find out whether a medication named plerixafor is safe and effective in patients with WHIMS, which stands for warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. In this study, we will compare plerixafor to granulocyte colony-stimulating factor (G-CSF), the currently recommended treatment for inherited neutropenia, for the prevention of infections in children and adults with WHIMS. The following informed consent document gives background information on the disorder, explains the research goals of the study we are proposing, the reasons for trying plerixafor, and the specific methods we will use to give you the medication. Once you know about the study and the tests that will be done, you will be asked to sign this form to join this study.

YOUR UNDERLYING DISEASE

You have been diagnosed with a rare inherited condition called WHIMS caused, by various mutations (genetic changes) that increase the activity of a gene called CXCR4. CXCR4 plays an important role in your immune system development as well as how the blood stem cells work in your bone marrow. Blood stem cells are cells that can form all parts of your blood including red and white blood cells. Neutrophils make up the majority of your white blood cells (WBCs) and are particularly important in fighting off infections. When neutrophil counts drop below normal (a condition known as neutropenia), the body is less able to fight off infection. Excessive function of the CXCR4 gene causes mature neutrophils to be retained within the bone marrow rather than being released to the blood, and is one of the causes of severe inherited neutropenia (low white blood counts). Patients with WHIMS are at risk for severe warts that can become cancerous and also for skin, soft tissue, ear, mouth, sinus, and lung bacterial infections. The result of these infections can be very serious causing permanent disability and death.

Current treatments for WHIMS are based on limited clinical experience, and there are no controlled clinical studies just for this disease. The available treatments consist of daily or every other day injection of a white blood cell growth stimulating medication called granulocyte colony-stimulating factor (G-CSF), and monthly infusion of intravenous immunoglobulin (IVIG) or weekly injection with subcutaneous immunoglobulin. These therapies are expensive, non-specific, have significant side effects and toxicities, and do not fully correct all problems, especially warts and human papillomavirus (HPV) related cancers.

Two recently published studies done at the National Institutes of Health (NIH) and University of Washington have shown that plerixafor could safely restore the blood counts to normal in 9 WHIM patients for a 1-2 week period. A second study at the NIH has shown that this can be done for 6 months using twice daily low dose therapy in 3 patients. Therefore, plerixafor may offer a well-tolerated new treatment for WHIMS.

PURPOSE OF THE STUDY

The purpose of this study is to compare plerixafor versus granulocyte colony stimulating factor (G-CSF) for the prevention of infections in children and adults with WHIMS. The Food and Drug Administration (FDA) has already approved G-CSF for the treatment of severe neutropenia, and the use of plerixafor in combination with G-CSF to further increase the number of blood stem cells in the blood. However, the FDA has not approved plerixafor for specific treatment of WHIMS. Plerixafor will be used in this study with permission from the FDA for experimental use. That means we don't know if plerixafor is safe in people with WHIMS, or if it will work to treat WHIMS.

What is G-CSF?

Granulocyte-colony stimulating factor (G-CSF) is FDA-approved for treating inherited neutropenia (low neutrophil count). G-CSF is commonly given daily or every other day to increase the neutrophil counts in the blood. The NIH Clinical Center Pharmacy will purchase the G-CSF from Amgen.

What is plerixafor?

Plerixafor is an FDA-approved drug designed for occasional use in combination with G-CSF to increase the number of stem cells that can be collected prior to bone marrow transplantation. Plerixafor blocks the CXCR4 receptor that in WHIMS patients is overactive and normalizes its function thereby allowing the movement of mature neutrophils out of the bone marrow and into the blood. Plerixafor is not currently approved for long-term use, or the treatment of WHIMS or patients with neutropenia. Genzyme/Sanofi Corp is the manufacturer of plerixafor and will provide the drug for this study.

SUBJECT POPULATION

Twenty subjects (10 to 75 years of age) will be enrolled in the study. To be in the study, you must have a mutation in the CXCR4 gene, agree to use contraception if capable of having children, and have a local physician for your medical care.

