CONSENT FOR CANCER RESEARCH

Project Title: A Single Arm, Phase II study of Eltrombopag to Enhance Platelet Count Recovery in Elderly Patients with Acute Myeloid Leukemia undergoing Remission Induction therapy

Principal Investigator: Sudipto Mukherjee, MD (216) 444-0506

Sponsor: Investigator-Initiated (Novartis will supply study drug and provide some financial support)

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic.

1. Introduction

We are asking you to participate in a research study. The purpose of this document is to summarize your discussion with the research team and provide you with written information to help you decide whether you want to participate in research. Your decision is completely voluntary.

Your treating doctor may also be an investigator on this research study. If so, your doctor will have an interest in both your welfare and in the research study. You are not required to take part in this research study offered by your doctor. You may ask for a second opinion from another doctor who is not linked to this study. If you choose not to be in this study, the quality of your regular medical care will not be affected.

Please ask any questions you may have about the study or this consent form before signing it. Please take your time to make your decision. You will be given a copy of this form to keep.

2. Purpose

You are being asked to take part in this study because you have Acute Myeloid Leukemia (AML) and you will be receiving 7 + 3 high-dose remission induction chemotherapy (IC) with an anthracycline (daunorubicin or idarubicin) (for three days) and cytarabine (as continuous infusion for 7 days) to get your cancer in remission.

Who is doing this study?
This study is being conducted by Cleveland Clinic. The study is supported by Novartis. Novartis is providing the study drug, eltrombopag. Your study doctor has agreed to

participate in this study as a study investigator and will receive payments to cover some research costs such as the cost of performing tests and collecting and reporting study information.

Why is this study being done?
The purpose of this study is to find out if the study drug, eltrombopag, will help accelerate recovery of your platelet count (cells that help the blood clot) after you have received high-dose cytarabine-based chemotherapy. 7 + 3 remission induction chemotherapy (IC) causes low blood counts (white blood cells, red blood cells and platelets) for days or weeks. This may result in hospitalization, treatment with antibiotics and transfusions with blood products (red blood cells or platelets).

Eltrombopag is a drug that received FDA approval for the treatment of chronic ITP (idiopathic thrombocytopenic purpura). Chronic ITP is a bleeding condition due to a low number of platelets. Eltrombopag may also help increase the number of platelets during chemotherapy and may help prevent the risk of bleeding. Eltrombopag is administered orally and is in a class of medications called thrombopoietin receptor agonists. It works by causing the cells in the bone marrow to produce more platelets. Eltrombopag has not been approved for use in AML and it is being tested in research studies (considered investigational).

This study will help determine if eltrombopag can accelerate improvement in platelet counts following IC.

How many people will take part?
About 31 subjects will take part in this study and this study will be conducted at the Cleveland Clinic main campus. Your participation in this study will last for about 12 weeks.

What is involved in this study?
Before you are enrolled in the study, you will undergo certain tests to ensure that it is safe for you to go on the study. These are all considered as standard care. You will have a full medical history and physical examination along with blood, urine, and bone marrow tests to evaluate your disease, and other tests that the doctor might feel are needed to see if you can be on this study. Most of these tests would be done even if you do not take part in this study.

If you meet all of the criteria for being in the study, you will receive the study treatment. The study is broken down into four periods: screening, treatment, short-term safety follow-up, and long-term follow up."

The screening period includes a number of procedures to evaluate your cancer and overall health. All patients in this study will receive standard 7+3 IC for AML. Between the 14th and 17th day of starting IC, you will receive a bone marrow biopsy. If the bone marrow biopsy shows no evidence of leukemia, then, within 5 business days of this bone marrow biopsy, you will start the study drug Eltrombopag.

The treatment period only consists of the time that you will take the study medication (eltrombopag).

The short-term safety follow-up lasts for a total of 4 weeks from the stop date of the study drug (eltrombopag) or until the start date of post-remission therapy, whichever is earlier.

