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STUDY 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

ClinicalTrials.gov #: NCT02071901

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SUMMARY OF CHANGES

Version date/#	Section #	Description of change (s)
V1, 6/11/2013		Initial IRB Approval
V2, 3/17/2015	3, 6, 7, 8, 9	1) clarification of inclusion/exclusion criteria; 2) addition of safety information; 3) changes to treatment/dosing
V3, 4/28/2016	3, 8, 10	1) clarification of inclusion/exclusion criteria; 2) updated to off study monitoring; 3) revisions to study endpoints
V4, 6/21/2017	3, 4, 5, 7, 8, 10, 11	1) administrative/formatting changes throughout the protocol; 2) changed drug supplier from GSK to Novartis; 3) clarification of inclusion/exclusion criteria; 4) minor revision to study design/data collection; 5) revised study calendar; 6) clarification of defined complete response
V5, 8/8/2017	3, 4.1, 8, 9, 11.7	1) clarification of inclusion/exclusion criteria; 2) blood transfusion support in the study design; 3) updated treatment plan information; 4) revised ancillary laboratory test schedule; 5) AE collection period correction
V6, 5/14/2018	3.2	1) minor formatting and administrative edits throughout the protocol; 2) modified exclusion criteria #10 and removed exclusion criteria #11

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1.0 BACKGROUND AND STUDY RATIONALE

1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) presents at all ages, but is mainly a disease of older adults, with a median age of 67 years in the US population.(1) In the Swedish Acute Leukemia Registry, 68% of patients diagnosed with AML since 1973 were over age 60 years; between 1997 and 2005, 75% were aged 60 years or more.(2) Prognosis worsens with every subsequent decade beginning at age 30.(1,3) In a multivariate analysis of prognostic factors, age ≥ 60 years has consistently been shown to be a significant poor prognostic factor for complete remission (CR), overall survival (OS), remission duration, and relapse-free survival (RFS). Population-based studies have reported 3- and 5-year survival rates of only 9% to 10% and 3% to 8%, respectively, in patients over aged 60 and over, compared with 5-year survival rates of up to 50% for younger patients.(2,4,5) Poorer outcome is likely the result of less intensive therapy in this population, concurrent comorbidities, a higher likelihood of underlying hematopoietic disorders, and biologically poor risk disease. Once CR has been obtained, there is no standard postremission strategy in these patients. No prospective randomized study has ever established the benefit of postremission therapy in older adults; however, all large studies of AML have included postremission therapy out of concern that patients are all destined to relapse without postremission therapy, and no long-term survivors among older adults have achieved that status without post-remission therapy.

In older patients inability to achieve CR, particularly as a result of delayed platelet recovery, can lead to prolonged dependence on platelet transfusions, risk of bleeding and most importantly, inability to proceed with post-remission therapy. Recent data from M. D. Anderson Cancer Center and the Southwest Oncology Group showed that patients achieving CR were more likely to be alive at 3, and particularly at 5 years than patients achieving partial complete remission (CRp) (relative risk for 5-year survival, 3.0; 95% CI, 1.0 to 9.0; $P < .02$).(6) A multivariate analysis in the same cohort that adjusted for covariates including age at diagnosis, cytogenetics, prior chemotherapy, antecedent hematologic disorder (AHD), poor performance status, response (ie, CR, CRp) indicated that CR was independently associated with a longer relapse-free survival and OS relative to CRp. Leukemia patients not cured almost uniformly die from sequelae of being immunocompromised, thrombocytopenic, or both. It stands to reason that abrogation of periods of cytopenia following remission induction therapy could reduce complications, which in turn could lead to better outcomes for older adults.

1.2 PROMACTA® (Eltrombopag)

1.2.1 Scientific Background

TPO is the principal cytokine involved in the regulation of megakaryopoiesis and platelet production. Native TPO is a 60–70 kDa heavily glycosylated polypeptide of 332 amino acids produced by the liver parenchymal, bone marrow and sinusoidal epithelial kidney cells and is the natural ligand for the TPO-receptor.(7) Eltrombopag is an orally bioavailable, small molecule, TPO-R agonist that stimulates platelet production by a mechanism similar, but not identical to endogenous TPO. Eltrombopag selectively interacts with the transmembrane domain of the TPO-

R expressed on the surface of megakaryocytes and their precursor cells (8) at a site different from native TPO, resulting in activation of various signal transduction pathways.(9) The resulting changes in gene expression commit bone marrow progenitor cells towards the megakaryocytic pathway, leading to release of normally functioning platelets into the peripheral circulation. Unlike native TPO, eltrombopag does not cause platelet aggregation and degranulation.(10) Because eltrombopag is not a protein, it is not immunogenic and does not induce formation of neutralizing antibodies. As of 13 February 2012, eltrombopag has been approved for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) in 84 countries. Two Phase III studies have been completed (TPL103922/ENABLE 1 and TPL108390/ENABLE 2) in subjects with HCV-related thrombocytopenia. Based on these study findings eltrombopag is the first supportive care treatment approved for patients with thrombocytopenia with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.

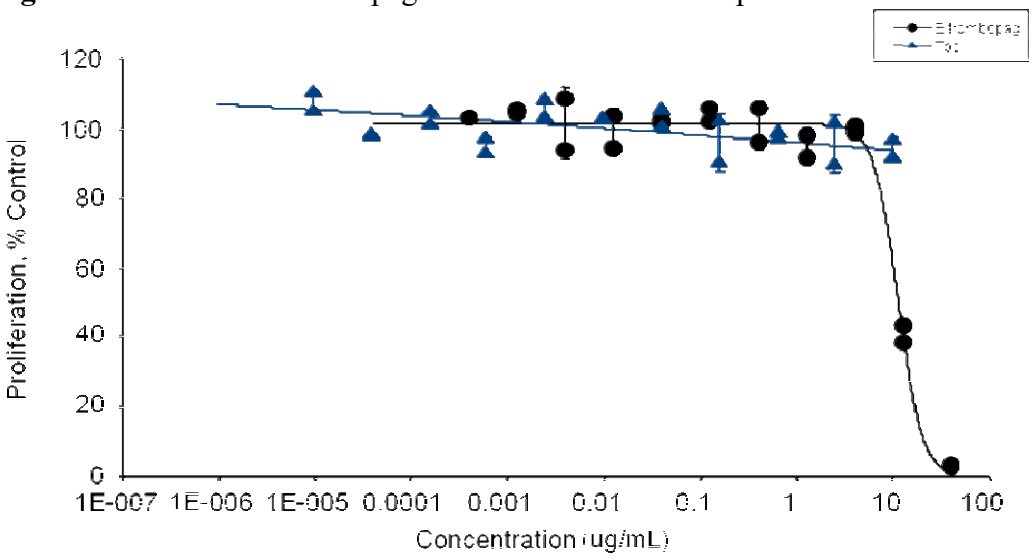
1.2.2 Pre-Clinical Studies

The details of pre-clinical and clinical pharmacology data are available in the Clinical Investigator's Brochure (CIB) provided by Novartis.(11) There is a theoretical concern that stimulation of the TPO receptor on the surface of hematopoietic cells may also increase the risk for hematologic malignancies. As such, extensive preclinical research to ascertain any potential relationship between treatment with eltrombopag and proliferation of malignant cells has been performed. Based on this research, there is no evidence in cell lines or in AML/MDS patient samples that eltrombopag stimulates malignant growth. In several independently conducted experiments (12-15), it has been consistently demonstrated that eltrombopag can inhibit the proliferation of leukemic cells at high concentrations (3-5x higher than used in ITP). These concentrations are expected to be reached in patients with MDS and AML following once daily administration of 200 to 300 mg of eltrombopag.

In contrast to the stimulating effects of eltrombopag on megakaryocytes, eltrombopag decreased the growth of 16 different leukemia and lymphoma cell lines in vitro.(13) The decrease in proliferation was due to death of the cells by a mechanism other than apoptosis. There was no significant effect on the differentiation of the leukemic cell lines. While recombinant TPO caused a small increase in the proliferation of lymphoblastic T-cell leukemia, eltrombopag did not induce a similar increase, but rather inhibited proliferation, even in the presence of TPO. While G-CSF increased the proliferation of OCI AML2 cells, eltrombopag decreased the proliferation.

Recently, a proliferation assay comparing the effects of eltrombopag and recombinant TPO has been conducted in 5 leukemic cell lines (Figure 1). Eltrombopag, but not recombinant TPO, had anti-leukemic effects in the 5 cell lines.

Figure 1. Effects of eltrombopag on OCI-AML3 cell line proliferation



The IC50 for eltrombopag in these preclinical experiments ranged from 6.4 to 14.2 µg/mL (Table 3). Based upon preliminary pharmacokinetic data from patients with MDS/AML in Part 1 of this study (n=7), the median eltrombopag steady-state Cmax and pre-dose trough concentrations after once daily administration of 100 mg eltrombopag were 13.5 and 4.13 µg/mL, respectively. As the PK of eltrombopag has been shown to be dose proportional, it is expected that doses of 200 to 300 mg eltrombopag in patients with MDS/AML will result in plasma concentrations at or above the IC50 values identified for anti-leukemic effects in the cell lines.