STUDY DESIGN

Participants are selected at random (by chance, as in a coin toss) to first receive either plerixafor or G-CSF injections twice a day for a period of one year. Participants and study staff directly involved with the participants are not told which drug is being provided therefore, both are "blinded" to the treatment. After the first year of treatment with one of the drugs, participants are switched to the other drug in the second year of treatment. Your study participation time is approximately 3 years and requires approximately 11 visits as an outpatient to the NIH Clinical Center and approximately 16 visits to a local medical facility for blood draws to measure your blood counts.

Screening Visit: Before starting the study, you will be asked to visit the NIH Clinical Center for about 2-3 days. The study doctor will ask you about your health and your medical history, examine you, and measure your height, weight and vital signs. You will be asked about any medications you have been taking. You may be required to have an ultrasound (imaging test using sound waves) of your spleen, heart tracing (electrocardiogram [ECG]) and echocardiogram (ultrasound test of the heart), CT Scan (computed tomography) of your sinus, chest, abdomen, and pelvis, and other medical procedures as may be deemed necessary by the study doctor. Blood and urine samples to measure your immune function and chemical balance, including tests for hepatitis B and C virus, and human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS) will be obtained. If you are a woman of childbearing potential, your blood or urine will also be tested to see if you are pregnant. These procedures are required to evaluate your eligibility and assess if it is safe for you to participate in the study.

The study doctor will assess the activity of your current disease by asking questions about the symptoms of your disease (like skin conditions) and medications you are taking for them. We may request an optional small skin or wart tissue sample and take photographs of any warts on your skin and oral, nasal and genital tissue with your permission. Depending on your medical history or the location and extent of your infections, you may be referred to and evaluated by various specialists at the NIH Clinical Center including skin doctors (dermatologist), female reproductive doctor (gynecologist), male reproductive doctor (urologist), hearing tests (audiologist), ENT (ear, nose, and throat doctors), oral specialists (dentist or oral surgeon), and blood doctors (hematologist or immunologist).

If you are now being treated with G-CSF, the dose will be adjusted and the frequency increased to twice per day. If you are not being treated with G-CSF, you will be trained and start with twice daily self-injection of G-CSF at a dose specified by the study doctor.

Initial Evaluation (approximately 2-20 weeks): After successfully completing the screening visit, you will begin an Initial Evaluation period of about 2-20 weeks from your home. You will continue the G-CSF injections as prescribed by the study doctor as well as your preventative regimens with antibiotics and/or immunoglobulin as applicable. You will visit your local medical facility for a blood draw to measure your blood counts at least once in this period, and more often if there is a change in G-CSF dose. If you experience any new or significant worsening of infections, you will be required to visit your local medical provider for diagnosis and treatment, and provide the medical records and results of your visit to the study doctor. You will be trained to complete a detailed health Memory Aid every day and submit the completed form to your study doctor every week. The Memory Aid will be submitted by secure email or by a mutually agreed method.

Randomization to Treatment Arms and Washout Period (2 days): After successfully completing the Initial Evaluation period, you will be assigned by random selection to start treatment with either plerixafor or G-CSF. Neither you nor the research staff will know which drug you have been assigned to take first. You will visit the NIH Clinical Center for approximately 2 days as an outpatient with your G-CSF injections withheld, prior to commencing the study treatment.

Equilibration Period (8 weeks): After starting your treatment, you will continue your twice a day injections from home, complete your daily health Memory Aid and submit the Memory Aid to your study doctor every week, go to your local medical facility for blood tests every 2 weeks or as requested by the study doctor, and go to your local medical

provider for any new or significant worsening of your infections and provide the results of the visit to your study doctor. This is a period of adjustment for the treatment drug to take full effect and an opportunity to adjust your treatment dose.

