

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term Safety and Efficacy of Darbepoetin Alfa Administered at 500 µg Once-Every-3-Weeks in Anemic Subjects With Advanced Stage Non-small Cell Lung Cancer Receiving Multi-cycle Chemotherapy

Protocol Number 20070782

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Patient Information and Consent Form

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Patient Initials: _____

You are being asked to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take as much time as you need to decide whether or not to participate and discuss your participation with family, friends, study nurse and/or your doctor.

This informed consent form is split into 2 parts:

- Part 1 tells you the purpose of this study and what will happen to you if you decide to participate.

- Part 2 provides detailed information about your rights as a research participant.

This document provides you with information about the study. Please read this informed consent form carefully and ask any questions you have about the study so you can make an informed decision about your participation. You are under no obligation to take part in this study and, if you decide not to, your future medical care will not be affected in any way. If you have questions at any time while reading this document, please ask Dr. Deveras who is the Principal Investigator for this study, your Study Doctor _____ or the Study Coordinator to explain any words or information you do not understand. If after reading this document, you are interested in participating, you will be asked to sign and date this informed consent form. You will receive a copy of this form to keep.

The conduct of this study has been approved and will be overseen by

Liberty IRB, Inc.
DeLand, FL 32724
(386) 740-9278

The Liberty Institutional Review Board is a committee that has reviewed this research study to help ensure that your rights and welfare as a research participant are protected and that the research study is carried out in an ethical manner.

PART 1 (Research Study Information):

1. BACKGROUND INFORMATION

a. What is the purpose of this research study?

The purpose of this study is to determine the safety of darbepoetin alfa, including effects on survival and cancer progression, as well as the need for blood transfusions.

Anemia is a condition where the number of red blood cells in your body is abnormally low. Red blood cells are important because they contain hemoglobin that carries oxygen throughout the body to tissues and organs. Chemotherapy used to treat cancer patients often causes anemia. Severe anemia can result in physical weakness (fatigue), shortness of breath, pale skin, and rapid heartbeat. Treating severe anemia by increasing the number of red blood cells in your body may reduce or eliminate some of these symptoms. Darbepoetin alfa is in a class of drugs known as erythropoiesis-stimulating agents (ESAs), which increase red blood cell production. Other ESAs include drugs named epoetin beta (Aranesp[®]) and epoetin alfa (Procrit[®]).

b. Who is funding this clinical study?

Amgen, Inc. (hereinafter referred to as "Amgen"), a for-profit drug company, is funding this clinical study. Amgen is the "sponsor" of the study, which means that Amgen takes responsibility for the management, and/or financing of this clinical study.

c. Why have I been asked to participate in this study?

You are being asked to take part in this research study because you have advanced stage non-small cell lung cancer. You are currently receiving or will be receiving chemotherapy for at least 2 more cycles and your chemotherapy treatment may cause severe anemia.

d. How many other people like me (subjects) will be participating in this study?

About 3000 subjects (what people who take part in a research study are called) will be enrolled in the study at about 500 sites in North America, Europe, Latin America, Australia, Asia, and Africa.

e. What kind of investigational product(s) will be tested in this study?

The investigational drug being tested in this study is darbepoetin alfa.

Darbepoetin alfa is currently approved in the United States (by the US Food and Drug Administration, or FDA), Canada, Australia, the European Union, Israel, and many other countries worldwide, for the treatment of anemia associated with chronic renal failure. It is also approved for the treatment of chemotherapy-induced anemia (anemia caused by chemotherapy) in patients with non-myeloid malignancies (cancers that did not originate from the bone marrow). It is considered investigational in this study for treating anemia in subjects with non-small cell lung cancer.

In this study, darbepoetin alfa or placebo (an inactive substance meaning it has no active drug in it) will be given once every 3 weeks at a dose of 500 micrograms (μg) by an injection given under the skin (subcutaneously). This dose of darbepoetin alfa has been approved by the FDA to treat chemotherapy-induced anemia. The investigational product will be started when the hemoglobin levels in your blood are equal to or less than 11 grams per deciliter (g/dL) and will be withheld (not given) when hemoglobin levels are greater than 12 g/dL.

The hemoglobin levels at which investigational product is started and withheld are different from the treatment instructions on the current approved label of darbepoetin alfa (Aranesp®). In the US label, darbepoetin alfa treatment is approved to begin when hemoglobin levels are below 10 g/dL. Once treatment with darbepoetin alfa starts, your study doctor should prescribe the lowest dose of darbepoetin alfa in order to lower the chance of getting red blood cell transfusions.

f. What are the chances that I will get the investigational product?

You will have a 2 in 3 (67%) chance of receiving darbepoetin alfa once every 3 weeks and a 1 in 3 (33%) chance of receiving placebo (no active drug) once every 3 weeks.

Investigational product is the name given for both active drug (darbepoetin alfa) and placebo.

g. Will I know which study product I am receiving?

No, this study is blinded, which means that neither you, the study doctor, nor the study staff will know which group (darbepoetin alfa or placebo) you have been assigned to. However, if there is a medical emergency, Dr. Deveras or your study doctor as listed on the first page of this consent will be able to obtain this information.

h. How long is the study?

This study consists of 2 parts:

The treatment period and the long-term follow-up period.

The **treatment period** includes a screening period of up to 21 days before enrollment to determine if you are eligible to participate. If you are eligible, treatment visits will occur once every 3 weeks. These visits will continue until after you complete your course of chemotherapy, and/or at the point your disease has progressed, if that comes first. At this time it is determined that you have completed the treatment phase of the study, an end of treatment visit will follow at the next study visit after disease progression.

