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STUDY TITLE: Treatment of refractory Diamond-Blackfan anemia with eltrombopag

STUDY SITE: NIH Clinical Research Center, Bethesda, MD

Cohort: Standard

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WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

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

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

You are being asked to participate in a research study sponsored by the National Heart, Lung, and Blood Institute at the National Institutes of Health because you have been identified as having Diamond-Blackfan anemia (DBA). Diamond-Blackfan anemia is often treated with steroids, often at high doses, to increase the number of oxygen-carrying cells (red blood cells or erythrocytes) in your blood. However, in your case, your doctors have determined that:

- steroids have not been effective for you, *or*
- the side effects of steroids are making it difficult or dangerous to continue, *or*
- your disease has returned even though it had responded previously.

For you, and patients like you, we are examining whether a drug called eltrombopag (brand name Promacta®) can increase your blood counts, allowing you to come off of or remain off of steroids, while requiring fewer or no blood transfusions.

Eltrombopag is a drug that was developed for patients with low numbers of another blood component: platelets. It was originally designed to mimic a protein called thrombopoietin (TPO). TPO is a naturally found in the body and stimulates the body to make more platelets when they are low. It has proven safe and effective in increasing the number of platelets for patients with low counts due to other conditions such as chronic hepatitis C or chronic immune thrombocytopenia purpura (ITP), an autoimmune disorder in which patients have chronically low platelet counts.

Studies have since found that in aplastic anemia, eltrombopag increases the number of other blood cells including the red blood cells that are also low in Diamond-Blackfan anemia. As a result, the U.S. Food and Drug Administration (FDA) has also approved eltrombopag as part of the therapy for treating severe aplastic anemia. Like Diamond-Blackfan anemia, aplastic anemia is a failure of the bone marrow to produce blood cells, but unlike Diamond-Blackfan anemia, which is present at birth and can be passed from parents to their children, aplastic anemia is usually acquired later in life; however, in a recent trial of eltrombopag in a moderate aplastic anemia, a patient with Diamond-Blackfan anemia responded to eltrombopag.

The purpose of this study is to test whether the eltrombopag will be safe and effective in treating Diamond-Blackfan anemia in general, especially for patients like you for whom steroid therapy has not provided a durable treatment. It is also unclear how eltrombopag improves counts in Diamond-Blackfan anemia. Therefore, it is secondary goal of this study to learn how eltrombopag functions in Diamond-Blackfan anemia.

During this study, you will take eltrombopag once a day, every day for six (6) months (24 weeks). During that time, you must have your blood drawn once every two (2) weeks (14 days) to monitor your body's response to eltrombopag and monitor for signs of side effects. These can be done at your home institution or at the NIH. You will need to return to the NIH at the end of the 6 months for blood tests, bone marrow biopsies and MRI scans to see how your bone marrow has responded to eltrombopag. This visit will take place at the NIH Clinical Center. Most visits, including testing, are performed within one day. Occasionally, especially for pediatric patients, the visit takes two days. The study staff will provide specific dates and times for your study visits and tests.

You may continue taking most medications that were prescribed before you started the study. Because these other medicines might interact with the study drugs, we ask that you tell us about all of your medications or changes in the medications you take, including prescription drugs, over-the-counter products, vitamins, and herbal supplements. We will inform you of any medications that you will need to stop while you are on eltrombopag.

If you have any new and concerning systemic symptoms (e.g. fevers, rigors, severe fatigue), respiratory symptoms (e.g. shortness of breath, persistent cough, chest pain), or gastrointestinal symptoms (e.g. diarrhea or blood in your stool), you should immediately notify your doctor for further evaluation.

Your participation will continue for at least six months at which point we will decide if you have demonstrated a response, including:

- increase in blood counts from your baseline, *or*
- fewer transfusions required.

If you do respond to and tolerate eltrombopag, you will be offered the opportunity to continue on an *extended* trial of eltrombopag, lasting for up to an additional three (3) years, unless you decide that you no longer want to be in this study, or the Sponsor decides to stop or interrupt the study.