Table 3 Eltrombopag IC50 Values

Leukemic Cell Line	IC50 ± Std Dev (µg/mL)
HL-60	6.4 ± 0.4
HEL 92.1.7	8.0 ± 1.0
OCI-AML3	9.8 ± 1.8
THP-1	13.5 ± 1.0
NOMO	13.5 ± 1.2
N2C-TPO	14.2 ± 1.7

The anti-proliferative effect on hematologic malignancies was investigated further in several additional experiments using bone marrow mononuclear cell (BM-MNC) samples from 10 patients with AML or MDS.(12) A decrease in malignant cell number was seen in 8 of 10 samples, while the cell number for 2 samples remained unchanged, after two weeks treatment with eltrombopag. The anti-proliferative effects did not reach statistical significance due to inter-individual variation. There was no significantly decreased apoptosis, no increased immature cells or blasts, nor any evidence of increased long-term self-renewal of AML or MDS BM-MNC in any of the samples. To test anti-proliferative effects of eltrombopag in animals (as eltrombopag only interacts with the human TPO-R), the following ex-vivo experiment was conducted. BM MNC from 3 patients with AML were transplanted into 3 cohorts of sublethally irradiated NOG

mice. Successfully transplanted mice were treated with or without eltrombopag. Confirming the results from the in vitro assays, treatment with eltrombopag did not enhance the in vivo engraftment of human AML cells in this xenotransplantation model.(12)

Recently, the same group has published that eltrombopag, at clinically achievable concentrations, inhibits proliferation and induces differentiation of leukemic cells through reduction of intracellular iron levels, independently of the TPO-R.(15) In vivo, eltrombopag prolonged survival in 2 murine models of leukemia. The anti-proliferative effects of chemotherapy in leukemic cell lines was enhanced by co-incubation with eltrombopag.(15) The authors showed that in contrast to eltrombopag, recombinant human TPO and another TPO-R agonist, romiplostim, do not modulate intracellular iron levels.

Similar results were observed by another independent study group using eltrombopag and a small molecule TPO receptor agonist that is very similar to eltrombopag.(16) In another independent investigation, bone marrow samples from 5 patients with MDS who had a low/intermediate-1-risk IPSS score were treated in vitro with eltrombopag, again demonstrating anti-proliferative effects upon co-incubation with eltrombopag.(14)

Please refer to the current version of the CIB (11) for further information regarding pre-clinical and clinical pharmacology studies.

1.2.3 Clinical Studies

Eltrombopag has been administered both to healthy volunteers and subjects with thrombocytopenia from a variety of etiologies, and it has been shown to improve platelet counts in those with thrombocytopenia. A total of 664 subjects have received eltrombopag in 16 clinical pharmacology studies, including 618 healthy subjects, 25 subjects with hepatic impairment and 21 subjects with renal impairment. Over 2400 subjects have received eltrombopag in completed or ongoing GSK-sponsored clinical efficacy studies in ITP, chronic liver disease or hematologic/oncologic malignancies globally.

Study PMA112509, a Phase I/II study of eltrombopag in thrombocytopenic subjects with advanced MDS or AML is currently ongoing. Part 1 of TRC114968 enrolled 17 subjects; 11 subjects completed the 8 weeks of treatment in Part 1. Preliminary safety data is available. Six subjects discontinued treatment early, 5 due to adverse events (AEs; 2 Grade 3 alanine aminotransferase [ALT] increase, 1 Grade 3 Nausea, 1 Grade 4 Laryngeal edema, 1 Grade 5 Sepsis, and 1 Grade 3 Gastrointestinal hypomotility) and 1 due to investigator discretion. Of the 11 subjects who completed Part 1, 5 entered the extension (Part 3). The most common AEs (in at least 3 subjects) were pyrexia, ALT increased, diarrhea, epistaxis, headache and pneumonia. Seven subjects reported 15 serious adverse events (SAEs; cystitis and hematuria; respiratory tract infection and sepsis; cerebral hemorrhage and pyrexia; ALT increased; cellulitis and hemolytic anemia; pyrexia, gastrointestinal hypomotility and vertigo; pneumonia, laryngeal edema and sepsis.). Reported AEs and SAEs were consistent with the disease under study and with those expected during treatment with eltrombopag. Three subjects died (2 – SAEs of sepsis and 1 – disease progression (not reported as an AE).

Preliminary pharmacokinetic data from the first 7 subjects enrolled in Part 1 of this study showed the median eltrombopag steady-state Cmax and pre-dose trough concentration after once daily administration of 100 mg eltrombopag were 13.5 and 4.13 μg/mL, respectively. These values are generally consistent with previous PK observations in healthy subjects and patients with ITP. As the PK of eltrombopag has been shown to be dose proportional, it is expected that doses of 200 to 300 mg eltrombopag utilized in this study will result in plasma concentrations at or above these IC50 values for the majority of the dosing interval (predicted 200mg Cmax and trough concentrations: 27 and 8.26μg/mL, respectively; predicted 300mg Cmax and trough concentrations: 40.5 and 12.39μg/mL, respectively). Please refer to the current version of the CIB (11) for further information regarding clinical studies.

One clinical trial assessing the role of eltrombopag in palliative setting in elderly AML patients (NCT01113502) recently completed recruitment and results are awaited. Several other eltrombopag trials are currently underway in MDS (lower- as well as in higher-risk disease) and in AML setting [NCT01286038, NCT01481220, NCT00961064, NCT01488565, NCT01440374, NCT00903422, NCT01550185].

1.3 Thrombocytopenia

Thrombocytopenia is a common problem in patients with acute leukemia and other hematologic malignancies treated with intensive chemotherapy. The current standard treatment strategy to prevent or manage thrombocytopenia-associated bleeding complications relies exclusively on supportive platelet transfusions. However, this therapeutic approach is expensive, time consuming and associated with risks of alloimmunization and bloodstream infections. Moreover, the effects of platelet transfusions last only for 3-7 days.(17) The incidence of alloimmunization to platelets range from 9-50 % (18,19) and in these patients, platelet transfusions are ineffective in raising platelet counts. Although use of leukoreduced products has reduced the risk of alloimmunization, it still remains at about 4 %.(18) Other immune-mediated problems include febrile reactions and transfusion-related acute lung injury (TRALI). The reported incidence of febrile reaction ranges from 0.13 to 37.5 % per unit in hematology/oncology patients.(20) The incidence of TRALI in patients receiving high-volume plasma products including apheresed platelets has been reported to range from 1 in 1,300 to 1 in 5,000 transfusions.(21-23) In addition, there remains a risk of infections from platelet transfusions. Estimated residual risk of acquiring Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) from donations from repeat donors (after nucleic acid testing) is 1 per 1,935,000 and 1 per 2,135,000, respectively.(24) The chance of acquiring Hepatitis B virus infection is approximately 1 in 200,000. The risk of bacterial transmission is approximately 1 in 50,000 apheresis platelets.(25, 26)

1.4 Rationale for using Eltrombopag in the Treatment of AML

To date, there is no effective strategy for managing thrombocytopenia in AML patients following induction chemotherapy (IC) other than supportive platelet transfusions, which are limited by supply, cost and transfusion refractoriness. Eltrombopag is capable of enhancing megakaryopoiesis without stimulating leukemic blasts or activating platelets – properties that make it a candidate drug of choice for therapeutic intervention in the post-induction phase of

AML treatment. Early platelet count recovery following IC has significant clinical implications including decrease in thrombocytopenia-related bleeding complications, reduced necessity for platelet transfusions, improved complete remission rates and timely initiation of post-remission therapy - factors that present challenges particularly in the management of older patients.

While most of the eltrombopag studies in AML are in the relapsed or refractory setting or in those unable to withstand aggressive induction chemotherapy, a phase 1/2 study has been opened to assess the efficacy of eltrombopag in AML patients undergoing consolidation therapy following achievement of CR. We propose a novel therapeutic strategy where eltrombopag will be used in older AML patients undergoing IC who have no morphologic evidence of disease on a day 14 bone marrow assessment, with the goal of accelerating platelet recovery. We hypothesize that as eltrombopag acts at a TPO receptor site which is different from the native TPO binding site, it will accelerate megakaryopoiesis by acting synergistically with endogenous TPO, the levels of which have been shown to rise twenty-fold with drop in platelet counts below 50000/μL in AML patients while undergoing cytotoxic chemotherapy.(27) Our proposed use of eltrombopag in AML-associated thrombocytopenia thus represents a shift in treatment paradigm, with expected benefits in terms of decreased treatment-related morbidity, cost and potentially improved disease outcome. Currently, there are no competing trials in the public domain for this proposed study.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To determine whether eltrombopag leads to early platelet recovery in older AML patients ($\geq$ 60 years) who attain morphologic remission on day 14 (range, day 14-17) bone marrow assessment following remission IC.