The long-term follow up lasts for five years. During this time period all study participants will be followed as part of standard of care for CCF leukemia patients.

Please refer to the study calendar located at the end of this document for additional details of the schedule of procedures.

3. Study Procedures

Screening

You will have the following tests and procedures during the screening period. Unless otherwise noted, the following are done within 28 days of the first day of treatment.

1. Sign an informed consent.
2. Relevant medical history, including a detailed history for any antecedent hematologic disorder (AHD) any prior other cancer (excluding AML) and all treatments used for these conditions including chemotherapy, radiation or combined modality therapy. Review of all medications used during the 4 weeks prior to screening date will be done.
3. Complete blood counts at the time of AML diagnosis.
4. Physical examination and vital signs, including measurement of blood pressure, pulse, respiratory rate, pulse oxymetry (oxygen saturation) height and body weight.
5. Assessment of Eastern Cooperative Oncology Group (ECOG) performance status score. The score assesses how the disease affects the daily living abilities of the patient such as self-care, ability to move and perform daily work.
6. Documentation of AML classification according to the World Health Organization (WHO) criteria.
7. Peripheral blood smear
8. Bone marrow aspiration and biopsy for the following studies: cytologic analysis; morphologic assessment; flow cytometry assessment of marrow aspirate; CD34 immunostaining where necessary to enumerate marrow myeloblast; fluorescent in situ hybridization (FISH) for MDS; metaphase cytogenetics; mutational analysis (especially c-kit mutations in favorable risk AML and NPM1, FLT3 and CEBPA mutations in patients with normal cytogenetics); and assessment of bone marrow fibrosis. All these tests are currently done as a routine standard of care. The results of mutational studies and metaphase cytogenetics are not necessary for starting the study drug.
9. Blood tests to assess blood counts, glucose, total protein, albumin, kidney abnormalities (blood urea nitrogen and creatinine), electrolytes (serum

bicarbonate, calcium, phosphorus, sodium, potassium and chloride), liver abnormalities [aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase].
10. Documentation of red blood cell and platelet transfusions received within 8 weeks prior to the date of screening.
11. Remote Hepatitis Panel. ELISA for HIV.
12. A 12-lead electrocardiogram (ECG), following at least a 5-minute rest while lying down.
13. Baseline eye examination will be performed only in those presenting with new symptoms of visual impairment at the time of diagnosis of AML or those with known eye conditions for which they are receiving treatments.
14. Chest x-ray, unless a previous x-ray taken during the 4 weeks prior to the first day of IC is available and shows no significant abnormality that would exclude the patient from the study.
15. Male participants with female partners of childbearing potential should have contraceptive measures addressed at screening, sufficient time to employ required contraceptive measures (barrier contraceptives) prior to start date of IC, and confirmation of adequacy of contraceptive measures prior to receiving study drug. Female participants of childbearing potential will need to be on either oral or injectable hormonal birth control medications for the entire period of treatment for leukemia.

The Treatment Period
If you are found to be eligible, you will start study treatment (eltrombopag) within 5 business days from the date of the day 14-17 bone marrow biopsy.

You will have the following tests/procedures while you are in the hospital
1. Vital signs and physical exam
2. Adverse event monitoring
3. Blood tests to measure blood counts and to track the presence or absence of response
    a. In the hospital, these blood tests will be performed daily
    b. If you receive the study medication while outpatient, you will receive a blood test within 72 hours of discharge and weekly thereafter
4. Documentation of all infections requiring treatment with intravenous antimicrobials (antibacterial, antiviral or antifungal) by date (the period to be covered for documentation starts at Day 1 of eltrombopag administration).
5. Documentation of all packed red cell and platelet transfusions.
6. 12 lead electrocardiograms pre- and post-dose on the first day of eltrombopag administration and thereafter if clinically indicated.

Blood samples will be stored for future testing at no cost to you. Your blood will be used only for research and will not be sold. The research done with your blood may lead to the development of new products in the future. You will not receive, either now or in the future, any compensation, royalty, or any other financial benefit which might result from

any product, procedure, or other items that may be developed from studying your blood or any information or data that is derived from such research.