The possible benefit from this study is that eltrombopag may help treat your Diamond-Blackfan anemia. If you decide to participate in this study, your health will be monitored very closely

which may provide a benefit to you. By being in this study, you will give doctors more information about how well eltrombopag works. It may help doctors understand your condition better and may help future patients with Diamond-Blackfan anemia.

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could choose to be treated by your home health care provider. Treatments include repeat trials of high-dose steroids, chronic transfusions, and hematopoietic stem cell transplant (sometime referred to as a bone marrow transplant or cord blood transplant). Alternative experimental therapies include high-dose leucine. Sotatercept and luspatercept are engineered proteins that disrupt the GDF11 pathway to increase red blood cell production. Trifluoperazine (Stelazine®) is an antipsychotic medication that may have activity in Diamond-Blackfan anemia. These, and other alternative experimental therapies, may be available at other research centers. You cannot participate in this study at the same time you are on other experimental treatments for Diamond-Blackfan anemia.

The remaining document will now describe more about the research study. This information should be considered before you make your choice. Members of the study team will talk with you about the information described in this document. 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). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

For parents or guardians consenting for their children: If the individual being enrolled is a minor then the term "you" refers to "you and/or your child" throughout the remainder of this document.

For caregivers consenting on behalf of people unable to give consent: If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

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

WHY IS THIS STUDY BEING DONE?

This is a research study. The purpose of this research study is to examine the safety and efficacy of eltrombopag in treating patients with Diamond-Blackfan anemia who have not responded to previous therapies such as steroids, or who were unable to tolerate those therapies. Eltrombopag has been approved by the U.S. Food and Drug Administration (FDA) to treat severe aplastic anemia in combination with other drugs or for patients who had previously received those drugs alone without a response. Eltrombopag has also been approved by the FDA to treat patients with chronically low platelet counts. Clinical trials which have shown that eltrombopag to be effective and safe in patients with moderate aplastic anemia have included patients with Diamond-Blackfan

anemia, but eltrombopag has not been specifically approved for efficacy and safety in this patient population.

We are asking you to join this research study because you have been diagnosed with Diamond-Blackfan anemia, and steroid therapy, whether it has worked for you in the past or not, is no longer considered the best therapy for you.

WHAT WILL HAPPEN DURING THE STUDY?

Eltrombopag (also called Promacta®):

You will take eltrombopag pills by mouth once a day for 24 weeks.

Before you take the first dose, you will need to have lab tests repeated within 7 days. If you are a female of childbearing potential, you must have the pregnancy test repeated within 7 days of your first dose (pregnancy and testing are discussed in detail below).

While you are taking eltrombopag, we will monitor you closely for side effects. You will need to have bloods tests performed every 2 weeks while you are taking eltrombopag. The tests can be done here at the NIH or by your home physician. We will also monitor you by occasional visits with physical examinations and procedures (no more than twice a year). Based on any side effects that you report or your laboratory results, we may change your eltrombopag dose. This may mean lowering your dose or temporarily stopping it. This may also mean stopping it completely, depending on what is in your best interest. The tests and visit schedule are explained in more detail below.

Extended access to study drug. There are currently no guidelines for length of therapy with eltrombopag. The limited experience we have for treating patients with Diamond-Blackfan anemia and related diseases with eltrombopag suggests that patients may benefit from extended treatment. If you continue to show benefit from the eltrombopag at the end of the 24 weeks of therapy, you will be allowed to continue through the extended access part of the trial.

You will continue taking eltrombopag until your blood cell counts improve to "robust" levels (hemoglobin level of 10 g/dL without transfusions) or no further response is expected. We will then follow your counts until 3 years after you discontinued eltrombopag. During this time, eltrombopag can be re-started if your counts fall to low levels again. The maximum time eltrombopag will be provided after signing the consent for the extended access part of the study is 3 years. After study completion, the research team will help coordinate continuing follow-up care with your referring physician.