At this point, you will enter the **long term follow up period**. Your doctor will follow your progress with study visits or phone contact by the study staff, if you are unavailable for study visits, every three months, until the conclusion of the study. The conclusion of the study will occur when about 2700 deaths occur.

You are free to withdraw from the clinical research study at anytime without affecting your future care. Also, Dr. Deveras, or your Study Doctor or Amgen Inc. may choose to withdraw you from this research study at any time.

2. STUDY PROCEDURES

a. What will I be responsible for if I participate in this study?

If you are eligible for this study, you will be responsible for attending all scheduled study visits including visits for imaging, following the study staff's instructions, and notifying study staff of any side effects you experience or medications (prescription and/or over-the-counter) that you take during the study.

You will not be allowed to take certain medications and treatments, such as investigational drugs, while you are on the study. The use of other ESAs will not be permitted during the study treatment period. If your doctor wants you to take these medications or treatments during the study, you may be withdrawn from the study.

Your participation in this study may be stopped without your consent if you do not follow the study staff instructions or if the study doctor feels that it is in your best interest to withdraw from the study.

You will also be required to notify any other doctors you see (apart from the study doctor) that you are participating in a research study.

b. What types of tests or procedures are involved with this study?

Screening Procedures

Before any study-specific procedures are performed, you must give your consent to participate in this study by signing and dating this consent form. Once you have signed this form you will be screened to determine if you are eligible to participate in this study. The screening procedures include:

- Medical history, including age, sex, ethnicity, tumor diagnosis and staging, tumor evaluation, previous medications, red blood cell transfusions, chemotherapy, anti-cancer surgery, and radiotherapy
- Physical examination including height and weight
- Vital signs (blood pressure, pulse, and temperature)
- Evaluation of how your disease affects your daily living activities and establish a baseline which can be used for comparison later to determine if your disease has progressed (Eastern Cooperative Oncology Group [ECOG] performance status)
- Hemoglobin results before you start chemotherapy
- Imaging scan before starting your chemotherapy treatment for non-small cell lung cancer to establish a baseline which can be used for comparison later to determine if your tumor has progressed. This imaging scan will be a computed tomography (CT), positron emission tomography-computer tomography (PET/CT) scans, or a magnetic resonance imaging (MRI) scan. If your study doctor suspects that you have bone metastases at screening, you will also need to obtain either a bone scan, MRI, CT, PET, PET/CT, or X-ray. If a bone scan or PET scan was performed, an X-ray, CT or MRI will be performed to confirm the bone metastases, if present. If a pre-chemotherapy image and/or bone scan is already available, you might not need to repeat this procedure for the study.

- Blood collection: about 2 tablespoons (30 milliliters [mL]) of blood will be taken at the screening visit. This blood will be sent to local and central laboratories for tests to ensure that you are eligible to participate in this study. These tests include: complete blood count (CBC) with hemoglobin, reticulocyte count, iron studies, Vitamin B12, folate levels, C-reactive protein (CRP), and blood chemistry
- If you are a woman able to become pregnant a blood sample will also be used for a pregnancy test. If your pregnancy test is positive you will not be allowed to participate in the study.
- Optional tumor sample collection: Your tumor tissue collected at any point since your diagnosis of non-small cell lung cancer may be obtained and submitted to a central laboratory if you provide your consent for this optional tumor sample collection. There will not be any additional study-specific biopsies or procedures required for this collection. The sample will be used to measure the level of erythropoietin receptor and other tests. These tests will determine if the tumor cells contain changes in genes, or changes in how genes turn on and off (gene expression), that may be linked with how your disease progresses or with your response to the investigational product. This may help researchers further their understanding in darbepoetin alfa and/or cancer. More information about this optional tumor sample collection is discussed later in this consent.

If you are a woman of childbearing potential according to the study doctor, a blood sample will also be used for a pregnancy test. If your pregnancy test is positive, you will not be allowed to participate in this study.

If you are eligible following the screening procedures you will be enrolled into the study.

Treatment Procedures

Study Day 1 (Week 1)

Study day 1 is the first day you will receive investigational product by subcutaneous (under the skin) injection.

At this visit, the doctor or study staff will take your vital signs, weight, and will ask you about the medications and medical procedures (for example, red blood cell transfusions, surgery, and radiotherapy) you have taken and if you have experienced any adverse (medical) events since you signed the study consent form. The study doctor will also evaluate how your disease affects your daily living activities.

About 2 tablespoons (30 mL) of blood will be collected and sent to local and central laboratories. The blood tests will include CBC with hemoglobin, blood chemistry, endogenous erythropoietin levels, and antibody levels.

Every 3 weeks until disease progression

After study day 1, you will need to come to the clinic every 3 weeks until your disease progresses (gets worse).

At these visits, the doctor or study staff will take your vital signs, weight, and will ask you about the medications and medical procedures (for example, red blood cell transfusions, anti-cancer therapy, anti-cancer surgery, and radiotherapy) you have taken and if you have had any adverse events. The study doctor will also evaluate how your disease affects your daily living activities.

About 1 tablespoon (15 mL) of blood will be collected and sent to local and central laboratories. The blood tests will include complete blood count (CBC) with hemoglobin, blood chemistry, and iron studies.

You will receive investigational product by subcutaneous (under the skin) injection at these every-3-week visits until about 3 weeks after you complete the course of chemotherapy, or at the time your disease progresses, if that comes first. If the investigational product was stopped before your disease progression, you will need to come into the clinic for study procedures once every 3 weeks and for imaging scans once every 9 weeks up until the occurrence of disease progression.