Your blood samples will be stored using a unique identifier and not linked to your medical record number. There will be a locked key code that links the sample to you. If you change your mind about your blood sample being used for research, this code can be broken. These stored blood samples will be drawn at the following time points:

- At the time of diagnosis of AML but prior to initiation of remission IC
- At the time of day 14 bone marrow assessment (range, 14-17) following remission IC
- On day 3 (+/- 1 business day) of study drug treatment.
- On day 6 (+/- 1 business day) of study drug treatment.
- At the time of bone marrow biopsy to confirm CR (usually between days 30-45 of remission IC)

The results of the study of your samples from this project will be used for research purposes only, and you will not be told the results of the tests. Your samples may be destroyed upon termination or expiration of the research study.

Your doctor may decide to take end the study drug (eltrombopag) treatment if your disease does not improve or if side effects of treatment would make it unsafe to continue. You will be informed of new developments that may become available that might affect your participation in the study. You may stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

Women of childbearing potential should be advised to avoid becoming pregnant and men should be advised to not father a child while receiving treatment. All men and women of childbearing potential must use acceptable methods of birth control throughout the study as described below:

- Females of childbearing potential: Recommendation is for 2 effective contraceptive methods during the study. Adequate forms of contraception are double-barrier methods (condoms with spermicidal jelly or foam and diaphragm with spermicidal jelly or foam), oral, depo provera, or injectable contraceptives, intrauterine devices, and tubal ligation.
- Male patients with female partners who are of childbearing potential: Recommendation is for male and partner to use at least 2 effective contraceptive methods, as described above, during the study or to abstain

Short-term Safety Follow-up
All study subjects, including the individuals who completed the study (met primary endpoint), will be followed for adverse events and response for 4 weeks from the stop date of eltrombopag or till the start date of post-remission therapy, whichever occurs earlier. The patients who are removed from study for unacceptable adverse events will be followed until that adverse event is resolved or stabilized.

Regardless of reason for discontinuation of the study drug (eltrombopag), the following will be documented during this period:

1. Blood tests to assess blood counts, glucose, total protein, albumin, kidney abnormalities (blood urea nitrogen and creatinine), electrolytes (serum bicarbonate, calcium, phosphorus, sodium, potassium and chloride), liver abnormalities [aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin and alkaline phosphatase].
2. Physical examination and vital signs, including measurement of blood pressure, pulse, respiratory rate, pulse oximetry (oxygen saturation) height and body weight.
3. Bone Marrow aspiration and biopsy between days 30-45 of IC to assess remission status and thereafter as deemed necessary by peripheral counts and/or clinical judgment.
4. Peripheral blood smear.
5. Serious and non-serious adverse events.
6. Documentation of all packed red cell and platelet transfusions.

Long-term Follow-up
All participants, regardless of reason for discontinuation, will be followed for survival and for AML transformation (an increase of blasts to a level ≥ 20% in peripheral blood or bone marrow) for five years from study registration and thereafter as part of standard of care for CCF leukemia patients.

4. Risks

Because of the risk of adverse reactions, you will need to inform your doctor of any side effects you experience during participation in the clinical study. Furthermore, due to the risk of side effects resulting from different combinations of drugs (called drug-drug interactions), you must inform your doctor of any medications you are taking, including over-the-counter medicines, vitamins, dietary and herbal supplements, during the course of the study. You must also notify your study doctor of any other medical treatments or procedures that may be necessary for you to undergo.

You may experience all, some or none of the side effects described below. There also may be other side effects that the researchers cannot predict. Side effects may be mild, moderate, or severe. Some side effects may not show up until several weeks after treatment is given. Many side effects may disappear after the drugs are stopped. Other side effects may be long lasting, permanent, or fatal. Your doctor may order other medications to make side effects less severe or to make you feel more comfortable. Additionally, transfusions may be required to prevent symptoms or problems such as developing anemia or bleeding. In the event that you experience any severe or unusual adverse reaction during the course of this study, you should immediately contact your study doctor.