Permitted standard of care for your disease (not investigational):

- **Transfusions:** You will receive blood and/or platelets if you need them
- **Women:** Estrogens or combination oral birth control pills as needed for uterine bleeding
- **Iron chelating agents:** If you have high iron (hemochromatosis), chelating agents such as deferasirox (Exjade/Jadenu) should be continued while you are on eltrombopag. We will monitor your iron levels, and help you decide if you should stop your chelating agent if your iron level is falling.

Non-permitted medications: The following treatments are not allowed to be taken during this study (they could interfere with eltrombopag):

- Romiplostim (N-Plate), or any related agents known as thrombopoietin receptor agonists
- Androgens (*i.e.* danazol and oxymetholone)
- IL-11 (Neumega)
- Investigational/non-marketed drugs or herbal supplements (unless the Investigator decides the medication will not interfere with the study drug)

Steroids

You cannot take steroids for anemia while on study. If you take steroids for a condition known as adrenal insufficiency (also called "replacement dosing" or "physiologic replacement") you should continue these. The research team will review your steroid management to make sure that this will not interfere with eltrombopag and prevent you from participating in this study.

Permitted medications

You may continue taking any medications prescribed before you started the study, as long as they are not related to your low blood counts. Your medicines might interact with the study drug (eltrombopag). This is why we ask that you tell us about all of your medications or changes in the medications you take. This includes prescription drugs, over-the-counter products, vitamins, and herbal supplements. If you are taking rosuvastatin (Crestor) to lower blood lipids, we may need to reduce your dose of eltrombopag and carefully monitor you.

Special instructions for eltrombopag

- **Timing in relation to food:** When eltrombopag is taken with a meal containing high fat or calcium, the amount of eltrombopag absorbed is decreased. Therefore, eltrombopag should be taken on an empty stomach (1 hour before or 2 hours after a meal).
- **Timing in relation to antacids:** When eltrombopag is taken with antacids, the amount of eltrombopag in the blood is decreased. Take eltrombopag at least 4 hours before or after products containing aluminum, calcium, magnesium, iron, selenium, and zinc. Examples of these products include antacids, mineral supplements, and dairy products.
- **Storing the study drug:** Store at room temperature. Room temperature is between 59°F to 86°F. It must be stored out of the reach of children.
- **Early stopping of eltrombopag:** We ask that you inform us immediately if you stop taking the study drug (eltrombopag) for any reason.

What procedures are involved in this research study?

If you agree to be in this study, you will be asked to complete all procedures before you take and as long as you remain on study drug. This means visits can occur with your NIH doctors or at your home doctor's office every two weeks. You will have to come to the NIH six (6) months after starting eltrombopag.

You will be responsible for following the NIH research team's instructions. You are also responsible for telling them of any changes in your health and if you decide to stop taking the study drug.

While you are taking eltrombopag please fax the following to the study coordinator: Ivana Darden, R.N. at 301-402-3088:

- Results of lab tests performed outside of the NIH

- Transfusion records
- Any medical notes your physician writes about you when see her or him
- Records from any hospitalizations, emergency room visits, or urgent care visits

What evaluations are done before you take your first dose of eltrombopag?

You must have the following tests done 7 days before your first dose. You may have them done here at the NIH or at your physician's office.

- A blood sample (1-2 teaspoons) to run tests to evaluate the make-up of your blood.
- For anyone of childbearing potential, a pregnancy test (urine or blood)

If these tests are not done at the NIH, please send a copy of the results to the research nurse.

What evaluations are done every two weeks while you are taking eltrombopag?

During your first six (6) months on eltrombopag, you must have the following tests done every 14 days (between 7 and 21 days). You may have them done here at the NIH or at your physician's office. We will accept tests up to seven (7) days before or after the expected date. Tests can be done more often if your doctor thinks they are necessary, but those outside of this window will not count towards the study requirements.

- A blood sample (1-2 teaspoons) to run tests to evaluate the make-up of your blood.

If these tests are not done at the NIH, please send a copy of the results to the research nurse.