2.2 Secondary Objectives

2.2.1 To determine the effect of eltrombopag on megakaryopoiesis - median time to reach platelet count $\geq$ 50,000 /μL and $\geq$ 100,000 /μL, number of days of platelet transfusion, rates of platelet transfusion-independence and the median time to reach platelet transfusion-independence.

2.2.2 To determine the effect of eltrombopag on the rates of clinically significant bleeding events (CSBE) [**Appendix I**].

2.2.3 To determine the effect of eltrombopag on erythropoiesis the median time to red blood cell transfusion independence.

2.2.4 To determine the effect of eltrombopag on granulopoiesis– the time taken to reach an absolute neutrophil count of $\geq$ 500 /μL.

225 To determine the safety and tolerability of eltrombopag in AML patients undergoing remission IC - incidence and severity of eltrombopag-related adverse events.

226 To determine the rates of CR, rates of CRp, time to attain CR, and time to initiation of postremission therapy.

3.0 SELECTION OF PATIENTS

3.1 Inclusion Criteria

1. Patients must be ≥ 60 years of age.

2. All categories of AML will be included except for acute promyelocytic leukemia (APL) [AML-M3 as defined by 1976 French-American-British (FAB) classification, or APL with t(15;17)(q22;q12); *PML-RARA* as defined by the revised 2008 World Health Organization (WHO) classification of myeloid neoplasms and acute leukemias], acute megakaryocytic leukemia [AML-M7 type as per FAB or AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1* as per WHO 2008 revised classification] and acute leukemias of ambiguous lineage (as per WHO 2008 revised classification)], undergoing 7 + 3 remission IC with cytarabine and an anthracycline (daunorubicin or idarubicin). All cases have to be histopathologically confirmed by a diagnostic bone marrow biopsy. Use of granulocyte colony-stimulating factor (G-CSF) for any indication must have been discontinued at least 7 days prior to entry into the study.

3. Patients with secondary AML arising out of MDS (all subtypes under WHO classification), chronic myelomonocytic leukemia (CMML); therapy-related AML and those with a prior autologous hematopoietic cell transplantation are eligible.

4. No morphological evidence of disease (defined as marrow myeloblast percentage of < 5% and/or documentation from hematopathologist indicating no morphological evidence of leukemia) on day 14 bone marrow examination (range, day 14-17; day 1 refers to the first day of IC) following remission IC.

5. Must be able to give voluntary informed written consent to participate in the study. Informed consent will be obtained prior to starting remission IC (can be obtained even on the first day of remission IC if obtained before administration of chemotherapy) and before any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

6. 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:
    a) 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.

b) 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.

7. ECOG performance status of 0 to 2 (**Appendix II**).

3.2 Exclusion Criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that, in the view of the treating physician, would place the participant at an unacceptable risk if he or she were to participate in the study or would prevent that person from giving informed consent.

2. Any active malignancy (unrelated, non-hematological malignancy) diagnosed within the past 12 months of starting the study drug (other than curatively treated carcinoma-in-situ of the cervix or non-melanoma skin cancer).

3. Secondary AML arising out of myeloproliferative neoplasms [as per the revised 2008 WHO classification of myeloid neoplasms and acute leukemias] and MDS/MPD neoplasms other than CMML [as per the revised 2008 WHO classification of myeloid neoplasms and acute leukemias]. Refractory Anemia with Ringed Sideroblasts with thrombocytosis (RARS-T) classified as MDS/MPN neoplasm, unclassifiable will be excluded. AML patients with presenting features suspicious of underlying unrecognized MPD such as marked splenomegaly ($\geq$ 20 cm) and thrombocytosis (>400,000 per microliter) will be excluded. Patients with relapsed or refractory AML will be excluded.

4. Radiation therapy, cytotoxic chemotherapy, and combined modality (both radiation and chemotherapy) used to treat other cancers or medical conditions and administered within 6 months prior to study enrollment. Use of hydroxyurea or emergent leukapheresis (for cytoreduction of highly elevated white blood cell counts) is permissible. Those AML patients who initially receive treatment with all-trans retinoic acid (ATRA) for presumptive diagnosis of APL but if APL is ruled out in final pathology will be eligible for the study.

5. Prior history of treatment with recombinant TPO or TPO-R agonists.

6. History of arterial or venous thrombosis [excluding line-thrombosis] within the last 1 year, or those with known inherited coagulopathies. Arterial or venous thrombosis includes pulmonary embolism, deep vein thrombosis of both upper [excluding line-thrombosis] and lower extremities, coronary artery disease managed medically or requiring intervention (percutaneous stent placement or coronary bypass surgery), cerebrovascular accident (for transient ischemic attacks clinical documentation is required), or involvement of other organs (such as hepatic, renal, spleen or other sites).

7. Any evidence of fibrosis on morphological examination of bone marrow at the time of AML diagnosis.

8. Concomitant participation in any other investigational treatment study. Simultaneous participation in non-therapeutic or observational studies will not be an exclusion criterion.

9. Uncontrolled intercurrent illness including, but not limited to uncontrolled infection, symptomatic or decompensated congestive heart failure, cardiac arrhythmia, unstable angina, cirrhosis or renal insufficiency (acute or chronic) on hemodialysis (at the time of diagnosis of AML).

10. Liver enzymes (AST and ALT) $\geq$ 3.5 times the upper limit of normal (ULN), and/or total bilirubin $\geq$ 3.5 x ULN on the start day of eltrombopag unless considered due to Gilbert's disease.

11. A known immediate or delayed hypersensitivity reaction or idiosyncrasy that, in the opinion of the Medical Monitor is due to drugs chemically related to eltrombopag or excipients (e.g. mannitol).

12. Known history of HIV or active hepatitis B or C.

13. No major surgery within 2 weeks prior to study enrollment.

14. Pregnancy or breast feeding

15. Male and female patients who are fertile who do not agree to use an effective barrier methods of birth control (i.e. abstinence) to avoid pregnancy while receiving study treatment.

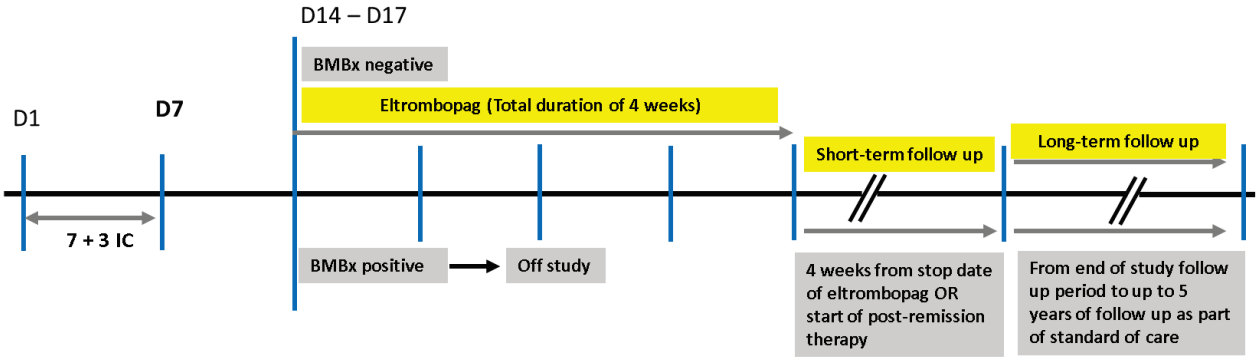
3. 3 Enrollment of all Minority groups and Females

The eltrombopag treatment will be offered to both genders and all racial and ethnic groups who meet the eligibility criteria of this clinical study.

4.0 STUDY DESIGN

4.1 Overall Design

This is a single institution, single arm, non-randomized phase II clinical trial with a sample size of 31 patients. The primary goal of this trial is to determine if eltrombopag can accelerate platelet count recovery in older AML patients (age $\geq$ 60 years) who have no morphological evidence of leukemia in the bone marrow following remission IC. The standard remission IC for AML in patients $\geq$ 60 years will consist of an anthracycline (daunorubicin or idarubicin) for 3 days and cytarabine as continuous intravenous infusion for 7 days. The patients in the study will receive supportive blood transfusions as part of standard of care at the Cleveland Clinic. Use of erythropoiesis stimulating agents (ESA) or granulocyte colony stimulating factors (G-CSF) during or following remission IC is not permitted. The study schema is shown below.



In those patients who have no morphologic evidence of disease on day 14 (range, 14-17) bone marrow evaluation, eltrombopag will be administered within 5 business days from the date of day 14 (range, 14-17) bone marrow biopsy. There will be a gap of at least one week (range, 7-9 days) between the last day of remission IC and initiation of eltrombopag, which will allow sufficient time for complete washout of the chemotherapeutic agents. Dose modification will be determined based on platelet counts and presence of adverse event(s).

5.0 STUDY TREATMENTS

5.1 Supplier

Novartis will supply **PROMACTA®** (eltrombopag).

5.2 Dosage Form

Eltrombopag 200 mg once daily (two 100 mg tablets) has been selected as the starting dose for this study except for subjects of East Asian heritage who will start initially at 100 mg (one 100 mg tablet) daily. The maximum dose of study medication is 300 mg once daily (three 100 mg tablets) for all subjects except for patients of East Asian heritage who will be escalated to a maximum of 150 mg (one 100 mg and one 50 mg tablet) daily.