Risks and side effects related to eltrombopag include:

More likely (events occurring over 10% of the time)
• Headache
• Indigestion or heartburn
• Nausea
• Diarrhea

Less likely (events occurring in between 1% and 10% of the time)
• Tiredness or weakness
• Hair loss
• New or worsening vision problems (for example, blurred or cloudy vision)
• Bleeding into the tissue that covers the eye and underside of the eyelid
• Increased risk of bleeding after stopping eltrombopag
• Abnormal skin sensations such as tingling, itching, or burning
• Bruising
• Dry mouth
• Sore throat causing inflammation of the pharynx (pharyngitis)
• Vomiting
• Flu symptoms: symptoms may include fever, headache, tiredness, cough, sore throat, and body aches
• Rash
• Upper respiratory tract infection; symptoms include runny nose, stuffy nose, and sneezing
• Stomach tenderness or pain
• Chest pain
• Back pain
• Muscle aches and pains
• Urinary tract infection; symptoms may include frequent or urgent need to urinate, low fever, pain or burning with urination
• Abnormal liver function tests (lab tests that show how the liver is working)

Rare (events occurring less than 1% of the time)
• Allergic reactions which can involve rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue.
• Blood clots in the veins causing pain, redness and swelling in the leg. These blood clots can sometimes travel to the lungs, brain or heart which could lead to shortness of breath, coughing up blood, heart attack, stroke or death.
• Changes in your bone marrow which may show up as abnormal results in your blood tests and may lead to your body making less blood cells. This may range from mild and cause no problems to severe that causes life-threatening blood problems.
• Liver damage which may result in unusual tiredness, yellowing of skin and eyes, stomach pain, dark urine, or clay colored stools. This may be life-threatening and even fatal.

Drug Interactions
If any physician other than the study doctor prescribes medication for you for another condition or you are taking over-the counter medications, vitamins, dietary or herbal supplements, you must inform the study staff. This is important because the interaction of some medications may cause serious side effects when taken with eltrombopag. Especially tell your study staff if you are taking certain medicines used to treat high cholesterol, called “statins” and/or blood thinning medicine.

Certain medicines may keep eltrombopag from working correctly. Take eltrombopag 4 hours before or four hours after taking these products:

- Antacids used to treat stomach ulcers or heartburn
- Multivitamins or products that contain iron, calcium (including dairy products and calcium fortified juices), aluminum, magnesium, selenium, and zinc which may be found in mineral supplements

Ask your study staff if you are not sure if your medicine is one that is listed above. Additionally, if you are currently taking medications that are not permitted on this study, you will have to safely stop taking them before you can enter the study. These include medications that stimulate platelet production, inhibit platelet function or make it more difficult to stop bleeding (anticoagulants). Your study doctor will determine if any of the drugs you are taking need to be stopped in order for you to take part in this study and he will determine whether it is safe for you to stop these medications. Your study doctor will inform you of the medication that you must avoid during the study.

Other Risks and Discomforts
Since the study medication, eltrombopag is investigational in this disease setting; there may be other risks that are unknown. The potential long term safety risk of eltrombopag as a single agent or when given with chemotherapy agents are currently unknown.

The risks of having blood drawn and or inserting the needle in your vein for giving cytarabine, include fainting, bleeding, bruising at the place on your arm where the blood was drawn or needle inserted, pain, swelling and rarely, infection or nerve damage. You should tell your study doctor about any side effects or new health problems that develop while you are participating in this study.