What evaluations are done at month 3 and 6 while you are taking eltrombopag?

You will need a comprehensive visit at 3 months and 6 months after you have started taking eltrombopag. The six (6) month visit must be at the NIH. The three (3) month visit may be at your home institution or at the NIH. During these visits, the following evaluations will be done:

- A clinical assessment, which will include a brief history with questions about how you are feeling, a physical exam, and measurement of your blood pressure, pulse, temperature, respirations (vital signs)
- A review of your medications
- A blood sample (1-2 teaspoons)
- A repeat pregnancy test in women of childbearing potential

If the 3-month visit is not done at the NIH, we will ask you to send a copy of the results to the research nurse, and we will contact you by phone or email to assess how you are doing.

At the 6-month visit at the NIH, you will also undergo:

- A bone marrow biopsy test
- A questionnaire about your quality of life
- A neurodevelopmental test, if you are a pediatric patient under 18 years of age
- An MRI of your liver to measure the iron concentration
- A 24-hour urine collection may be performed

If you are not responding to eltrombopag at the month 6 visit, you will be taken off study drug. If you are taken off study drug, we would like you to come back to the NIH in 6 months.

What evaluations are done at the optional visit after you stop taking eltrombopag?

The following will be done.

- A clinical assessment, which will include a brief history with questions about how you are feeling, a physical exam, and measurement of vital signs
- A blood sample (1-2 teaspoons)
- A series of blood samples (before your morning dose and then 2, 4, 6, and 8 hours after the dose to measure the amount of eltrombopag in your blood). A total of 2 teaspoons will be drawn. This test will only be done once, either at your 3-month visit or at your 6-month visit.
- A bone marrow biopsy test
- A questionnaire about your quality of life
- An MRI of your liver to measure the iron concentration

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for up to three (3) years and six (6) months. Initially, we will ask you to take the eltrombopag for 24 weeks (6 months). If we see an improvement in your blood cell counts, you will be asked to participate in the extended access part of the study. You will continue taking eltrombopag after the 6-month evaluation.

After 24 weeks of treatment, if there is no improvement in your blood cell counts, we will ask that you come back for a follow-up visit. This will occur 6 months after your last dose of eltrombopag. This visit is optional.

During the initial 6 months of your treatment, you will need to have blood drawn at your home institute every 2 weeks. We will request that you have at least one visit with your home provider or at the NIH after taking eltrombopag for 12 weeks (3 months). If you continue to take eltrombopag after the initial 6 months, you will need bloodwork once a month for the next six (6) months, and then every 3 months while you remain on eltrombopag. During that time, you will need to come to the NIH every six months. After you come off of eltrombopag, we will continue to monitor you at the NIH for up to three years.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 25 eligible people participate in this study at the NIH.

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

<u>Risks related to eltrombopag</u>

The following possible risks are reported in adults taking eltrombopag for disease other than Diamond-Blackfan anemia. The diseases include chronic immune thrombocytopenic purpura (ITP), chronic hepatitis C, and severe aplastic anemia (SAA). The patients received a maximum dose between 50 to 150 mg per day.

Progression of underlying disease or progression to a new myelodysplastic syndrome (MDS) and/ or new acute myelogenous leukemia (AML, a type of blood cancer) has occurred in patients with ITP (immune thrombocytopenia purpura), MDS, AML and SAA (severe aplastic anemia). In some patients with these diseases who are treated with eltrombopag, changes in bone marrow cells

occurred. In some cases, this may indicate a progression to cancer. The role of eltrombopag in these changes is not known. These changes have also been seen with other drugs in the same class of compounds as eltrombopag. During this study, we examine your blood and bone marrow periodically for these changes.

Severe rash: There is a risk that you may develop a severe rash that may require hospitalization and discontinuation of eltrombopag.

Boxed Warning:

> RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C
>
> In patients with chronic hepatitis C, PROMACTA® in combination with interferon and ribavirin may increase the risk of hepatic decompensation (decompensation means the liver can no longer repair itself).