Depending on your hemoglobin level, your dose of investigational product may be kept the same, decreased, or temporarily stopped to maintain your hemoglobin level equal to or below 12 g/dL.

If you are in the darbepoetin alfa group and after week 5 on the study you have 2 or more transfusions at least 3 weeks apart but no more than 6 weeks apart, darbepoetin alfa treatment will be discontinued and you will receive placebo injections for the remainder of the study. In this event, neither you nor your study doctor will know that this change has occurred. This is a safety measure taken by the study sponsor to limit your exposure to any risks associated with darbepoetin alfa if you are not benefiting from this treatment.

Imaging scans (same type of scan as used during screening) will be performed once every 9 weeks until your disease has progressed. These imaging scans may also include a bone scan or PET scan confirmed with an X-ray, CT or MRI, in addition to the type of scan used at screening, when your study doctor suspects you have new bone metastases. If your study doctor believes that your disease may have progressed, he or she may ask you to obtain an imaging scan sooner than every 9 weeks. All imaging scans collected for the study will be sent to a central storage facility for archiving. At some point in the future, these imaging scans may be read by an expert at this central storage facility if the need arises.

End of Treatment Procedures (the next study visit after disease progression)

After disease progression, you will be asked to come into the office at the next every-3-week visit for the End of Treatment visit. At this visit, the study doctor or study staff will take your vital signs, weight, and ask you about the medications and medical procedures (for example, red blood cell transfusions, anti-cancer therapy, anti-cancer surgery, and radiotherapy) you have taken and if you have had any adverse (medical) events since your last visit. The study doctor will also evaluate how your disease affects your daily living activities.

About 1.5 tablespoons (25 mL) of blood will be collected and sent to local and central laboratories. The blood tests will include: CBC with hemoglobin, blood chemistry, and antibody levels.

You will not receive any investigational product at this visit.

By signing this consent form, you are authorizing Amgen to use your blood samples for those procedures identified in the study protocol. Throughout the study, Amgen may decide to do additional testing on your blood samples for safety-related procedures.

Long-term follow-up

Following disease progression, you will enter the long-term follow-up portion of the study. You will need to visit the clinic once every 3 months and the study staff will collect limited information about your treatment and medications you take until the End of Study. If you cannot attend these visits, the study nurse may call you to collect this information.

Throughout the study, you may receive blood transfusions and other supplemental medications (for example, iron, folate, vitamin B₁₂ supplementation) when needed as determined by your study doctor.

Consent to Optional Tumor Sample Collection

The tumor sample collection during screening is an optional part of this study. The paragraphs below describe the information regarding this optional tumor sample collection. You can still be a part of the study even if you say 'no' to taking part in the optional tumor sample collection.

If you agree, your tumor sample from a previous biopsy and the matching pathology report will be collected during the screening period and shipped to Amgen for storage. These tumor samples are stored for future testing to detect specific protein(s) on the tumor cells such as the erythropoietin receptor, and changes in the genes. There will not be any additional study-specific biopsies or procedures required for this collection.

This tumor sample and any derivatives (such as components of your cells) may be stored for up to 20 years. You retain the right to have the sample material destroyed at any time by contacting the study doctor. If you decide to have your samples destroyed, any data and/or analyses that were done before the request will not be removed; however, all of your remaining samples will be destroyed, and no additional analysis will be done with your samples. The study doctor will provide Amgen with the required study and your unique subject code numbers, so that your tumor samples and derivatives can be located and destroyed. Amgen will be the exclusive (only) owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at your request or otherwise, at the end of the storage period.

Since exploratory sample evaluations are not expected to benefit you directly or to alter your treatment course, these results will not be placed in your medical record and will not be made available to you, members of your family, your personal physician, or other third parties, except as specified above.

By signing below, I agree that Amgen can perform research on my tumor samples as described above.

By signing below, I understand that the same agreements apply to the optional tumor sample analyses as to my agreement to participate in the study.

Yes No

PRINT subject's name

Date¹

Subject's signature
Time _____

¹Each person who signs the consent must personally enter the date for his/her signature.

c. What happens when the research study ends?

Your participation in this study will end after you complete the long-term follow-up portion of the study.

You may decide to discontinue your participation at any time. Your decision to withdraw your consent will not affect your future medical care. If you choose to withdraw from the study, you must notify Dr. Deveras or your Study Doctor so that your part in the study may be stopped and your future care can be discussed.

If you decide to withdraw from the study, your doctor will continue to follow your progress for 30 days after the last dose of investigational product administration and you should complete the End of Treatment Period visit at the next every-3-week visit.

You may also decide to discontinue receiving investigational product any time during the study. If you decide to discontinue investigational product during the treatment period, you will be asked to stay in the study and come into the clinic for study procedures until the occurrence of disease progression. If you decide to discontinue from the study procedures before your disease progresses, you will be asked to stay in the study for long-term follow-up. During long-term follow-up, your Study Doctor or site staff will collect limited information on your survival status and medications you take until the End of Study.

If you experience any ill effects after the End of Study, please contact the study investigator, Dr. Deveras or your Study Doctor at (386) 254-4212.

3. SAFETY – POTENTIAL RISKS AND DISCOMFORTS

a. What are the general risks of participating in this research study?