Risks from a Bone Marrow Aspiration and Biopsy
A bone marrow aspiration is a procedure in which a small sample of bone marrow is removed, usually from the hip bone. A small area of skin and the surface of the bone underneath are numbed with an anesthetic. Then, a special wide needle is pushed into the bone. A sample of liquid bone marrow is removed with a syringe attached to the needle. The bone marrow is sent to a laboratory to be looked at under a microscope. This procedure will be done at the same time as the bone marrow biopsy.
A bone marrow biopsy is a procedure in which a small sample of bone with bone marrow inside it is removed, usually from the hip bone. A small area of skin and the surface of the bone underneath are numbed with an anesthetic. Then, a special, wide needle is pushed into the bone and rotated to remove a sample of bone with the bone

marrow inside it (a core sample). The sample is sent to a laboratory to be looked at under a microscope. This procedure will be done at the same time as the bone marrow aspiration.

When the local anesthesia (numbing medicine) is given, you may initially feel a burning sensation in your skin and bone surface for several seconds. During the procedure, you may temporarily feel pressure and/or pain of varying degrees. If necessary, you may ask your doctor for additional local anesthesia or a medication to ease your stress. You also may experience bleeding, and/or bruising after the procedure is completed and you may experience soreness in the area for a few days afterwards. Rarely, infection can develop. Bone marrow aspirations and bone marrow biopsies are considered standard of care for AML patients and may be done even if you are not participating in a clinical trial.

Reproductive Health/Sexual Activity
Men and women should not attempt pregnancy and women should not be pregnant or breast-feeding while participating on this study. Both women capable of becoming pregnant or men capable of fathering children must agree to use an effective method of birth control while taking the study drug. Barrier contraceptives (condoms or diaphragms) with spermicide, intrauterine devices, hormonal contraceptives (Depo-Provera, Norplant), oral contraceptive pills, and complete abstinence are examples of effective methods. If you or your partner become pregnant while taking the study drug, it is important that you notify your study nurse/physician immediately. You may be required to stop the study drug at which time other treatment options will be discussed with you.

5. Benefits

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with your condition in the future.

6. Alternatives to Participation

Because this is a research study, participation is voluntary. Instead of being in this study, you have these options:
• Standard 7 + 3 remission IC and supportive care in terms of aggressive infection prophylaxis and control and blood product transfusions including red blood cells and platelets.
• Taking part in another study
• No therapy at this time, with care to help you feel more comfortable.

Please talk to your doctor about these and other options for your treatment. Your medical care and treatment will not be affected if you choose not to participate.

During the course of the study, your study doctor will let you know about any new information that may affect your willingness to remain in the study. If new information is learned that may affect you after the study has been completed, you will be contacted by the study doctor.

7. Costs and Compensation

You and/or your insurance company will be financially responsible for tests and procedures that are part of this study and needed for your regular medical care (care you would have received whether or not you were in this study). Taking part in this study may lead to added costs to you or your insurance company. Some insurance companies will not pay for these costs. You will have to pay for any costs not covered by your insurance company. Please ask about any expected additional costs or insurance problems. The drug company who manufactures eltrombopag will provide this drug free of charge to all participants. All other drugs will not be supplied and will be billed to your insurance company. Your doctor will answer any questions you may have.

In addition, the items below will be paid by the study. This means that you or your insurance company will not have to pay for these to be done:
• ECG(s)- Baseline EKG done prior to start of 7+3 IC and any subsequent ECG done during the rest of the hospital stay for evaluation of any change in patient's medical condition is considered standard of care and will be paid by you or your insurance company. ECG's will be performed a few hours prior to and immediately after taking the study drug on the first day the patient starts treatment with the study drug and thereafter checked once weekly for the entire duration the patient remains on the study drug. These ECG's will be covered by the study.
• Eye exam(s)
• Repeat bone marrow exams done if your doctor suspects any problems (the baseline bone marrow exam done to confirm diagnosis of AML and the bone marrow performed on day 14 from the start of 7+3 IC is considered standard of care and will be paid by you or your insurance company)
• Optional bone marrow samples for research

You will receive no payment for taking part in this study.