Additional Serious Side Effects include the following:

Liver problems: Eltrombopag may damage your liver and cause serious illness and death. The research team will order blood tests to check your liver function before you start taking eltrombopag and during treatment with eltrombopag. In some cases, eltrombopag treatment may need to be stopped. Tell the research team right away if you have any of these signs and symptoms of liver problems:

- Yellowing of the skin or the whites of the eyes (jaundice),
- Unusual darkening of the urine,
- Unusual tiredness, or
- Pain in the right upper stomach area.

High platelet counts and higher chance for blood clots. Your risk of getting a blood clot is increased if your platelet count is too high during treatment with eltrombopag. Your risk of getting a blood clot may also be increased during treatment with eltrombopag if you have normal or low platelet counts. You may have severe problems or die from some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes. The doctor will check your blood platelet counts and change your dose or stop eltrombopag if your platelet counts get too high. Tell your doctor right away if you have signs and symptoms of a blood clot in the leg, such as swelling, pain, or tenderness in your leg.

The most common side effects of eltrombopag in people with diseases other than Diamond-Blackfan anemia include:

For people with severe aplastic anemia (SAA):

- Anemia (low red blood cell count) (Very common – more than 10% of patients)
- Nausea, diarrhea, stomach pain (very common - more than 10% of patients)
- Fatigue, dizziness, fever, fevers with very low white blood cells (febrile neutropenia) (very common - more than 10% of patients)
- Cough, runny nose, shortness of breath, sore throat (common - less than 10% of patients)
- Headache (very common - more than 10% of patients)
- Pain in arms or legs, muscle spasms, joint pain (very common - more than 10% of patients)
- Skin redness, increased liver function tests (very common - more than 10% of patients)

- Small blood vessel problem that result in kidney failure (rare – less than 0.1% of patients)

For adult patients with Idiopathic Thrombocytopenia (ITP):

- Nausea, diarrhea (very common - more than 10% of patients)
- Vomiting, dry mouth (common - less than 10% of patients)
- Muscle aches, back pain, chest pain, joint pain, arm pain, leg pain (common – less than 10% of patients)
- Abnormal skin sensations, such as tingling, itching, burning, rash, hair loss (common – less than 10% of patients)
- Abnormal liver function test results (common – 5% of patients)
- Infections (throat, urinary tract) (common – up to 10% of patients)
- Headache (10% of patients)
- Small blood vessel problem that result in kidney failure (rare – less than 0.1% of patients)
- Drug Induced Liver injury (uncommon – less than 1% of patients)

For children (ages 1 to 17 years old) with ITP:

- Headache (very common – more than 10% of patients)
- Infections that result in a head or chest cold (very common – more than 10% of patients)
- Infections that result in a runny nose, stuffy nose, sneezing (common – up to 10% of patients)
- Stomach pain, diarrhea, tooth pain (common – up to 10% of patients)
- Fever (common – up to 10% of patients)
- Cough, sore throat, runny nose, stuffy nose (common – less than 10% of patients)
- Small blood vessel problem that results in kidney failure (rare – less than 0.1% of patients)

Unknown side effects: Treatment with eltrombopag may involve risks that are currently unknown. If significant new findings develop during the study, we will report them to you as soon as possible. New information might affect your willingness to participate in this study.

Risks related to concurrent use of other medications: To avoid the possibility of unknown effects from combining therapies, you cannot take medications for Diamond-Blackfan anemia other than those allowed by the study. The research team will discuss with you your current treatments for Diamond-Blackfan anemia before you start the study.

Risks related to blood tests

Side effects of blood sampling include pain, bleeding, and/or bruising in the area where the blood was drawn, lightheadedness, or, rarely, fainting due to temporary lowering of blood pressure. If you feel dizzy, we will ask you to lie down for a few minutes to avoid falling and hurting yourself. Infection at the blood-drawing site could also occur.