Darbepoetin alfa is an investigational product (a research study drug) in this study. Close to 33,590 patients have been given darbepoetin alfa in clinical trials. More than 5,290,000 patients have been prescribed darbepoetin alfa for treatment by doctors in clinical practice. As with all drugs, darbepoetin alfa can cause side effects. A side effect is an undesirable effect or a worsening of a medical condition you had before starting in the study, which might occur while you are taking the investigational product. Section 3b describes the side effects seen with darbepoetin alfa. However, unexpected side effects may occur that have yet to be reported.

Your Study Doctor will monitor you closely during this study and discuss with you any questions regarding risks, discomforts, and side effects. If significant new findings develop during the course of this study that might affect your willingness to participate, information will be reported to you as soon as possible. If you have any concerns about this study at any time, you should contact Dr. Deveras, the Principal Investigator, or your Study Doctor at (386) 254-4212, (24-hour phone number).

b. What are the known side effects of the investigational product?

You should be aware that darbepoetin alfa may possibly have a negative impact on your cancer. Darbepoetin alfa has been used experimentally to try to raise hemoglobin levels beyond the amount needed to avoid red blood cell transfusion, or to raise hemoglobin levels in patients with advanced cancer who were not getting chemotherapy. In some of these studies, in patients with cancer, in which some patients received chemotherapy and others did not, there was a higher risk of:

- death
- serious blood clots
- serious cardiovascular (heart) events

- and/or poor cancer outcomes in patients given darbepoetin alfa compared to patients who were not receiving darbepoetin alfa.

It is not known whether these risks exist when darbepoetin alfa is given according to the FDA-approved directions for use.

Additionally, there are some studies that were designed to administer darbepoetin alfa outside of the approved directions for use. Some of the clinical studies were in patients with advanced head and neck cancer receiving radiation therapy, in patients receiving chemotherapy for metastatic breast cancer or lymphoid malignancy, and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy. These studies have shown a shortened overall survival and/or increased the risk of tumor progression or recurrence when darbepoetin alfa was used to reach a hemoglobin level higher than approved use. In these studies, the target hemoglobin was higher than of this study.

In clinical studies of patients with cancer, darbepoetin alfa also increased the risk of:

- **Very common (occurring 10% or more of the time):**
 - Edema (swelling)
- **Common (occurring from 1% to less than 10% of the time):**
 - Blood clots in blood vessels
 - Blood clots in lungs
 - Skin rash
 - Pain at injection site

In clinical studies in patients with chronic kidney failure and where ESAs were given to try to reach a hemoglobin equal to or more than 13 g/dL, there was a higher risk of death and cardiovascular events such as heart attack, heart failure, stroke, and clotting of vascular access used for dialysis. A rapid increase in the number of red blood cells may also contribute to these risks.

In a clinical study in patients with anemia, diabetes and chronic kidney failure not on dialysis and where darbepoetin alfa was given to target a hemoglobin of 13 g/dL compared to placebo, there was an almost 2 times increased risk of stroke. In this same study of chronic kidney failure patients, more deaths occurred in the group of patients who reported a history of cancer and were treated with darbepoetin alfa to the study target hemoglobin of 13 g/dL, compared to patients treated with placebo. The relationship between death and treatment with darbepoetin alfa in patients with a history of cancer is not known.

In clinical studies of patients with chronic kidney failure, darbepoetin alfa also increased the risk of:

- **Very commonly (occurring 10% or more of the time):**
 - Hypertension (high blood pressure)
- **Commonly (occurring from 1% to less than 10% of the time):**
 - Blood clots in blood vessels
 - Skin rash
 - Pain at injection site

In clinical studies of patients with heart failure, darbepoetin alfa also increased the risk of:

- **Commonly (occurring from 1% to less than 10% of the time):**
 - Pain at injection site
 - Hypertension (high blood pressure)

In addition to the side effects reported during clinical trials, the following side effects have been identified from reports received by Amgen from ESA use outside of the clinical trial setting:

- Serious allergic reactions - These reactions can cause: a drop in blood pressure, fast heart rate, shortness of breath, wheezing, swelling around the mouth or eyes, or a rash over the whole body.
- Convulsions (fits or seizures)
- Hypertension (high blood pressure), in patients with cancer
- Antibodies against darbepoetin alfa that block your body's ability to make red blood cells – This condition is known as antibody-mediated pure red cell aplasia (PRCA). If this happens, study drug will be stopped and you may receive blood transfusions or other treatment for an unknown period of time. If your body is making antibodies against darbepoetin alfa, extra blood samples will be collected for further testing.

If you need to have surgery, tell your surgeon that you are in this research study. Treatment with ESAs before surgery may increase your chance of forming a blood clot in a blood vessel.

Additional information about the risks of darbepoetin alfa can be found in the attached Medication Guide.

c. What are the risks associated with using the investigational product in combination with other medications?

No information is currently available about any risks associated with the use of darbepoetin alfa in combination with other medicines, because no such studies have been performed to date.

d. What are the risks associated with procedures done in this research study?

Blood collection

During the study, you will have blood taken to measure your hemoglobin level and other factors that might be affected by darbepoetin alfa. Possible side effects are tenderness, pain, bruising, bleeding and/or infection at the site of the needle puncture. Having your blood drawn may also cause you to feel nauseated and/or lightheaded.

Injections of investigational product or contrast agent for imaging scans

Subcutaneous (under the skin) injections may cause momentary discomfort and possible bruising or local skin infection at the injection site. However, trained medical personnel will perform the injections and will make every effort to minimize any discomfort.