For more information on clinical trial and insurance coverage, you can visit the National Cancer Institute's (NCI) website at
http://cancer.gov/clinicaltrials/understanding/insurance-coverage
You can print a copy of the 'Clinical Trials and Insurance Coverage' information from this website. Another way to get information is to call 1-800-4-CANCER (1-800-422-6237) and ask NCI for a free copy.

8. Research-Related Injury

If injury occurs as a result of your involvement in this research, medical treatment is available from Cleveland Clinic or another medical facility but you/your medical insurance will be

responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research-related injury. To help avoid injury, it is very important to follow all study directions.

9. Privacy and Confidentiality

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Dr. Sudipto Mukherjee and the research staff at Cleveland Clinic for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- The National Cancer Institute (NCI) and other government agencies involved in keeping research safe for people
- Data coordinating centers
- Novartis and its agents and other outside collaborators or laboratories
- Your insurance company
- The National Committee for Quality Assurance
- The Food and Drug Administration
- The Department of Health and Human Services
- Other Institutional Review Boards or Data Safety and Monitoring Boards
- Other outside collaborators or laboratories that are participating in this study, if any

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to Dr. Sudipto Mukherjee, Cleveland Clinic, 9500 Euclid Ave, CA-62, Cleveland, OH 44195. Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected.

The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

10. Voluntary Participation

Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

11. Questions About the Research

You can talk to your study doctor or nurse about any questions or concerns you have about the study. During business hours you may contact Dr. Sudipto Mukherjee at 216-444-0506 . You also have the option to contact the page operator at (216) 444-2200 or toll free at (800) 223-2273, and ask for the oncologist (cancer doctor) that is on call.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database

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.

12. Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

Optional Bone Marrow Samples for Research
Eltrombopag may cause changes in your bone marrow. These changes may lead to abnormal blood cells or your body making less blood cells. The mild form of these bone marrow changes is called “increased reticulin” which may progress to a more severe form called “fibrosis”. The mild form may cause no problems while the severe form may cause life-threatening blood problems.

If you consent, we would like to obtain bone marrow samples (a small sample of bone marrow is placed on a glass slide for microscopic examination) for research to be sent to a central laboratory for review for “increased reticulin”. These bone marrow samples will come from the bone marrow aspirate and biopsy you already had done as part of your standard care to confirm remission.

In addition, if a repeat bone marrow exam is performed because the treating physician suspects a problem, we would like to obtain bone marrow samples from that examination for review.

Your bone marrow samples will be stored using a unique identifier and not linked to your medical record number. There will be a locked key code that links the sample to you. If you change your mind about your bone marrow sample being used for research, this code can be broken.

_____ I consent to my bone marrow samples being used for the research described above
_____ I do not consent to my bone marrow samples being used for the research described above

The results of the study of your samples from this project will be used for research purposes only, and you will not be told the results of the tests. Your samples may be destroyed upon termination or expiration of the research study.

The following study calendar will be used:

	Pre-induction	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
						Inpatient/Outpatient	
Induction chemotherapy (IC)							
Study Medication[a]							
Informed Consent	X						
Demographics[b]	X						
Disease Characteristics[c]	X						
Transfusion History[d]	X	X	X	X	X	X	X
Review of concurrent medications	X	X	X	X	X	X	X
Physical Examination[e]	X	X	X	X	X	X	X
CSBE[f]	X	X	X	X	X	X	X
Performance status[g]	X						
Hematology[h]	X	X	X	X	X	X	X
Serum Biochemistry[i]	X	X	X	X	X	X	X
Chest x-ray	X						
Peripheral Blood Smear[j]	X					X	
Bone marrow biopsy[k]	X		**D14 - 17**			**X**	
Ophthalmology exam[l]	X						
12 lead ECG	X			**X**[m]			
Adverse event monitoring				X	X	X	X

Pre-induction assessment refers to evaluation at the time of diagnosis of AML prior to start of remission induction chemotherapy. Weeks as enumerated in the table refer to the time from the start date (day 1) of remission induction chemotherapy.