5.3. Pharmaceutical Presentation and Packaging

White, round, film-coated tablets without debossing are provided, containing eltrombopag olamine equivalent to 100 mg of eltrombopag free acid. Tablets are packaged in white HDPE bottles with white plastic, induction-seal, and child-resistant caps.

5.4 Storage and Handling

The recommended storage condition is stated on the product label and, where required, the label also includes the expiry date.

5.5 Receipt of Study Drug

The Investigator or designee is responsible for taking an inventory of each shipment of **PROMACTA®** (eltrombopag) received, and comparing it with the accompanying study drug

accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Novartis or its representative. The bottle numbers, if present, must be recorded when **PROMACTA®** (eltrombopag) is received and dispensed.

5.6 Storage

At the study site, the investigational study drug will be stored in a locked, safe area to prevent unauthorized access. **PROMACTA®** (eltrombopag) should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

5.7 Unused Study Drug Supplies

Novartis will instruct the Investigator on the return or destruction of unused **PROMACTA®** (eltrombopag). If any eltrombopag is lost or damaged, its disposition should be documented in the source documents. **PROMACTA®** (eltrombopag) study supplies will be retained at the clinical site pending instructions for disposition by Novartis. Participants will be instructed to return empty bottles and unused capsules.

5.8 Drug Dispensing Requirements

In investigational studies, eltrombopag will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained in requirements specific to counseling of subjects. Once trained these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing and that the subject understands the risks associated with eltrombopag. In all females of child bearing age, negative result of required pregnancy testing will be verified and documented.

5.9 Standard of Care Therapies

Participants should receive all supportive care therapies (blood product transfusions, antibiotics, antiemetics, growth factors, etc.) that are required for treatment of the symptoms of disease or for infections or other adverse events.

5.10 Concomitant Medications and Non-drug Therapies

5.10.1 Permitted Medications and Non-Drug Therapies

A reasonable effort will be made to document any medications the subject received within the 30 days prior to the first day in the study. If any medication is required at any time within 7 days before first day in the study through the completion of the short-term follow-up visit, subjects should consult the investigator.

5.10.2. Use of Growth Factors

Subjects will not be allowed to receive granulocyte colony stimulating factor (G-CSF)/pegylated G-CSF, or other growth factors (e.g., epoetin alfa) during this study. Use of these drugs is not considered standard institutional practice at Cleveland Clinic during IC for AML.

5.10.3. Food, Antacids, Cations and Vitamin/Mineral Supplements

Eltrombopag should be taken on an empty stomach (1 hour before or 2 hours after a meal). Allow at least a 4 hour interval between eltrombopag and other medications or products containing polyvalent cations (e.g. calcium, magnesium, aluminum, zinc selenium or iron) such as antacids, dairy products, and mineral supplements to avoid significant reduction in eltrombopag absorption due to chelation.

Administration of eltrombopag with a polyvalent cation-containing antacid decreased plasma eltrombopag exposure by 70%, and a similar reduction was observed when eltrombopag was administered with a high-calcium meal. Therefore, every effort must be made to educate subjects on how to take investigational product with medications or foods containing these polyvalent cations. Details of these and all concomitant medications should be recorded in the CRF.

Subjects requiring routine (e.g. daily) acid suppression should be encouraged to take H2 antagonists like ranitidine, famotidine or nizatidine, or proton pump inhibitors like omeprazole, esomeprazole or lansoprazole. Subjects requiring occasional acid suppression may take liquid or chewable antacids (calcium carbonate, aluminum hydroxide or magnesium hydroxide), provided investigational product is taken at least 4 hours before and 4 hours after consumption of cation-containing antacids.

Mineral supplements (such as calcium, magnesium, aluminum, zinc, selenium or iron) are permitted during the study but investigational product must be taken at least 4 hours before and 4 hours after consumption of these supplements. Similarly, eltrombopag must be taken at least 4 hours before and 4 hours after consumption of dairy products (such as milk, yogurt, and cheese).

5.10.4. HMG-CoA Reductase Inhibitors (statins)

Subjects will be permitted to use HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA) inhibitors during the study, but these drugs should be used with caution and a 50% dose reduction of the HMG-CoA reductase inhibitor is recommended, with close monitoring for safety, such as liver chemistry and signs and symptoms of myolysis, and efficacy, such as cholesterol and triglycerides (refer to individual product information for monitoring recommendations).

Preclinical data showed that eltrombopag is an inhibitor of the transporters OATP1B1 and BCRP. Therefore, a clinical drug interaction study to evaluate the impact of eltrombopag on the PK of rosuvastatin, an OATP1B1 and BCRP substrate, was conducted in healthy subjects. Co-administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of rosuvastatin administered on Day 5 increased plasma rosuvastatin Cmax 2.03-fold and AUC (0-∞) 55%. Concomitant administration of eltrombopag and other OATP1B1 or BCRP substrates should be used with caution.

5.10.6. Blood product transfusions

Transfusion of blood products will be allowed as per the Cleveland Clinic institutional guidelines. For details please refer to section 4.1.

6.0. SAFETY DATA AND ASSESSMENT

6.1. Common Side Effects and Toxicities (*Reference*: Eltrombopag Investigator Brochure)

A detailed description of safety profile of eltrombopag in clinical pharmacology studies as well as in clinical trials involving patients with chronic liver disease, ITP and Hematology/Oncology related thrombocytopenia studies is available in the Clinical Investigator's Brochure provided by Novartis. The drug related toxicity will be scored based on the National Cancer Institute Common Toxicity Criteria Scale Version 4, which can be obtained from the CTEP website (http://ctep.cancer.gov/reporting/ctc.html). The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia, myelodysplastic syndromes (MDS) and AML.

6.2 Hepatic monitoring

Eltrombopag administration can cause hepatobiliary laboratory abnormalities. In clinical studies in chronic ITP with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and indirect bilirubin were observed. These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate impaired liver function. In two placebo controlled studies in chronic ITP, adverse events of ALT increase were reported in 5.7 % and 4.0 % of eltrombopag and placebo treated patients respectively. In 2 controlled clinical studies in thrombocytopenic patients with HCV, ALT or AST $\geq$ 3 x ULN were reported in 34 % and 38 % of the eltrombopag and placebo groups, respectively. Eltrombopag administration in combination with peginterferon/ribavirin therapy is associated with indirect hyperbilirubinaemia. Overall, total bilirubin $\geq$ 1.5 x ULN was reported in 76 % and 50 %of the eltrombopag and placebo groups, respectively. Serum ALT, AST, and total bilirubin should be measured prior to initiation of eltrombopag. If total bilirubin is elevated, fractionation should be performed. If the abnormalities are confirmed, serum hepatic function tests will be monitored daily inpatient as part of standardized care and once weekly as outpatient until the abnormalities are resolved, stabilized or returned to baseline levels.

6.3 Thrombotic/Thromboembolic Complications

Platelet counts above the normal range present a theoretical risk for thrombotic/thromboembolic complications. In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Use caution when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome). Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the study target levels. In ITP studies, 21 thromboembolic/thrombotic events were observed in 17 out of 446 subjects (3.8 %). The TEE events included: embolism including pulmonary embolism, deep vein thrombosis, transient ischemic attack, myocardial infarction, ischemic stroke, and suspected PRIND (prolonged reversible ischemic neurologic deficiency). Eltrombopag should not be used in patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. In 2 controlled studies in thrombocytopenic patients with HCV receiving interferon based therapy, 31 out of 955 subjects (3 %) treated with eltrombopag experienced a TEE (3 %) and 5 out of 484 subjects (1 %) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (1 % in patients treated with eltrombopag versus < 1 % for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. The majority of TEEs resolved and did not lead to the discontinuation of antiviral therapy. In a controlled study in thrombocytopenic patients with chronic liver disease (n = 288, safety population) undergoing elective invasive procedures, the risk of portal vein thrombosis was increased in patients treated with 75 mg eltrombopag once daily for 14 days. Six of 143 (4 %) adult patients with chronic liver disease receiving eltrombopag experienced thromboembolic events (all of the portal venous system) and two of 145 (1 %) subjects in the placebo group experienced thromboembolic events (one in the portal venous system and one myocardial infarction). Five eltrombopag treated subjects with a TEE experienced the event within 14 days of completing eltrombopag dosing and at a platelet count above 200,000/µl.

6.4 Bleeding Following Discontinuation of eltrombopag

Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. Assessment of bleeding will be performed throughout the study from screening until the last dose of study drug or patient withdrawal from the study. Bleeding will be assessed by the WHO Bleeding Scale (Appendix V: WHO Bleeding Scale). Platelet counts will be monitored as part of daily CBC measurements during the period of hospitalization and thereafter once weekly as outpatient following discharge for 4 weeks following discontinuation of eltrombopag.