CT scans (if performed)

There is a slight risk of developing an allergic reaction to the contrast material (dye). The reaction can be mild (such as itching, rash) or severe (such as difficulty breathing or sudden shock). Death resulting from an allergic reaction is rare. Most reactions can be controlled using medication. Be sure to tell your doctor if you have allergies of any kind (such as hay fever, iodine allergy, eczema, hives, or food allergies). The contrast material used during CT scanning can cause water loss or damage to the kidneys that may lead to kidney failure. This is a concern if you have poor kidney function, dehydration, or diabetes.

You will be exposed to a limited and medically acceptable dose of radiation during the procedure. There is a slight risk from being exposed to any radiation, including the low levels of X-rays used for a CT scan. You may also experience discomfort related to lying still in an enclosed space for a prolonged period of time.

MRI scans (if performed)

There are no known harmful effects from the strong magnetic field used for MRI. The magnet may affect pacemakers, artificial limbs, and other medical devices that contain iron. You must tell the study staff if you have any metal devices in your body.

There is a slight risk of developing an allergic reaction if contrast material is used during the MRI scans. The contrast agent will be injected into a vein and may cause nausea, headache, hot flushes, dizziness, and irregular heartbeat. You may also experience discomfort related to lying still in an enclosed space for a prolonged period of time.

Bone scans (if performed)

You will receive an injection of a radioactive material with very low radioactivity. The radioactive material does not cause any side effects and is attracted to diseased bone cells throughout the body. A special camera takes the image and shows the diseased bone as dense, grey to black areas, called "hot spots." These areas may be cancer, but arthritis, infection, and other bone diseases can look the same. Your study doctor will conduct an additional X-ray, CT, or MRI scan to confirm whether you have bone metastases.

X-rays (if performed)

You will be exposed to a limited and medically acceptable dose of radiation during the procedure. There is a slight risk from being exposed to any radiation.

PET scans (if performed)

You will receive an injection of a radioactive material with low radioactivity. The radioactive material does not cause any known side effects and is attracted to specific cells throughout the body. A special camera takes an image and shows areas of active cancer as "hot spots." You will be exposed to a limited and medically acceptable dose of radiation during the procedure. You may also experience discomfort related to lying still in an enclosed space for a prolonged period of time.

e. Could treatment with darbepoetin alfa be harmful to an unborn or breast feeding baby?

It is not known if darbepoetin alfa is harmful to an unborn baby. Potential risks include loss of the pregnancy (a miscarriage) and birth defects. If you have intercourse during this study, you should understand that even with the use of effective birth control there is still a small chance that a pregnancy could occur. You and your doctor must discuss your method(s) and agree they are effective.

Females of Childbearing Potential

Pregnant women and women planning to become pregnant may not take part in this study. You must have a negative pregnancy test before you start investigational product. Women who could become pregnant should inform their sexual partner of their participation in this clinical study and use 2 highly effective methods of birth control, such as abstinence (not having sex), sterilization, birth control pills, Depo-Provera injections, or contraceptive implants, throughout the entire study and for an additional 1 month after stopping investigational product.

The potential for darbepoetin alfa to be found in breast milk has not been studied. Babies should not be fed breast milk produced during the study and for an additional 1 month after the end of the mother's treatment with investigational product.

Sexually Active Males

The potential for darbepoetin alfa to be found in semen and its effect on sperm have not been studied. If you are male and you have a partner of childbearing potential, you should inform her of your participation in this clinical study and use highly effective methods of birth control during treatment with investigational product and for an additional 3 months after stopping study drug. Highly effective methods of birth control include abstinence (not having sex), vasectomy, or a condom in combination with hormonal birth control or barrier methods used by the woman. **Men should not donate sperm while they are in this study.**

f. What if my partner or I become pregnant during the study?

If you are female and become pregnant or suspect you are pregnant during this study, you must tell your study doctor immediately and treatment with investigational product will be stopped. Your study doctor will ask for your consent for Amgen to obtain information on the pregnancy outcome for you and the baby.

If you are male and your partner becomes pregnant during this study, you must tell your study doctor immediately. Your study doctor will ask you for contact information and consent for Amgen to obtain information on the pregnancy outcome for the mother and baby. Male study subjects whose partners are pregnant must practice abstinence or use a condom to ensure that an unborn child is not potentially exposed to investigational product via semen.

4. POTENTIAL BENEFITS

a. What are the expected therapeutic benefits of this investigational product?

Treatment with darbepoetin alfa is not intended to treat or cure your cancer. However, it may increase the number of red blood cells in your body and may reduce or eliminate many of the symptoms caused by severe anemia such as physical weakness (fatigue), shortness of breath, pale skin, and heart pounding. Darbepoetin alfa may reduce the need for blood transfusion.

b. Will I benefit from participating in this research study? Will others?

There is no guarantee that you will receive any benefit while in this study. The study will help us determine the effect of darbepoetin alfa on survival and its safety in subjects with cancer and anemia caused by chemotherapy.

This study may also provide information for doctors to use darbepoetin alfa to treat other cancer subjects with anemia in the future. It is hoped that darbepoetin alfa may reduce the need for subjects like you to require blood transfusions.

Individual subjects will not derive a benefit from taking part in exploratory procedures. However, future subjects may benefit from what is learned. This information may help physicians learn more about the use of the investigational product in chemotherapy-induced anemia treatment.

5. ALTERNATIVE THERAPY

a. If I choose not to participate in this study, are there other treatments or medications available to me, instead of this investigational product?

If you choose not to participate in this study, alternative medical treatment is available to you. You can receive other therapy and medical care that is provided for subjects with anemia related to their cancer, or receive blood transfusions to correct your anemia. Please ask your doctor for further information about your anemia and other treatment options that are available to you.

b. Are there benefits with these other treatments? Are there risks?