Risks related to bone marrow biopsy

Because Diamond-Blackfan anemia affects your blood, we will need to take samples of your bone marrow (where blood is produced). We will numb the area above your hip bone with a local anesthetic. The anesthetic can cause some temporary stinging and burning. When the area is numb, we will remove a sample of the bone and marrow with a thin needle. You may feel a pulling

sensation and discomfort as the marrow is withdrawn. The amount of marrow taken is very small and will not further compromise your body's ability to form blood. A pathologist will read the sample to confirm your diagnosis. The only potential complications of this procedure are bleeding at the site and local infection. Both are very rare. Bleeding can be stopped by applying local pressure, and an infection can be treated with antibiotics.

Risks related to MRI scans

Having an MRI scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when you are inside the scanner, or by lying in one position for a long time. MRI scanners are often loud, but you will be provided with hearing protection. The scans, as planned will typically take 15-20 minutes, but may take longer. If you experience significant discomfort, we can provide calming medications to help with anxiety. For some patients, especially children, it may be necessary to use sedation (such sedation would be covered by a separate consent form). The presence of metal such as piercings or jewelry can cause harm or injury when in the MRI scanner, including, but not limited to burns. You will be screened for any metal before all scans, and many medical implants are MRI-safe, but notify the research team, your doctor, and the technologist performing the scan if you have any metal implants. We do not plan to use contrast for these scans.

Risks related to genetic testing

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

What are the risks related to pregnancy?

The effects of eltrombopag upon pregnancy and the developing fetus are not known. Therefore, if you are pregnant, breastfeeding, or plan to become pregnant during the time you would be enrolled on this study (the next four to six years), you cannot participate.

We will require all enrolled subjects who are capable of becoming pregnant to have a pregnancy test before beginning this study and intermittently throughout their time on the study, regardless of sexual activity, martial or relationship status, or the use of contraceptive methods. You must use effective birth control methods and try not to become pregnant while taking eltrombopag on this study and continuing until at least 30 days after the last dose eltrombopag. "Effective birth control methods" include:

- Total abstinence (no sexual intercourse).
- Surgical sterilization including tubal ligation (tubes tied) or hysterectomy (removal of uterus or womb) in women or a vasectomy in men.
- Oral contraceptives (birth control pills), intrauterine devices (IUD), implantable or injectable contraceptives in combination with barrier methods (such as a condom or diaphragm) used with a spermicide.
- Barrier methods (such as a condom or diaphragm) used with a spermicide.

The contraception methods described above may not protect against HIV infection (AIDS) and other sexually transmitted diseases. If you need more information about this, please ask your study doctor.

You must tell the study doctor if your birth control method fails while you are in the study. If you think or know you have become pregnant while participating in this research study, please contact the research team member identified at the top of this document as soon as possible. If you plan to become pregnant in the future, you should wait 30 days from the last dose of eltrombopag. Please discuss this with the research team.

If you are a sexually active person with a partner capable of becoming pregnant, it is important that your partner not become pregnant during your participation in this study. There may be unknown risks to a fetus or risks to your partner we did not anticipate. You and your partner must agree to use effective birth control methods listed above if you want to take part in this study. If you think your partner has become pregnant during your participation in this study, please contact the research team member identified at the top of this document as soon as possible. If you and your partner plan for your partner to become pregnant after your participation in this study, please discuss this with the study team.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

However, the goal of this study is to examine whether eltrombopag improves blood counts in patients with Diamond-Blackfan anemia, and as such eltrombopag may help to treat your anemia, reducing or even eliminating blood transfusions, reducing your exposure to other medications such as steroids, and potentially delaying or even eliminating the need for hematopoietic stem cell transplantation in the future.