Treatment Period (52 weeks): After your 8-week period of adjustment at home, you will visit the NIH Clinical Center for evaluation as you begin the Treatment period. You will continue your routine as in the Equilibration period, *visit the NIH Clinical Center approximately every 4 months, and visit your local medical facility for blood tests at the approximate midpoint period (about 2 months) between your visits to the NIH.*

Switching to the Alternate Treatment Arm (Washout, Equilibration, and Treatment Periods – 60 weeks): At the end of your first year of treatment, you will visit the NIH for an evaluation and complete your first study year injections at least 2 days prior to commencing the 2nd study drug treatment. As with the first year, you will undergo an 8-week Equilibration and 52-week Treatment period with the 2nd study drug. It is also possible that you may be switched to the alternate treatment arm prior to fully completing the first treatment arm if you are not able to tolerate or respond to the first treatment.

Reverting to Your Pre-Study Treatment (Post-Treatment Period 4 months):
At the end of your second year of treatment, you will visit the NIH Clinical Center to complete your final study injections and revert to your pre-study G-CSF regimen. You will continue completing your daily health diary and submit it to your study doctor every week or as requested, and visit your local medical provider for any new infections and provide the results of your visit to your study doctor. You will visit your local medical facility for blood tests approximately every 2 weeks in the first month or as instructed by the study doctor, and at approximately 2 months until your End of Study visit to the NIH Clinical Center. If you are capable of conceiving or having children, you must continue birth control through this period.

When this study is completed, you will be returned to the care of your local physician. *It is important to stress that participation in this protocol does not constitute a promise of long-term medical care here at the NIH Clinical Center*. You may decide not to take part in this study or you may choose at any point to stop receiving the study drug and withdraw from the study; in either case you will be returned to the care of your local physician.

STUDY PROCEDURES

Physical exam with medical and medication history: You will be evaluated by the study staff and will undergo a physical exam. You will be asked about how you are feeling, if you've had any recent illness, and about the medications you are taking now and have taken in the past, including non-prescription drugs. Your height and weight will also be measured at some of the visits.

Vital signs: Your height, weight, blood pressure, heart rate, respiratory rate, and temperature will be recorded.

EKG: This procedure records the normal electrical activity of your heart. Electrodes, which are soft, sticky patches attached to wires, will be placed on the skin of your chest, arms, and legs. The procedure doesn't cause any harm, however the sticky patches used for the procedure may cause minor discomfort when removed, especially if they're placed in a region of the chest with hair.

Echocardiogram: This procedure will be done only if you haven't had it done in the past 5 years. The echocardiogram takes pictures of your heart using sound waves, which are displayed on a monitor, to measure the size of the heart muscle and to see how well it works. It's like a sonogram that pregnant women get to see how the baby is growing. It doesn't hurt, but you will need to remain quiet and follow directions.

CT Scan Sinus, Chest, Abdomen, and Pelvis: These x-rays are performed if medically necessary to assist in the evaluation of your illness. The dose of radiation from the x-rays and CT scans will be kept as low as possible. Unless the person is pregnant, this level of radiation is generally considered safe.

DEXA Scan: Dual-energy X-ray Absorptiometry (DEXA) is a low-dose x-ray procedure to measure the loss of bone density; this test is commonly used to test for osteoporosis. Unless the person is pregnant, this level of radiation is generally considered safe.

Spleen ultrasonogram: The sonogram takes pictures of your spleen using sound waves, which are displayed on a monitor; it's like a sonogram that pregnant women get to see how the baby is growing. It doesn't hurt, but you will need to remain quiet and follow directions.

Pulmonary Function Test (PFT): The pulmonary function test is performed to assess your lung function by measuring the volume of air moving in and out. You will be requested to blow air forcefully into a machine. You might experience some dizziness or headache from the exertion when undergoing the test and experience some coughing or shortness of breath after the tests.

Audiology Tests: If you have a history of hearing loss and ear infections, an audiologist will evaluate your hearing function. You will sit in a sound proof room and asked to raise your arms to various tones that are generated as part of the test.

Ear, Nose, and Throat (ENT) Consultation: If you have concerns or have had recent or recurring infections in your sinus, ears, nose, or throat, an ENT consultation will be arranged to evaluate the status or risk of infection. The ENT specialist may use various tools to illuminate and examine your ears, nose, and throat.