A blood transfusion is another treatment for anemia. A blood transfusion will quickly and effectively treat anemia, however there are risks associated with transfusions such as allergic reactions and the potential to contract infectious diseases such as hepatitis viruses and other infectious organisms. The likelihood that infections can be passed along from transfusions varies for different infectious organisms. It is generally lower than 1 case in 1 million units of blood transfused for human immunodeficiency virus (HIV) and hepatitis C viruses. For hepatitis B virus, the risk is about 1 case in 250,000 units of blood transfused. The risk of bacterial infection is about 1 case in 500,000 units of blood transfused. Transfusion-related acute lung injury (TRALI) is a serious complication in which fluid builds up in the lungs soon after transfusion. The risk of this varies widely from approximately 1 case in 5000 to 1 case in 500,000 units of blood transfused. The likelihood for serious allergic reactions, known as acute hemolytic reactions, to happen also vary widely from 1 case in 250,000 to 1 case in 1 million units of blood transfused. The risk of receiving the wrong type of blood is about 1 case in 14,000 to 18,000 units of blood transfused. Please ask your Study Doctor about the benefits and risks of other treatment options for your anemia.

This completes Part 1 of the Informed Consent Form. If you are interested in participating, please read Part 2 of the Informed Consent Form, which provides information about your rights as a research participant.

PART 2 (Rights of the Research Participant):

6. POTENTIAL COSTS/REIMBURSEMENTS

a. What will this study cost me?

It is not anticipated that you will incur any additional costs if you participate in this study. You will receive investigational product free of charge. You will not be charged for any extra doctor's visits, blood work, tests, or procedures required for this study.

b. Will I be reimbursed for any normal expenses that I incur as a result of participating in the study?

You will not receive any money for participating in this study.

c. Will I be compensated for the use of any of my biologic samples?

You should know it is possible that through the use of your biological samples (for example, blood, tissue) for this study, a commercial pharmaceutical product may be developed. If you decide to sign this consent form you are releasing (giving) to Amgen Inc., your blood sample, the by-products of your sample, and any products developed from the sample or use of the sample. Amgen, other researchers, or research companies may patent or sell discoveries that result from this research. Neither Amgen, the Principal Investigator, nor the study doctor will compensate you if this happens.

7. CONFIDENTIALITY

a. How will the confidentiality of my records be maintained?

The handling of medical information obtained in clinical research is governed by national and international data protection regulations and medical confidentiality. The medical information collected during this study will first be checked to make sure it is accurate. It will then be transferred into the study database(s) and processed to allow the results of this study to be analyzed and reported or published for scientific purposes.

The confidentiality of your medical records will be maintained to the extent permitted by the applicable laws. If results of the trial are published, your identity will remain confidential. The results and other information from the study may be submitted to regulatory agencies in countries where the investigational product may be submitted for approval.

Neither your results nor your samples will be identified with your name. Data regarding your participation in this study will be associated with you when it is submitted to Amgen by using a subject identification number, your date of birth, and your gender.

b. Who will have access to my medical information if I sign this informed consent form?

It is a requirement that your involvement in this study be noted in your medical records. If your primary care physician is different from the study doctor for this study, he/she may also be notified. Direct access to your records will be required by authorized representatives of Amgen including monitors and auditors to check the information collected for the study. Your medical records may also be reviewed and copies made by members of either the institutional review board/independent ethics committee responsible for this trial site, a regulatory agency, or an authorized Amgen representative. These individuals will see your name, other personal information such as date of birth and gender, and your medical information, but shall not disclose your name to anyone else.

By signing this consent form, you (or your legally acceptable representative) authorize access to this confidential information.

Some of the data collected from you, including laboratory samples and imaging scans, which may contain confidential information will be sent to a central vendor for analysis, interpretation, and reporting results back to Amgen and/or the study doctor. The confidentiality of your information provided to the central vendor will be maintained by the central vendor staff members.

Since exploratory sample evaluations are not expected to benefit you directly or to alter your treatment course, these results will not be placed in your medical record and will not be made available to you, members of your family, your personal physician, or other third parties, except as specified below.

8. COMPENSATION FOR INJURY

a. What do I do if I think I have an injury/illness related to my participation in this study?

If you think you have an injury/illness that is related to the study, you should immediately notify Dr. Deveras, the Principal Investigator, your Study Doctor, _____, or one of the Study Staff members working on the study. The investigator and the study staff may be reached at

Halifax Health
Center for Oncology
303 N. Clyde Morris Blvd.
Daytona Beach, FL 32114
(386) 254-4212

If you have a study-related injury/illness, the Principal Investigator, your Study Doctor or one of the Study Staff members will make sure that you receive necessary treatment.

b. If I have an injury/illness related to my participation in the study, will I be compensated in any way?

Amgen will reimburse you for reasonable medical expenses for the treatment of any injury/illness that is directly related to the properly administered investigational product. Amgen will not compensate you for treatment that is paid for by a third party.

Amgen also will not compensate (pay) you for other injury- or illness-related costs, such as lost wages. You are not waiving any legal rights by participating in this study.

No compensation is available from Amgen other than that provided by law. You do not give up any of your legal rights by signing this consent form.