6.5 Bone Marrow Reticulin Formation and Risk of Bone Marrow Fibrosis

Thrombopoietin (TPO) receptor agonists, including eltrombopag, may increase the risk for development or progression of reticulin fibrosis within the bone marrow. Baseline information on bone marrow reticulin fibrosis is routinely obtained as part of bone marrow evaluation at the time of AML diagnosis at Cleveland Clinic. Prior to initiation of study medication, the peripheral blood smear will be examined to establish a baseline level of cellular morphologic abnormalities.

A follow up peripheral blood and bone marrow smear for any new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) will be performed at 6 week time point (from IC) when the remission status is routinely assessed (i.e. day ~30-45 bone marrow). If any new abnormalities are detected, additional bone marrow biopsies will be performed at periodic intervals based on clinical judgment.

6.6 Malignancies and progression of malignancies

There is a theoretical concern that TPO-R agonists may stimulate the progression of existing hematological malignancies such as MDS. Across the clinical trials in ITP (n = 493) and HCV (n = 1439) no difference in the incidence of malignancies or hematological malignancies was demonstrated between placebo and eltrombopag treated patients. This is consistent with information derived from non-clinical research, where no malignant cell proliferation has been demonstrated upon co-incubation of eltrombopag with MDS cell lines, multiple leukemic cell lines and solid tumor cell lines (colon, prostate, ovary and lung).

6.7 Cataracts

Cataracts were observed in toxicology studies of eltrombopag in rodents. Routine monitoring of patients for cataracts is recommended. In controlled studies in thrombocytopenic patients with HCV receiving interferon based therapy (n = 1439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8 % of the eltrombopag group and 5 % of the placebo group. Screening ophthalmic assessments will be performed in those patients who complain of new or recent onset of visual symptoms or visual impairment at the time of AML diagnosis or those with known prior or existing ocular conditions. Ocular conditions that will need baseline evaluation include any vitreoretinal diseases, age-related macular degeneration, optic nerve disease, glaucoma and corneal diseases as well as patients in whom cataracts are clinically suspected. In those cases, a detailed ocular examination will be performed by an ophthalmologist and will include check for refractive errors, slit-lamp examination of anterior ocular structures, slit-lamp biomicroscopy of posterior pole and indirect ophthalmoscopy. Subsequent assessments including follow up exams will be performed if clinically indicated. For patients developing ocular symptoms during eltrombopag therapy, a detailed assessment will be carried out as mentioned earlier and will be documented as adverse effect. The baseline ophthalmic assessments where indicated needs to be completed prior to administration of the study drug.

6.8 Risk of QT/QTc Prolongation

There is no indication of a QT/QTc prolonging effect of eltrombopag at doses up to 150 mg daily for 5 days. The effects of PROMACTA at doses up to 150 mg daily for 5 days on the QT/QTc interval was evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg, single oral dose) crossover trial in healthy adult subjects. Assay sensitivity was confirmed by significant QTc prolongation by moxifloxacin. A 12-lead ECG will be obtained for each patient at screening (baseline). A pre- and post-dose 12-lead ECG will be performed. The post-dose ECG is to be performed within a 2-4 hour window post-dose (preferably within 3 hours after administration of study medication). If assessment cannot be

performed at 3 hours post-dose, record actual time of ECG performed. Thereafter, ECG will be performed if clinically indicated.

7.0. TREATMENT PLAN

7.1. Eltrombopag Administration

Consecutive eligible patients will receive eltrombopag at an initial oral dose of 200 mg once daily. For patients of East-Asian heritage (Japanese, Chinese, Thai, Taiwanese and Korean), the starting dose will be 100 mg orally once a day.

7.2. Dose Rationale

Eltrombopag 200 mg once daily has been selected as the starting dose for this study (100 mg for subjects of East Asian heritage). The maximum dose of study medication is 300 mg once daily (150 mg in subjects of East Asian heritage). The rationale for allowing dose titration up to 300 mg once daily is based on the following considerations:

- The effective dose for eltrombopag for AML patients with chemotherapy-induced thrombocytopenia is unknown, and 300 mg is the maximum dose that is currently being considered in the eltrombopag clinical program, as described in the CIB.(11)

- In a placebo-controlled Phase II study (NCT00102726) in 183 cancer patients receiving carboplatin and paclitaxel, eltrombopag was dosed at 50 mg, 75 mg and 100 mg with placebo as control arm in 1:1:1:1 ratio) for 10 days after carboplatin and paclitaxel administration for up to 8 cycles. Eltrombopag was generally well tolerated as described in the CIB. (11). The study results for the 100 mg group demonstrated that there was evidence for increased platelet production in all three treatment arms after the nadir, with a gradual rise in platelet counts from Day 8 to 18 of chemotherapy. No apparent safety issues at 100 mg were identified.(28)

- In a Phase II, non-randomized, open label pilot study of eltrombopag in aplastic anemia patients treated with immunosuppressive therapy and with refractory thrombocytopenia (NCT00922883), no observed toxicities were reported in this study to date with intrasubject dose escalation of eltrombopag starting at 50 mg and going up to 150 mg.(29) The higher dose was continued in an extension phase. Improvements of both platelet and erythrocyte values have been observed following eltrombopag exposure in these patients.

- In ITP subjects, a dose exposure and response relationship has been seen for eltrombopag doses of 30 mg to 75 mg once daily. There was no significant difference between the safety profile of ITP subjects receiving 30, 50 or 75 mg of eltrombopag when administered for up to 6 weeks.

- In HCV subjects, a dose, exposure and response relationship has been seen for eltrombopag doses of 30 mg to 75 mg once daily, with geometric mean AUC (0-τ)

approximately 2-fold higher than that observed in ITP patients at the same dose. There was no significant difference between the safety profile of HCV subjects receiving 30, 50 or 75 mg of eltrombopag, and the frequency of adverse events in these subjects did not increase in a dose-dependent manner. Two Phase III studies have recently completed (TPL103922/ENABLE 1 and TPL108390/ENABLE 2) in subjects with HCV-related thrombocytopenia and led to its FDA approval in November of 2012. The pooled data from these studies demonstrates that eltrombopag treatment increased platelet counts in thrombocytopenic subjects with HCV infection to a level sufficient to allow initiation and maintenance of antiviral therapy for subjects who would otherwise be ineligible or poor candidates for peginterferon-based antiviral therapy. Such antiviral therapy plus eltrombopag enabled 21% of patients to achieve a sustained viral response (SVR) rate; 13% of subjects in the control arm (which also included eltrombopag during the OL Phase of the study) achieved an SVR. The results were statistically significant.

- In vitro, there is a clear relationship between the eltrombopag concentration and the anti-proliferative effect of eltrombopag on leukemic cells.(11-13) Based on preliminary PK from Part 1 of this study, it is expected that doses of 200 to 300 mg eltrombopag will result in plasma concentrations at or above the in vitro IC50 values demonstrating anti-leukemic effects in preclinical experiments for the majority of the eltrombopag dosing interval.

- In healthy subjects, a clear dose, exposure and response relationship has been seen for eltrombopag doses of 10 mg to 200 mg administered once daily for 5 days. Eltrombopag was well tolerated in healthy subjects at all dose levels. A starting dose of 100 mg once daily eltrombopag (50mg for East Asians) has been studied in 46 subjects with chemotherapy-induced thrombocytopenia. No apparent safety issues at 100 mg were identified.

- Based on the PK in subjects with chemotherapy-induced thrombocytopenia (solid tumors), and anticipating similar PK in patients with hematologic malignancies, the predicted exposure in subjects with MDS or AML receiving 300 mg eltrombopag is expected to average 358 ug.h/mL at steady-state (typical 50 year old male subject), with significant intersubject variability. This is the similar to the exposure observed in patients with HCV receiving 75 mg eltrombopag. Covariates of exposures are gender, age, and East Asian Heritage. Scaling the exposure of subjects with solid tumors enrolled in the 100 mg dose group to a dose of 300 mg results in an average exposure of 513µ g.h/mL, 51% higher than the exposure observed in patients with HCV receiving 75 mg eltrombopag.

- Preliminary results of a Phase II, multicenter, prospective, placebo-controlled, single blind study of eltrombopag (EQoL-MDS) administered at a 50 mg initial daily initial dose with increased every 2 weeks in low and intermediate-1 risk adult MDS patients with PLT count <30 Gi/L suggest safety of eltrombopag in terms of drug-related adverse events and disease progression. In such patients, eltrombopag treatment is effective in raising PLT counts and in reducing the risk of bleeding and is associated with significant improvements in quality of life.(30)

- There is evidence that higher doses of growth factors are required in subjects with cancer: the effective erythropoietin (EPO) dose in MDS is several times higher than the doses used in renal anemia.(1,14,16, 31-34) Anticipating impaired absorption and bioavailability of orally administered eltrombopag in AML patients resulting from mucositis of the gastro-intestinal tract, an often observed side effect of intensive remission IC, we plan to administer higher doses than have been utilized in other non-oncologic settings.

- To ensure subject safety, the current study uses a dose escalation scheme in which subjects are exposed to the lowest dose necessary to achieve the desired platelet count target. Only subjects who have tolerated the previous dose and have not yet benefited from study medication will be considered for the next highest dose, dependent on platelet counts. This approach minimizes potential risks while allowing the subject the maximum potential for benefit.