Gynecology or Urological Consultation: A gynecologist (for female patients) or urologist (for male patients) will evaluate your genitals for warts and HPV infection. The examination will take place in a private room and surface scrapings or a small piece of tissue may be taken for additional evaluation.

Dermatology Consultation: A dermatologist will evaluate your skin for warts and HPV infections. The examination will take place in a private room and skin scrapings or a small piece of skin may be taken for additional evaluation.

Dental Consultation: A dentist will evaluate your teeth, gums, and mouth for infections and the presence of HPV lesions. Oral swabs of your oral cavity as well as x-rays may be taken as part of the evaluation.

Clinical Photography of Skin Lesions or Warts: We will take pictures of your warts and skin lesions including a comprehensive set of the external surface of your body and detailed photographs of the hands and feet, which often are sites of infections. Pictures will be taken prior to the first study treatment and after each one-year treatment period. Additional photos may be taken of particular warts and other types of skin infections, including infections of the buttocks and genitals if applicable. These pictures will help us determine if the treatments improved the appearance of your warts or if new warts have appeared in other parts of your body. The photographs will be coded and will not have your name on them. If such pictures are used for publication, you will not be identified in any way.

Urine collection: A sample will be collected for routine analysis to check if your kidneys are working well.

Pregnancy test: If you are a woman of childbearing age, your blood or urine will be tested to see if you are pregnant.

Blood draw: Blood will be drawn from a vein in your arm to measure your blood cell counts, to monitor your liver and kidney function, and to evaluate markers of your disease. The total volume of blood collected during the study will not exceed the guidelines for blood collected for research in adult and children subjects at the NIH Clinical Center. While in the study, please inform study staff if you are participating in other studies or have blood drawn for any other reason. The risks associated with drawing blood from a vein in your arm include pain, bruising, lightheadedness, fainting, and rarely, infection at the site. Some of the blood draws will be done at your local laboratory or physician's office. The study doctor will let you know the exact time of when the blood draws should be done prior to your morning injection, and arrange for the results to be sent to your study doctor.

HIV and Other Viral Testing: As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS; for hepatitis A, B, and C which cause liver disease; and for HTLV-1/-2, which

cause diseases similar to multiple sclerosis and hairy cell leukemia. If you are positive for any of these viral infections, we will tell you what the results mean, how to find care, how to avoid infecting others, how we report newly diagnosed HIV infection, and the importance of informing your partners at possible risk because of these infections.

Wart Biopsy: Wart biopsies may be requested for diagnosis or research; biopsies conducted only for research purposes are optional. If you agree to a wart biopsy, an experienced practitioner will perform the procedure. Only local anesthetics will be used to prepare the biopsy site; no conscious sedation or general anesthesia will be given. The risks of wart biopsy include local pain, bleeding, infection, and potential scar and keloid formation (wide scar). Antibiotics and oral analgesics (numbing medicine) will be used to manage pain and infection.

Bone Marrow Biopsy: Bone marrow biopsies may be requested for diagnostic or research purposes; biopsies conducted only for research purposes are optional. If you agree to a bone marrow biopsy, an experienced practitioner will perform the procedure and use appropriate measures to reduce any discomfort during the procedure. The risks of bone biopsy include local pain, bleeding, and infection. Topical antiseptic and oral or injected pain medicines (numbing medicine) will be used to manage pain and infection after the procedure.

Request for Excess Tissue: If you have had tissue removed for medical indications at the NIH or elsewhere that is not required for your medical care and would otherwise be discarded, with your permission, we may request it to be sent to us for pathology and other research studies.

Quality of Life Questionnaire (health survey): During your visits to the NIH, you will be requested to complete a questionnaire about your overall health and well being. The survey is commonly used in many studies and has 36 short multiple-choice questions and should take about 20 minutes to complete.

Memory Aid card/reporting new infections/treatments: You will be instructed on how to complete your Memory Aid card every day to record the following: location of each injection, side effects you're experiencing, changes in the medications you're taking, changes in the symptoms you're having, the date and duration of any fevers or new antibiotic treatments, the diagnosis of any new infections, or any hospitalizations. You will have to submit your Memory Aid entries every week to your study doctor. You will be instructed on how to submit your Memory Aid entries.