Week 1 is the week when the patient receives the standard 7+ 3 (cytarabine and anthracycline) remission induction chemotherapy

a. **Study Medication**: Eltrombopag dose as assigned. The drug will be started within 5 business days from the date of day 14 bone marrow biopsy if the day 14 bone marrow biopsy (range, 14-17) shows no morphological evidence of leukemia and will be continued for a total of 4 weeks unless discontinued earlier for reasons stated in the protocol.

b. **Demographics:** Date of birth, race, ethnicity, and gender.

c. **Disease Characteristics:** Date of AML diagnosis, AML category as classified by WHO, primary vs. secondary AML, type of secondary AML (antecedent hematologic disorder, therapy-related including prior radiation therapy and or cytotoxic chemotherapy for any condition).
d. **Transfusion History:** Transfusion requirements of red blood cells and platelets up to 8 weeks prior to the diagnosis of AML and during hospital stay.
e. **Physical Examination:** Weight, height (during screening only), body temperature (oral), blood pressure, pulse rate, respiratory rate and pulse oximetry (oxygen saturation).
f: **CSBE:** Clinically Significant Bleeding Events includes hematuria, gastrointestinal bleed, retroperitoneal bleeding, intra-cranial bleed, epistaxis not controlled by conservative measures and muscle or soft tissue hematomas. CSBE will not include petechial skin rash, ecchymosis or mucosal petechiae.
g. **Performance Status** as per ECOG scale.
h. **Hematology**: CBC with differential will be monitored daily during hospital stay. Once the patient is discharged, CBC with differential will be checked within 72 hours, thereafter CBC with differential will be checked weekly until the subject's platelets reach 100,000/µL. Once the platelet counts reach 100,000/µL, the labs will be done at the discretion of treating physician as part of routine standard of care.
i. **Serum Biochemistry**: Complete metabolic panel (CMP) will be checked daily during hospital stay. CMP will include albumin, total protein, alkaline phosphatase, total bilirubin, SGOT[AST], SGPT[ALT], sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, and calcium. Magnesium and phosphorus will be resulted if clinically indicated. Once the patient is discharged, CMP will be checked weekly until the subject's platelets reach 100,000/µL. Once the platelet counts reach 100,000/µL, the labs will be done at the discretion of treating physician as part of routine standard of care. ELISA for HIV and remote hepatitis panel will be checked only once at the time of study screening (pre-induction).
j. **Peripheral Blood Smear:** Will be performed prior to start of induction chemotherapy, typically between day 30 and 45 of induction chemotherapy while checking for remission status and at the end of the study period (optional) based on clinical assessment.
k. **Bone marrow biopsy:** Bone marrow evaluation will include cellularity analysis, morphological assessment of all three cell lineages, assessment of blast percentage, fibrosis and metaphase cytogenetics. Tests for molecular mutations and FISH studies will be done as necessary as part of standard of care where indicated. **D14-17** denotes marrow evaluation between day 14 to 17 from the start date of IC to check for persistent disease. **D30-45** denotes marrow evaluation typically between day 30 to 45 from the start date of IC to check for remission status or refractory disease. The need for additional bone marrow biopsies including end of study bone marrow biopsy will be determined clinically based on peripheral blood count abnormalities or morphology
l: **Ophthalmologic evaluation**: Complaints of any new or recent onset visual symptoms at the time of AML diagnosis. Those with known prior or existing ocular conditions such as any vitreoretinal diseases, age-related macular degeneration, optic nerve disease, glaucoma and corneal diseases as well as patients in whom there is clinical suspicion of cataracts will be evaluated at baseline. A follow up exam will be done at 2 months after stopping the drug if clinically indicated.
X^{m}:A 12-lead ECG will be obtained for each patient at screening (baseline). A pre- and post-dose 12-lead ECG will be performed on the first day of eltrombopag administration. The post-dose ECG is to be performed within a 2-4 hour window post-dose (preferably within 3 hours after administration of study drug). Thereafter, 12 lead ECGs will be performed as clinically indicated.