- Modified dosing for subjects of East Asian heritage has been implemented for the following reasons. In healthy Japanese subjects, plasma eltrombopag AUC (0-τ) was approximately 80% higher when compared to non-Japanese healthy subjects who were predominantly White. Similarly, in patients with ITP, plasma eltrombopag exposure was approximately 70% higher in East Asian subjects as compared to non–East Asian subjects who were predominantly White.

- There are limited data on the use of eltrombopag in patients aged 65 years and older. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between subjects aged at least 65 years and younger.

7.3 Dose Adjustments for Eltrombopag

If after 2 weeks, the platelet count fails to reach 50,000/μ L or above, the dose will be increased to 300 mg orally daily (150 mg orally daily for East-Asians). Depending on tolerability, dose modification will be individualized based on the patient's platelet count response according to the following rules:

Dose Modification / Adjustment of Eltrombopag	
If platelet count is ≤ 50,000/μL after 2 weeks of treatment with starting dose of eltrombopag*	Increase daily dose to 150 mg for East –Asians and 300 mg for all other ethnicities
If platelet counts are between 50,000 and < 100,000/μL (untransfused) on the starting or escalated dose of eltrombopag	Continue on the same dose
If platelet counts reach ≥ 100,000/μL (untransfused) on the starting or escalated dose of eltrombopag at any time on study	Discontinue eltrombopag

* Starting dose will be 100 mg for East-Asians and 200 mg for other ethnicities.

7.4 Dose delays, modifications or discontinuation for non-hematologic side effects

7.4.1 Infection: Subjects who experience an infection requiring intravenous antibiotics will not have eltrombopag discontinued. If the subject experiences infection severe enough to require vasopressors or intubation, the drug will be withheld until the patient is stable.

7.4.2 Liver function abnormalities: In the event of an increase in the ALT level to ≥3 times the ULN in patients with normal liver function or ≥ 3X baseline in patients with elevations in transaminases before treatment, eltrombopag will be discontinued until ALT is ≤ 2.5 times the ULN or from baseline. For all patients (whether on starting dose or escalated dose prior to discontinuation), eltrombopag will be restarted at the starting dose. Eltrombopag will be discontinued permanently if the toxicity reappeared on the starting dose. Other criteria for permanent discontinuation of eltrombopag will be if ALT levels increase (≥3 times the ULN in patients with normal liver function or ≥3X baseline in patients with elevations in transaminases before treatment] and are:
- progressive, or
- persistent for ≥ 1 week, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

7.4.3 Cardiac arrhythmia: Onset of new onset arrhythmias during treatment with eltrombopag that can be adequately managed will not be a reason for discontinuation of eltrombopag. In patients with normal baseline QTc intervals (prior to starting eltrombopag), a QTc prolongation of ≥ 500 milliseconds (ms) will be a reason for temporarily discontinuing eltrombopag only if no other secondary etiology (electrolyte abnormalities or other concomitantly administered QTc prolonging drugs) could be identified and corrected. If QTc prolongation of > 500 ms is clinically attributed to eltrombopag, then EKG should be checked daily till QTc returns to baseline and eltrombopag can be resumed at the discontinued dose. If QTc > 500 ms occurs following reintroduction of eltrombopag, then eltrombopag should be permanently discontinued.

7.4.5 Renal impairment: No dose adjustments or discontinuation of eltrombopag is necessary in patients who develop acute kidney injury (with or without hemodialysis support) during remission IC or while on eltrombopag.

7.5 Dose delays, modifications or discontinuation for hematologic side effects

7.5.1 Thrombosis/Embolism: Subjects who experience a deep venous thrombosis (excluding line-related thrombus) or a pulmonary embolus, a TIA or stroke, or a myocardial infarction at any time while on eltrombopag will discontinue the drug and go off study. Patients with platelet counts of > 50,000/ul at the time of thrombosis will be treated with enoxaparin or another appropriate anticoagulant as clinically indicated. They will be treated for the thrombotic event as otherwise clinically-indicated.

7.5.2 Peripheral blood abnormalities: The development of significant worsening of anemia or neutropenia while on study will require discontinuation of eltrombopag and additional evaluation including a bone marrow biopsy as clinically indicated.

7.6 Dosing Delays and Subject Replacement

In case there is an interruption of treatment or if any medication dose is missed this would be captured and subsequently documented on the Dosage Administration Case Report Form (CRF). If the patient's treatment is interrupted, the missed dose will not be replaced. If a patient misses a study dose due to noncompliance (as determined by the treating physician), then the patient would be removed from the study. Subsequently this subject would need to be replaced. If the treatment is interrupted for 1 week due to adverse effect(s) from study medication therapy, then the patient would be removed from the study and the subject(s) would not be replaced.

7.7 Duration of Therapy and Off Study Criteria

Depending on tolerability, eltrombopag can be administered to all assigned study subjects for a total duration of 4 weeks (counted from the first day of eltrombopag administration) unless they meet one of the following criteria for removal from the study:

1. Withdrawal of consent. The patient's desire to withdraw from the study may occur at any time. The investigator should carefully consider whether the patient's withdrawal of consent is due to an adverse event, and if so, record the adverse event as the reason for withdrawal.
2. Violation of the study protocol, including a patient's failure to return for required treatments or assessments or failure on the part of participants with reproductive potential to practice effective birth control or non-compliance.
3. At the treating physician's clinical discretion, if any specific medical or psychosocial changes in patient's condition makes them unacceptable to further participate in the study.
4. If bone marrow biopsy performed to establish remission status (around day 30-45 of remission IC), confirm refractory or persistent disease or if there is leukemic involvement of extramedullary site (biopsy confirmation of skin or organ lesions, central nervous system involvement confirmed either by cerebrospinal fluid analysis or radiological exams) at any time during study.
5. Adverse events, including intolerance of eltrombopag not resolved by dose reduction, life threatening acute hypersensitivity reaction, persistent hepatotoxicity (refer to section 7.4.2), thrombosis/embolism (DVT, PE, stroke, TIA, myocardial infarction) other than central line thrombosis (refer to section 7.5.1) or evidence of disease progression on treatment (myeloid sarcomas). Participants who are removed from the study due to adverse events will be treated and followed according to established medical practice. All pertinent information concerning the outcome of such treatment will be entered in the CRF.

7.8 Duration of Follow Up

All study subjects who achieved a platelet count of 100,000/μL will be followed for a total up to 4 weeks from the stop date of eltrombopag or till the start date of post-remission therapy, whichever occurs earlier, for adverse events and response. The patients who are removed from study for unacceptable adverse events will be followed until that adverse event is resolved or stabilized. All patients will thereafter be followed for 5 years from study enrollment for relapse and survival endpoints as part of institutional standard of care policy for all treated AML patients.

8.0 CLINICAL MONITORING

8.1 Pre-induction Evaluation

Screening evaluation must be completed before starting remission IC and should include the following:

1) A signed informed consent.
2) Relevant medical history, including a detailed history for any antecedent hematologic disorder (AHD) and all treatments used for AHD including cytotoxic chemotherapy, radiation, or combined modality therapy. Review of all medications used during the 4-week period prior to screening date will be done.
3) CBC with differential at the time of diagnostic bone marrow biopsy for confirmation of AML. Documentation of all transfusions (red blood cells and platelets) along with dates of transfusion dating back to 8-weeks from the date of screening.
4) Physical examination and vital signs, including measurement of blood pressure, pulse, respiratory rate, pulse oximetry (oxygen saturation), height and body weight.
5) Assessment of ECOG performance status.
6) Documentation of AML classification according to the revised WHO 2008 classification.
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 myeloblasts; 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 with reticulin and collagen staining. All these tests are currently done as routine standard of care. The results of mutational studies and metaphase cytogenetics are not necessary for starting patient on the study drug.
9) Comprehensive metabolic panel evaluations, including blood glucose, total protein, albumin, creatinine, blood urea nitrogen (BUN), serum bicarbonate (CO_2), calcium, phosphorus, sodium, potassium, chloride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin and alkaline phosphatase.
10) Remote hepatitis panel. ELISA for HIV.