RISK ASSOCIATED WITH RADIATION EXPOSURE

This research study involves exposure to radiation from Dual-energy X-ray Absorptiometry (DEXA) scans, an x-ray procedure to measure the loss of bone density. You will receive three scans with an exposure of 0.000030 rem each: prior to start of treatment and at the end of each one-year treatment. The total radiation you will receive from the three DEXA scans in this study is 0.000090 rem. This radiation exposure is not required for your medical care and is for research purposes only. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer. Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. If you are breast-feeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

RISKS ASSOCIATED WITH THIS STUDY (PLERIXAFOR OR G-CSF)

In this study, 9 subjects have received both study drugs (plerixafor and G-CSF) as of May 2017. A subject experienced a new severe rash (psoriasis-like) beginning a week after commencing the 1st study drug, which resolved after switching to the alternate study drug and topical steroid treatment. Another subject, who has never received G-CSF prior to the study, experienced pain and swelling in his hands and knees on each of the study drugs and was discontinued from both study agents. The subject was diagnosed with Arthralgia and Reactive Arthritis and his symptoms resolved with oral steroid treatment.

RISKS ASSOCIATED WITH PLERIXAFOR

Risks associated with long-term use of plerixafor: The FDA has approved plerixafor for single or short-term use in mobilizing stem cells (blood cells in the bone marrow are released to circulate in the blood). However, the FDA has not approved plerixafor for daily treatment or use over long periods. The risks of prolonged treatment with plerixafor are not known. In this study, you will receive plerixafor twice a day for about 14 months, but at a daily dose that is much lower (approximately 3-12 times lower) than has been approved for single or short-term use in stem cell mobilization.

Risks associated with plerixafor injection: Plerixafor is usually injected at a dose of 0.24 mg/kg once or for several daily injections. For this study, plerixafor will be injected at a dose of 0.01-0.04 mg/kg twice a day, which is an injected amount that is much lower than is typically used. Nevertheless, the most common side effects as listed in the product label that can be associated with plerixafor at doses much higher than the dose you will receive in this study are listed below – please inform the study doctor if you experience any of these reactions:

Injection site reactions: When you are given a dose of plerixafor, this will be injected under your skin and may cause slight pain, redness, bruising, or itching where the study drug is injected. Most of these resolve within minutes and require no treatment. We will treat any prolonged reactions (if problematic) with standard medical therapies.

Bone Pain: Bone pain is often experienced as a deep dull pain that cannot always be easily localized. Bone pain can often be readily controlled through over the counter medication such as Advil or Tylenol.

Joint Pain or Arthralgia/Arthritis: Pain in the joints without swelling (arthralgia) has been reported frequently when plerixafor is given in conjunction with G-CSF. Initial treatment is with over the counter medication such as Advil or Tylenol. Arthritis is a joint pain with swelling and stiffness. If you have any joint problems, you should report it to your study doctor. Additional diagnosis and treatment might be needed.

Gastrointestinal side effects: Various side effects related to gastrointestinal (gut) function have been reported after doses of 0.24 mg/kg including abdominal pain, diarrhea, constipation, nausea, flatulence (gassiness), and vomiting. In general, these have not resulted in the need to stop the medication.

Thrombocytopenia and bleeding: Lower platelet counts (thrombocytopenia) have been reported with use of plerixafor. We will check this with periodic blood counts and the drug will be stopped if dangerously low levels are encountered.

Splenic enlargement (large spleen size): An increase in spleen size has been shown to occur in rats treated with plerixafor at proportionately much higher doses than used here. Although this has not been reported as causing any severe problems in humans, we will monitor for clinical signs of problems by asking you about left shoulder or abdominal pain under your left rib cage. If these symptoms occur, call your doctor immediately and inform your study doctor.

Risk of allergic reactions: Mild to moderate reactions such as itchiness, swelling around the eye, difficulty in breathing, or low oxygen in the blood during has been observed during or within 30 minutes of plerixafor injection. Stop the injection right away and call your doctor or seek emergency care right away.