9. ASSURANCES

If I agree to participate in this study, what can I be assured of:

- Your participation is voluntary, and you are free to withdraw from the clinical research study at anytime without prejudice to your future care. If you decide to withdraw, you should notify your doctor so that your part in the study may be stopped in an orderly manner and that your future care can be discussed. Also, Dr. Deveras, Principal Investigator or your Study Doctor or Amgen may choose to withdraw you from this research study at any time.
- You or your legally acceptable representative will be kept informed, in a timely manner, of any information that may relate to your willingness to continue participation in the study. At the discretion of your doctor(s) and Amgen, you or your legally acceptable representative may be asked to sign a revised informed consent or consent addendum that provides this information.
- You may ask questions at any time about this study. If you feel that you have experienced an adverse reaction to the investigational product(s) or procedures, or if you feel unusually unwell during the study, you should contact your Study Doctor _____ at (386) 254-4212.

If you have any questions about the informed consent process or your rights as a research subject then you should contact

Liberty IRB, Inc.
DeLand, FL 32724
(386) 740-9278

The Liberty Institutional Review Board is a committee that has reviewed this research study to help ensure that your rights and welfare as a research participant are protected and that the research study is carried out in an ethical manner.

SIGNATURES

In signing this document, you are confirming that:

- 1) Your concerns and questions about this research study have been answered to your satisfaction.
- 2) You have had alternative treatments discussed with you.
- 3) You agree to be part this study and that you have received your own copy of this document.
- 4) You agree that Amgen's research using your medical data collected in connection with this study may lead to the development of commercial pharmaceutical products. Amgen and other researchers may use these data and may patent or commercialize discoveries or inventions that result from this research. Neither Amgen nor other participants in this research will compensate you if this happens.
- 5) You understand that your participation in the study is voluntary and that you are free to withdraw at any time, without giving any reason, and without your medical care or legal rights being affected.

PRINT subject's name	Date/Time	Subject's signature
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PRINT name of the person who conducted the informed consent discussion	Date/Time	Signature of person who conducted the informed consent discussion
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PRINT Study Doctor's name	Date/Time	Study Doctor's signature
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¹Each person who signs the consent must personally enter the date for his/her signature.

MEDICATION GUIDE

Aranesp[®] (Air-uh-nesp) (darbepoetin alfa)

Read this Medication Guide:

- before you start Aranesp,
- if you are told by your healthcare provider that there is new information about Aranesp,
- if you are told by your healthcare provider that you may inject Aranesp at home, read this Medication guide each time you receive a new supply of medicine.

This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Talk with your healthcare provider regularly about the use of Aranesp and ask if there is new information about Aranesp.

What is the most important information I should know about Aranesp?

Using Aranesp can lead to death or other serious side effects.

For patients with cancer:

Your healthcare provider has received special training through the ESA APPRISE Oncology Program in order to prescribe Aranesp. Before you can begin to receive Aranesp, you must sign the patient-healthcare provider acknowledgment form. When you sign this form, you are stating that your healthcare provider talked with you about the risks of taking Aranesp.

These risks include that your tumor may grow faster and you may die sooner if you choose to take Aranesp.

You should talk with your healthcare provider about:

- Why Aranesp treatment is being prescribed for you.
- What are the chances you will get red blood cell transfusions if you do not take Aranesp.
- What are the chances you will get red blood cell transfusions even if you take Aranesp.
- How taking Aranesp may affect the success of your cancer treatment.

After you have finished your chemotherapy course, Aranesp treatment should be stopped.

For all patients who take Aranesp, including patients with cancer or chronic kidney disease:

- If you decide to take Aranesp, your healthcare provider should prescribe the smallest dose of Aranesp that is needed to reduce your chance of getting red blood cell transfusions.
- You may get serious heart problems such as heart attack, stroke, heart failure, and may die sooner if you are treated with Aranesp to reach a normal or near-normal hemoglobin level.
- You may get blood clots at any time while taking Aranesp. If you are receiving Aranesp

for any reason and you are going to have surgery, talk to your healthcare provider about whether or not you need to take a blood thinner to lessen the chance of blood clots during or following surgery. Clots can form in blood vessels (veins), especially in your leg (deep venous thrombosis or DVT). Pieces of a blood clot may travel to the lungs and block the blood circulation in the lungs (pulmonary embolus).

Call your healthcare provider or get medical help right away if you have any of these symptoms of blood clots:

- Chest pain
- Trouble breathing or shortness of breath
- Pain in your legs, with or without swelling
- A cool or pale arm or leg
- Sudden confusion, trouble speaking, or trouble understanding others' speech
- Sudden numbness or weakness in your face, arm, or leg, especially on one side of your body
- Sudden trouble seeing
- Sudden trouble walking, dizziness, loss of balance or coordination
- Loss of consciousness (fainting)
- Hemodialysis vascular access stops working

See "What are the possible side effects of Aranesp?" below.

What is Aranesp?

Aranesp is a man-made form of the protein human erythropoietin that is given to reduce or avoid the need for red blood cell transfusions. Aranesp stimulates your bone marrow to make more red blood cells. Having more red blood cells raises your hemoglobin level. If your hemoglobin level stays too high or if your hemoglobin goes up too quickly, this may lead to serious health problems which may result in death. These serious health problems may happen even if you take Aranesp and do not have an increase in your hemoglobin level.

Aranesp may be used to treat a lower than normal number of red blood cells (anemia) if it is caused by:

- Chronic kidney disease (you may or may not be on dialysis).
- Chemotherapy that will be used for at least two months after starting Aranesp.

Aranesp should not be used for the treatment of anemia:

- If you have cancer and you will not be receiving chemotherapy that may cause anemia for at least 2 more months.
- If you have a cancer that has a high chance of being cured.
- In place of emergency treatment for anemia (red blood cell transfusions).