11) A 12-lead electrocardiogram (ECG), following at least a 5-minute rest in supine position.
12) Baseline ophthalmological examination to be performed only in those presenting with new symptoms of visual impairment or insufficiency at the time of diagnosis of AML or those with known ocular conditions with accompanying vision defects.
13) Chest x-ray (2 views – PA and lateral), unless a previous x-ray taken during the 4 weeks prior to Day 1 of remission IC is available and shows no significant abnormality that would exclude the patient from the study.
14) Male participants with female partners of childbearing potential should have contraceptive measures addressed at screening, sufficient time to employ required contraceptive measures prior to Day 1 of IC, and confirmation of adequacy of contraceptive measures prior to receiving study drug.
15) Serum pregnancy test for women of childbearing status

8.2 Monitoring while taking eltrombopag

The following procedures will be conducted:

1) Daily vital signs and physical exam while inpatient and once weekly as outpatient only in those patients still receiving eltrombopag.
2) Adverse event (AE) monitoring and documentation will begin starting from the date of study drug initiation. Any AE resulting during or following remission IC but preceding study drug initiation will not be attributable to the study drug. AE's will be recorded as definite, probable, possible, unlikely or unrelated by the treating team in the daily clinical progress note and abstracted for study documentation by approved study personnel (physicians, research nurses and study coordinators).
3) 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.
4) Complete metabolic panel (CMP) will be checked daily during hospital stay. Once the patient is discharged, CMP will be checked weekly until the subject's platelets reach 100,000/µL.
5) Documentation of all infections requiring treatment with intravenous antimicrobials (antibacterial, antiviral or antifungal) by date (the period to be covered for documentation purposes starts at day 1 of study drug administration).
6) Concurrent medication review (with each clinical assessment) for the entire period on the study drug.
7) Documentation of all red blood cell and platelet transfusions including dates of transfusion while on eltrombopag.
8) 12 lead electrocardiograms pre- and post-dose on the first day of eltrombopag administration and thereafter only if clinically indicated. The post-dose ECG is to be performed within a 2-4 hour window post-dose (preferably within 3 hours after administration of study medication). If assessment cannot be performed at 3 hours post-dose, record actual time of ECG performed.

9) All study subjects who achieve a platelet count of 100,000/μL will be followed for a total up to 4 weeks from the stop date of eltrombopag or till the start date of post-remission therapy, whichever occurs earlier, for adverse events and response. Adverse events that are related to the study drug (eltrombopag) will be followed through resolution or stabilization. CBCs and CMPs will be collected per standard of care as well as AEs for 4 weeks after stopping eltrombopag or till the start date of post-remission therapy, whichever occurs earlier.

8.3 Short-term Safety Follow-up

1) Bone marrow aspiration and biopsy typically between days 30-45 of IC to assess remission status and thereafter as deemed necessary guided by peripheral counts and or clinical judgment.
2) Peripheral blood smear typically between day 30-45 of remission IC at the time of bone marrow biopsy performed to evaluate remission status and at the end of the study period (optional) based on clinical assessment.
3) Concurrent medication review (with each clinical assessment)
4) CBC with differential and CMP
5) Adverse event (AE) monitoring and documentation
6) Vital signs and physical exam
7) Documentation of all red blood cell and platelet transfusions

8.4 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 as part of standard of care for CCF leukemia patients.

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[n]				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.
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.
n: Adverse events that are related to the study drug (eltrombopag) will be followed through resolution or stabilization.

9 ANCILLARY LABORATORY RESEARCH STUDIES

9.1 Collection of samples
During the course of participating on this study, additional blood samples will be collected – 3 X 5 cc (SST tubes) and 3 X 3 cc (3.2% sodium citrate tubes).

9.2 Intended use: The following laboratory research studies will be done and will be correlated with the presence or absence of response.
• Quantification of microvesicles at different time points of AML treatment - during remission IC and while on eltrombopag
• Analysis of micro RNA (miRNA) in the microvesicles from different time points of AML treatment - during remission IC and while on eltrombopag.
The different time points of assessment are as follows:
1) At the time of diagnosis of AML but prior to initiation of remission IC
2) At the time of day 14 bone marrow assessment (range, 14-17) following remission IC
3) On day 3 (+/- 1 business day) of study drug treatment.
4) On day 6 (+/- 1 business day) of study drug treatment.
5) At the time of bone marrow biopsy to confirm CR (usually between days 30-45 of remission IC)

9.3 Tracking: Samples will be ordered and tracked using Clinical Trial Draw – Specimen Processing Requisition Form which will accompany the specimen. Samples will not be sent outside CCF.

9.4 Storage: Research samples will be stored with identifiers in the secure laboratory of the co-investigator, Dr. Keith McCrae.

9.5 End of study procedures: Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

9.6 Loss or destruction of samples: Should we become aware that a major breech in our plan for tracking and storage of samples has occurred, the IRB will be notified.

10.0 STUDY ENDPOINTS

10.1.1 Primary endpoint

The proportion of patients achieving a platelet count of $\geq$ 50,000/μL by day 24 of IC on eltrombopag therapy. The treatment response parameters for platelet count recovery for this trial was derived from a cohort of 200 older AML patients (excluding acute promyelocytic leukemia and acute megakaryocytic leukemia) who underwent aggressive 7 + 3 cytarabine-based remission IC at the Cleveland Clinic between 2000 and 2011. The total CR rate in our historical cohort was 41%.

The median time to CR (defined as the time from the start date of IC to the achieving CR per

IWG criteria) was 34 days (range, 14-66). The median time to reach platelet counts > 50,000/μL was 24 days (range, 17-57) from the start date of IC.

10.1.2 Response to Eltrombopag

Complete Response to eltrombopag will be defined as improvement in platelet count (independent of platelet transfusions) to ≥ 100,000 /μL with eltrombopag that lasts for at least 4 weeks after discontinuation of eltrombopag. The date of achieving complete response to eltrombopag was defined as the first day of the four-week period with platelet count greater than 100,000 /μL off eltrombopag and independent of platelet transfusions. If the patient with platelet counts ≥ 100,000/μL transition to subsequent post-remission therapy within the 4-week timeframe of eltrombopag discontinuation, then that will be considered a complete response.

Partial Response to eltrombopag will be defined as any improvement in platelet count to ≥ 50,000 /μL but less than 100,000 /μL despite use of the highest dose of eltrombopag for the entire duration of the study or drop in platelet counts to < 100,000 after achieving complete response (necessitating resumption of eltrombopag treatment).

No response (NR) **is defined as failure to fulfill the above criteria for either complete response or partial response after 8 weeks of eltrombopag therapy and despite use of maximal escalated dose of eltrombopag.**

10.2. Secondary endpoints

1) Kinetics of megakaryocyte recovery: Parameters to be assessed will include median time to reach platelet count ≥ 50,000 /μ L and ≥ 100,000 /μ L, number of days of platelet transfusion, rates of platelet transfusion-independence, median time to reach platelet transfusion-independence and rates of CSBE. The initial time point for assessing different platelet recovery periods will be the first day of remission IC. The number of days of platelet transfusion will be defined as the total number of days in the cycle, beginning with the first day of study drug administration, in which a patient received transfusion. The time to transfusion-independent platelet recovery will be defined as the number of days from the first day of IC until the first of the 5 consecutive days with platelet count equal to or greater than 50,000 /μ L without a platelet transfusion. For patients who do not achieve platelet recovery before the end of the study, the time to platelet recovery will be censored on the last day of the study. CSBE refers to all bleeding events that require intervention including, but not limited to, transfusional support (red blood cells, platelets and other blood products such as fresh frozen plasma or cryoprecipitate). CSBE will include hematuria, gastrointestinal bleed, retroperitoneal bleed, intra-cranial bleed, uncontrolled epistaxis and muscle or soft tissue hematomas.

2) Kinetics of granulocytic recovery: Parameters to be assessed will include the median time to reach absolute neutrophil count (ANC) equal to or greater than 500 /μ L (first of the five consecutive days with ANC ≥ 500 / μ l) and the median time to reach ANC equal to or greater than 1000 /μ L (first of the five consecutive days with ANC ≥ 1000 / μ l) counted from the first day of study drug administration. A neutrophil response will be defined as an absolute increase in ANC of more than 1000 /μL within 4 weeks of remission IC.

3) Kinetics of erythrocytic recovery: Parameters to be assessed will include the median number of days needed to reach a hemoglobin level > 8g/dl (first of the 5 consecutive days with hemoglobin > 8g/dl) starting from the first day of study drug administration, maximal rise in hemoglobin level after achieving transfusion-independence and rates of red blood cell transfusion-independence within 4 weeks of IC An erythroid response in patients with a pretreatment hemoglobin level of < 8 g/dL (transfusion-dependent) will be defined as an increase in the hemoglobin level by 1.5 g/dL or more without transfusion of packed red cells that is sustained for at least 2 weeks (from the start date of eltrombopag) or a 50% reduction in the number of units of packed red cells transfused in the 2 consecutive weeks following eltrombopag use compared to the transfusion requirement in the 2 weeks preceding use of the study drug.

4) Characterization of platelet response to eltrombopag by AML subtype (WHO classification), etiology of AML (*de novo* versus secondary) and cytogenetic risk groups.

5) Treatment/Disease outcomes: CR rates, time to attain CR, CRp rates, time to initiation of post-remission therapy, rates of refractory or persistent disease, survival and safety profile.

Safety will be evaluated from the incidence and severity of adverse events based on clinical assessment and laboratory evaluations, determined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP). Survival will be calculated from the day of study enrollment until the last follow-up or death. Disease-free survival will be calculated from the date of complete remission until relapse, the date of last follow-up, or death.

Response criteria of AML patients to IC will be based on AML International Working Group (IWG) criteria (**Appendix III**). Modified AML response criteria include: morphologic leukemia free state, morphologic CR, cytogenetic CR, molecular CR and CRp. IWG criteria do not require presence of bone marrow cellularity (usually profoundly hypocellular from the effects of cytotoxic chemotherapy) or absence of dysplasia as a criterion for remission status.