Risk of fainting or low blood pressure: Low blood pressure and fainting has been observed within 2 hours of plerixafor injection. If you experience low blood pressure with injections, appropriate precautions should be taken.

Fetal harm in pregnant women: The fetal risks associated with plerixafor are not known, but animal data has shown some risk. Because of this, all study patients must agree not to become pregnant or impregnate a female. Females of childbearing potential must have a negative pregnancy test before beginning the study agent. You and your partners must use 2 methods of birth control and continue contraception until the end of the study.

Breast-feeding: Because there is an unknown but potential risk to infants who are being breast-fed from a mother who has been treated with plerixafor, participants must agree not to breastfeed during the study.

RISKS ASSOCIATED WITH G-CSF

Risks associated with long-term use of G-CSF: The FDA has approved G-CSF for the treatment of inherited neutropenia (low neutrophil count). However, patients on long-term treatment of G-CSF over several years may have a cumulative risk (risk that increases with amount and length of use) of genetic mutations which may lead to Myelodysplastic Syndrome (MDS) a form of pre-leukemia, and Acute Myeloid Leukemia (AML). Leukemia is a form of cancer in your blood caused by uncontrolled growth of white blood cells and is fatal if not treated with chemotherapy and/or bone marrow transplant. The manufacturer's product label reports a cumulative risk of 16.5% after 8 years of G-CSF treatment for patients with inherited neutropenia. Although the results from the manufacturer are not specifically limited to patients with WHIMS and patients with WHIMS are thought to be at less risk of this complication, and the dose used in this protocol is less than typically used for other studies, the risk of leukemia in long term G-CSF treatment may be a concern.

Risks associated with G-CSF injection: G-CSF is usually injected at a dose of 2.3 to 40 µg/kg/day. For this study, G-CSF will be injected at a dose of 0.5-2.0 µg/kg twice a day, which is an injected amount that is much lower than is typically used. Nevertheless, the most common side effects as listed in the product label that can be associated with G-CSF at doses much higher than the dose you will receive in this study are listed below – please inform the study doctor if you experience any of these reactions:

Injection site reactions: When you are given a dose of G-CSF, this will be injected under your skin and may cause slight pain, redness, bruising, or itching where the study drug is injected. Most of these resolve within minutes and require no treatment. We will treat any prolonged reactions (if problematic) with standard medical therapies.

Bone Pain: Bone pain is often experienced as a deep dull pain that cannot always be easily localized. Bone pain can often be readily controlled through over the counter medication such as Advil or Tylenol.

Joint Pain or Arthralgia/Arthritis: Pain in the joints without swelling (arthralgia) has been reported frequently with G-CSF. Initial treatment is with over the counter medication such as Advil or Tylenol Arthritis is a joint pain with swelling and stiffness. If you have any joint problems, you should report it to your study doctor. Additional diagnosis and treatment might be needed.

Thrombocytopenia and bleeding: Lower platelet counts (thrombocytopenia) have been reported with use of G-CSF. We will check this with periodic blood counts and the drug will be stopped if dangerously low levels are encountered.

Splenic rupture: Splenic rupture, including exceedingly rare fatal cases, has been reported following the administration of G-CSF. However, these are at doses typically much higher than used in this study, We will monitor for clinical signs of problems by asking you about left shoulder or abdominal pain under your left rib cage. If these symptoms occur, call your doctor immediately and inform your study doctor.

Risk of serious allergic reactions: Allergic-type reactions have been reported in <1 in 4000 of subjects treated with G-CSF. These reactions can cause rash and itchiness over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eye, fast pulse, and sweating may occur during or within 30 minutes of G-CSF injection. Stop the injection right away and call your doctor or seek emergency care right away.

Immunogenicity: As with all therapeutic proteins, there is a potential for causing allergies and antibodies to develop against the drug. Low blood cell counts resulting from an antibody response to proteins have been reported on rare occasions in subjects treated with other similar drugs so there is a chance that your body might develop an immune reaction to the G-CSF drug that could either block the drug's effect or cross react with your body's natural G-CSF.