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

In the future, other people might benefit from this study because it will help doctors understand how eltrombopag affects Diamond-Blackfan anemia. It will also give doctors new and better information into how the changes seen in Diamond-Blackfan anemia cause the anemia and how it

responds to drugs such as eltrombopag. Even if this trial is unsuccessful, the data we gain may help doctors design future drugs and trials to treat Diamond-Blackfan anemia.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, we will discuss the following standard alternative treatments to Diamond-Blackfan anemia, which, depending on your age, disease status, iron levels, and the availability of stem cell donor, may be available and appropriate for your disease including:

- Transfusions of red blood cells
- Steroid therapy
- Bone marrow transplantation
- Other experimental therapies
- No therapy

Note, although eltrombopag is commercially available, it is not currently indicated for use in Diamond-Blackfan anemia, therefore it is generally not available to patients with Diamond-Blackfan anemia except as part of trials such as this one. Choosing not to participate in this trial will not affect your ability to participate in other clinical trials at the NIH and NHLBI, including any future trials with eltrombopag or related agents.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places. If this happens, the research team will tell you about it and talk with you about whether you want to continue in the study. If you decide to continue in the study, we will ask you to sign an updated consent form.

Return of research results

Clinically relevant research results will not be shared with you. This does not include any results that are collected as part of your routine care. Any clinically actionable genetic results will be shared with you, with the option of discussing these results with one of our geneticists.

EARLY WITHDRAWAL FROM THE STUDY

Your participation in this study is voluntary, and you may stop at any time. It is possible that after receiving new information about the treatment, the research team will consider it to be in your best interest to withdraw from the study. A member of the research team will explain the reasons and arrange for your care to continue.

Your participation on this research study may end for the following reasons:

- You have side effects that make it unsafe for to keep taking the drug
- Your blood counts are not improving
- You become pregnant
- The research team decides that it is not in your best interest to continue on the study

If at the end of the study you are having any side effects related to the study drug, you might be asked to return for additional tests until the side effects have gone away.

The principal investigator of this study (David Young, M.D., Ph.D.), the medically-responsible sponsor of the trial (Cynthia Dunbar, M.D.), the Institutional Review Board (IRB), the Food and Drug Administration, or Novartis (supplier of the study drug) may stop this study at any time, for any reason, without your consent. For safety reasons, the Data Safety Monitoring Board may also recommend stopping this study without your consent. You would be told of that new information.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

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

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

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

_____ Yes _____ No

Initials Initials

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

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

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

_____ Yes _____ No

Initials Initials

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

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

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. These researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

Will your genomic data be shared outside of this study?

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

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

Your specimens and data may be stored by the NIH until they are no longer of a scientific value, at which time they will be destroyed.

Risks of storage and sharing of specimens and data

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

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

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

You will not receive compensation for participation in this study.

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

This study offers reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center. All major procedures (bone marrow tests, research tests, MRI, *etc.*) and study drugs are included under this; however, you or your insurance may be charged for bloodwork not performed at the NIH Clinical Center.

CONFLICT OF INTEREST (COI)

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

Novartis Pharmaceuticals is providing eltrombopag for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Novartis for this trial. Novartis has provided Dr. Cynthia Dunbar and Dr. Neal Young funding for prior trials separate from this trial.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor the National Heart, Lung, and Blood Institute (NHLBI) Office of Clinical Director (OCD) at the NIH or their agent(s)
- Qualified representatives from Novartis Pharmaceuticals Corporation, the pharmaceutical company who produces eltrombopag.
- Novartis' authorized agents
- Governmental agencies in other countries where the study drug may be considered for approval

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.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

4. is disclosed with your consent.

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

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

Privacy Act

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

POLICY REGARDING RESEARCH-RELATED INJURIES

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

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, **David J. Young, M.D., Ph.D., email: david.young2@nih.gov, phone: 301-827-7823**. You may also contact the Study Coordinator: Ivana Darden, R.N., email: ivana.darden@nih.gov, phone: 301-827-2988. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

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

Signature of Research Participant	Print Name of Research Participant	Date

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

Signature of LAR	Print Name of LAR	Date

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

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date
Signature of Parent/Guardian *(as applicable)*	Print Name of Parent/Guardian	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only: This section is only required if you are doing the oral short-consent process with a non-English speaking subject and this English consent form has been approved by the IRB for use as the basis of translation.

Witness:

Signature of Witness*	Print Name of Witness	Date

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

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

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