Aranesp has not been proven to improve the quality of life, fatigue, or well-being.

Who should not take Aranesp?

Do not take Aranesp if you:

- Have cancer and have not been counseled by your healthcare provider regarding the risks of Aranesp or if you have not signed the patient-healthcare provider acknowledgement form before you start Aranesp
you have not signed the patient-healthcare provider acknowledgment form before you start Aranesp treatment.

- Have high blood pressure that is not controlled (uncontrolled hypertension).
- Have been told by your healthcare provider that you have or have ever had a type of anemia called Pure Red Cell Aplasia (PRCA) that starts after treatment with Aranesp or other erythropoietin protein medicines.
- Have had a serious allergic reaction to Aranesp.

What should I tell my healthcare provider before taking Aranesp?

Aranesp may not be right for you. **Tell your healthcare provider about all your health conditions, including if you:**

- Have heart disease.
- Have high blood pressure.
- Have had a seizure (convulsion) or stroke.
- Are allergic to latex.
- Have any other medical conditions.
- Are pregnant or planning to become pregnant. It is not known if Aranesp may harm your unborn baby. Talk to your healthcare provider about possible pregnancy and birth control choices that are right for you. If you are pregnant, discuss with your healthcare provider about enrolling in Amgen's Pregnancy Surveillance Program or call 1-800-772-6436 (1-800-77-AMGEN).
- Are breast-feeding or planning to breast-feed. It is not known if Aranesp passes into breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines with you and show it to your healthcare provider when you get a new medicine.

How should I take Aranesp?

See "What is the most important information I should know about Aranesp?"

For patients with cancer:

Before you begin to receive Aranesp, your healthcare provider will:

- Ask you to review this Aranesp Medication Guide.
- Explain the risks of Aranesp and answer all your questions about Aranesp.
- Have you sign the patient-healthcare provider acknowledgment form.

For all patients who take Aranesp:

- Continue to follow your healthcare provider's instructions for diet, and medicines, including medicines for high blood pressure, while taking Aranesp.
- Have your blood pressure checked as instructed by your healthcare provider.

- If you or your caregiver has been trained to give Aranesp shots (injections) at home:
Be sure that you read, understand, and follow the "Instructions for Use" that come with Aranesp.
Take Aranesp exactly as your healthcare provider tells you to. Do not change the dose of Aranesp unless told to do so by your healthcare provider.
Your healthcare provider will show you how much Aranesp to use, how to inject it, how often it should be injected, and how to safely throw away the used vials, syringes, and needles.
If you miss a dose of Aranesp, call your healthcare provider right away and ask what to do.
If you take more than the prescribed amount of Aranesp, call your healthcare provider right away.

What are the possible side effects of Aranesp?

Aranesp may cause serious side effects.

- See "What is the most important information I should know about Aranesp?"
- High blood pressure.** High blood pressure is a common side effect of Aranesp in patients with chronic kidney disease. Your blood pressure may go up or be difficult to control with blood pressure medicine while taking Aranesp. This can happen even if you have never had high blood pressure before. Your healthcare provider should check your blood pressure often. If your blood pressure does go up, your healthcare provider may prescribe new or more blood pressure medicine.
 - Seizures.** If you have any seizures while taking Aranesp, get medical help right away and tell your healthcare provider.
 - Antibodies to Aranesp.** Your body may make antibodies to Aranesp. These antibodies can block or lessen your body's ability to make red blood cells and cause you to have severe anemia. Call your healthcare provider if you have unusual tiredness, lack of energy, dizziness, or fainting. You may need to stop taking Aranesp.
 - Serious allergic reactions.** Serious allergic reactions can cause a rash over your whole body, shortness of breath, wheezing, dizziness and fainting because of a drop in blood pressure, swelling around your mouth or eyes, fast pulse, or sweating. If you have a serious allergic reaction, stop using Aranesp and call your healthcare provider or get medical help right away.

The needle cover on the prefilled syringe contains latex. If you know you are allergic to latex, talk to your healthcare provider before using Aranesp.

Common side effects of Aranesp include:

- shortness of breath
- cough
- low blood pressure during dialysis
- abdominal pain
- edema (swelling) of the arms or legs

These are not all of the possible side effects of Aranesp. Your healthcare provider can give you a more complete list. Tell your healthcare provider about any side effects that bother you or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Aranesp?

- Do not shake Aranesp.
- Protect Aranesp from light.
- Store Aranesp in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze Aranesp.** Do not use Aranesp that has been frozen.
- Throw away the Aranesp vial or prefilled syringe after one use. Do not re-use even if there is medicine left.

Keep Aranesp and all medicines out of the reach of children.

General information about Aranesp

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Use Aranesp only for the condition for which it has been prescribed. Do not give Aranesp to other patients even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Aranesp. If you would like more information about Aranesp, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Aranesp that is written for healthcare professionals. For more information, go to the following website: www.aranesp.com or call 1-800-77-AMGEN.

What are the ingredients in Aranesp? Active Ingredient: darbepoetin alfa **Inactive Ingredients:**

polysorbate 80, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, and

sodium chloride in Water for Injection, USP. This Medication Guide has been approved by the U.S. Food

and Drug Administration.

Manufactured by:

AMGEN[®]

Amgen Manufacturing Limited, a subsidiary of Amgen Inc. One Amgen Center Drive Thousand Oaks, CA
91320-1799

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Liberty IRB Approved 0901/09, Rev. 1
Liberty IRB Approved 08/26/10, Rev. 2
Liberty IRB Approved 11/03/11, Rev. 3

Participant Initials _____