Aortitis - inflammation of the aorta: Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported in patients who received G-CSF. Symptoms may include fever, abdominal pain, feeling tired, and back pain. Call your healthcare provider if you experience these symptoms.

Fetal harm in pregnant women: The fetal risks associated with G-CSF are not known, but animal data has shown some risk. As a condition for participating in this study, participants must agree not to become pregnant or impregnate a female. Females of childbearing potential must have a negative pregnancy test before beginning the study agent. You and your partners must use 2 methods of birth control until the end of the study.

Breast-feeding: It is not known if G-CSF is excreted in human milk. Due to the potential risk to infants who are being breast-fed from a mother who has been treated with G-CSF, participants must agree not to breastfeed during the study.

BENEFITS ASSOCIATED WITH THE STUDY

If you take part in this study, the treatment drugs are expected to increase your neutrophil counts, but their effectiveness in reducing your risk of infection are not known, and that is what this study is designed to answer. This study is not designed to provide you with any direct benefit in terms of relieving your neutropenia in the long term.

ALTERNATIVES TO PARTICIPATING IN THIS STUDY

You may choose to not participate in this study and obtain care from your usual health care providers.

STOPPING STUDY PARTICIPATION

You can stop participating in this study at any time. Tell a member of the study staff if you no longer want to participate. This decision will not affect your ability to receive care at the NIH Clinical Center or your participation in other studies. Blood and tissue samples and data collected prior to this request will be stored for the duration of the study, unless you specifically request the removal of all your samples from the study.

EARLY REMOVAL FROM THE STUDY

You may be removed from this study without your consent for the following reasons:

- You develop a health problem, an abnormal lab test, or any medical disease that, in the opinion of the study doctor, puts you at increased risk of harm or is not in your best interest.
- The study is stopped or cancelled.
- You become pregnant.
- You don't keep your appointments or refuse to undergo study procedures as required.

COMPENSATION

You will not be paid for your participation in this study. However, if you agree to biopsies performed for research, we will compensate you $120 for a skin/wart biopsy and $200 for a bone marrow biopsy - or the equivalent in gift cards for participants under age 18.

COSTS ASSOCIATED WITH THE STUDY

There will be no charge to you or your health insurance company for any tests, procedures or medications that are directly related to this study. This includes blood tests required by the study and drawn at your local medical facility. Cost of other medical care provided outside the NIH during this period will not be covered.

NEW FINDINGS

Any new findings discovered during this study that are considered relevant to your health will be fully discussed with you.

UNANTICIPATED MEDICAL INFORMATION

During the course of this study, it is possible (although not likely) that we will obtain unanticipated information about your health. If this information is considered to be relevant to your health care, we will provide it to you or, if you prefer, to your referring physician.

STORED SAMPLES/DATA AND FUTURE RESEARCH

If you agree to participate in this study, you also agree to let us store your blood samples, biopsies, and data for future research. The stored samples/data may help us learn more about WHIMS. The samples/data will be labeled with a code that only the study staff can link to you. Any information that can be traced back to you will be kept as private as possible. If you change your mind and decide you don't want us to store your samples, please contact us. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy all your samples.

Your coded samples/data might be sent to other study doctors for their research. Other information, such as your sex, age, health history, or ethnicity might also be shared. Your samples will not be sold, and you will not be paid for any products that result from this research. Future research that uses your samples/data may not help you, but it may help us learn more about WHIMS and other health problems. In general, the research tests performed in this study are not like routine medical tests, and they may not relate directly to your medical care.

CONFLICT OF INTEREST

The NIH reviews its staff researchers at least yearly for conflicts of interest. You may ask your study staff for additional information or a copy of the Protocol Review.

CLINICALTRIALS.GOV

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

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The 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 National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. David McDermott, Building 10, Room 11N107, Telephone (301) 496-8483.

You may also call the Clinical Center Patient Representative at (301) 496-2626.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM MAY 21, 2018 THROUGH MAY 20, 2019.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____