11.0 ADVERSE EVENTS

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an adverse events (AE) or severe adverse events (SAE).

11.1 Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE include:
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
• New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
• Signs, symptoms, or the clinical sequelae of a suspected interaction
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that do not meet the definition of an AE include:
• Medical or surgical procedures (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
• Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. This includes hematologic abnormalities, as these will be related to the disease and/or the IC.

Grading of Adverse Events

1	Mild	Symptom barely noticeable to subject; does not influence performance or functioning. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of subject.
2	Moderate	Symptom of a sufficient severity to make subject uncomfortable; performance of daily activities influenced; subject is able to continue in study; treatment for symptom may be needed.
3	Severe	Symptom causes severe discomfort. May be of such severity that subject cannot continue. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or subject hospitalized.
4	Life-threatening	Symptom(s) place the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more serious form, might have caused death.

Attribution of Adverse Events

1	**Not related**	This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)
2	**Unlikely (must have two)**	In general, this category can be considered applicable to those adverse events which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug. An adverse event may be considered unlikely if or when: 1. It does not follow a reasonable temporal sequence from administration of the test drug. 2. It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It does not follow a known pattern of response to the test drug. 4. It does not reappear or worsen when the drug is re-administered.

3	**Possibly (must have two)**	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered possibly related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It follows a known pattern of response to the test drug.
4	**Probably (must have three)**	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An adverse event may be considered probably related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia). 4. It follows a known pattern of response to the test drug.

5	**Definitely (must have all)**	This category applies to those adverse events which, the Investigator feels are incontrovertibly related to test drug. An adverse event may be assigned an attribution of definitely related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It disappears or decreases on cessation or reduction in dose with re-exposure to drug. (Note: this is not to be construed as requiring re-exposure of the subject, however, a category of definitely related can only be used when a recurrence is observed.) 4. It follows a known pattern of response to the test drug.

11.2 Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening
NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization
NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity, or
NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or

development of drug dependency or drug abuse.
g. All Grade 4 non-hematologic laboratory abnormalities assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Serious hematologic AEs are not included in the definition of an SAE, as these are related to the disease and/or to the IC.
h. Serious hematologic AEs except for unprovoked arterial and venous thromboembolic events are not included in the definition of an SAE, as these are related to the disease and/or to the IC. Superficial thrombophlebitis and central line associated thrombosis will not be considered SAE.

11.3 Relationship to Investigational Product

It is a regulatory requirement for investigators to assess relationship to investigational product based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. “A reasonable possibility” is meant to convey that there are facts/evidence or arguments to suggest a causal relationship.

Facts/evidence or arguments that may support “a reasonable possibility” include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

11.4 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.0, with the exception of hematologic AEs.

However, any clinically significant safety assessments that are associated with the underlying disease or with IC are not to be reported as AEs or SAEs, except for findings judged by the investigator to be more severe than expected for the subject’s condition or death.

Data will be collected for typical disease-related events such as anemia, leucopenia, worsening of thrombocytopenia or infections. All events of possible drug-induced liver injury with hyperbilirubinemia (defined as ALT ≥2.5 x ULN plus bilirubin ≥2 x ULN and/or INR > 1.5 or ALT ≥2.5 x ULN) require reporting as an SAE. Bilirubin fractionation is performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 x ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

11.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

During the study period, the following conditions will not qualify as an AE or SAE provided they are not considered attributable to study medication:
• Cases of disease progression.
• New or worsened cytopenias even if they result in treatment, and/or hospital admissions.
• Serious infections including neutropenic fever/neutropenic sepsis, line-infection, PCP pneumonia, Clostridium difficile infection
• Neutropenic fever/neutropenic sepsis

• Red cell or platelet transfusions

11.6 Pregnancy

Any pregnancy that occurs during study participation must be reported. To ensure subject safety, each pregnancy must be reported to Novartis within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to Novartis. In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Novartis as described above.

11.7 Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of Investigational Product and through the short-term follow up period. Treatment related AEs will be followed through resolution / stabilization, regardless if this requires clinical monitoring beyond the short-term follow up period. SAEs will be collected over the same time period as stated above for AEs. Any SAEs assessed as related to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a subject consents to participate in the study; all SAEs will be followed through resolution. All SAEs will be reported to Novartis within 24 hours, as indicated.

Novartis Reporting

All serious adverse events must be reported by facsimile within 24 hours to Novartis at Fax #877-778-9739. Should the designated SAE fax number be non-functional, SAEs should be sent to the designated SAE mailbox: clinicalsafetyop.phuseh@novartis.com

A Novartis SAE report coversheet should be included when reporting any SAE and must include the Novartis study number (CETB115DUS02T), the study title, investigator contact information, and a signature.

Emergency or after-hours contact information
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.

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to Novartis within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of eltrombopag and considered by the investigator to be related or possibly related to eltrombopag must be reported to Novartis if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

FDA Reporting

All SAEs that are unexpected (i.e., not in the current PROMACTA™ (Eltrombopag) package inserts or the Investigator Brochures) and associated with use of the study drug must be reported to FDA within 15 calendar days, or within 7 calendar days if the SAE was fatal or life-threatening. Novartis will be responsible for FDA reporting of all necessary SAEs.

11.8 Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to Novartis is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

The sponsor-investigator has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The sponsor-investigator will comply with specific regulatory requirements relating to safety reporting to the regulatory authority, /Institutional Review Board (IRB), Novartis, and sub-investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Novartis will file it with the CIB and will notify the IEC /IRB, if appropriate according to local requirements.

12.0 STATISTICAL CONSIDERATIONS

The primary goals of this trial are to assess the efficacy and safety of a short course of eltrombopag in elderly AML patients who have no morphological evidence of residual disease on bone marrow biopsy following standard 7+3 induction therapy. The primary endpoint is the proportion of patients with early (by day 24 from the start of induction) platelet recovery to $\geq$50,000/μL. Based on historical data and our own institutional data (unpublished) approximately 60% of patients can be expected to recover platelets to $\geq$50,000/μL by day 24 without additional supportive care beyond platelet transfusions. An increase in the recovery rate to $\geq$80% would be considered indicative that eltrombopag has significant efficacy in this population.

A two-stage accrual design with a maximum accrual goal of 31 eligible and evaluable patients will be used to test this hypothesis. Twelve eligible patients will be studied initially. If eight or more (67%) have full platelet recovery by day 24 an additional 19 eligible patients will be assessed. If overall 21 or more of the 31 patients have platelet recovery (observed recovery rate $\geq$68%) eltrombopag will be accepted for further testing. With this design, there is a $\geq$56% likelihood of stopping early if eltrombopag's true recovery rate is $\leq$60%, whereas there is at most a 7% chance if the true recovery rate is $\geq$80%. The overall likelihood of rejecting eltrombopag if it is not active is $\geq$81% while there is at most a 9% chance of rejection if it is active.

Adverse events will be graded and categorized using CTCAE version 4.03 criteria. Assuming the trial reaches its maximum accrual goal of 31 eligible patients the likelihood of a particular type and/or grade of toxicity will be estimable using a 95% confidence interval that has a half-width of at most 18%. The likelihood of observing at least one such event is $\geq$ 80% even if the underlying risk is little as 5%.

Secondary goals of the trial include estimating the frequency of platelet transfusion independence, the effect of eltrombopag on hemoglobin, and neutrophils, the risk of clinically significant bleeding, clinical efficacy, and time to initiation of post-remission consolidation therapy.

In general categorical data will be summarized as frequency counts and percentages, measured (non-time dependent) data will be summarized as medians and ranges, and "time-to-event" data, such as platelet and neutrophil recovery, and time to CR will be summarized using the Kaplan-Meier method. Exploratory analyses (univariable) will utilize methods such as Fisher's exact test and chi-square tests (categorical data), the Wilcoxon signed-rank, rank-sum, and Jonckheere-Terpstra tests (measured data), and the log rank test and proportional hazards models (time-to-event data). Logistic regression and proportional hazards models will be the primary tools used for any multivariable analyses performed. All tests of statistical significance will be two sided and in general no adjustment to p-values will be made for multiple comparisons due to the exploratory nature of these analyses.

13.0 REGULATORY CONSIDERATIONS

Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations. This is the responsibility of the sponsor-investigator.

Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see appendix). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Novartis requests that the protocol and informed consent documents be reviewed by Novartis or designee prior to IRB/IEC submission.

Patient Information and Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risk Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Novartis or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's

confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Data Management

Electronic Case Report Forms (eCRFs) will be developed to include all necessary patient information, laboratory data, treatment data, and adverse event data. This data will be housed securely within the web-based ONCORE database and will be password protected. The ONCORE database is 21 CFR Part 11 compliant. The Database Manager at CCF will train the data entry designee(s) on the ONCORE system. Upon completion of the training and electronic signature certification, the Database Manager will create a user account in ONCORE for the data entry designee(s). The data entry designee(s) will proceed with entering the patient(s) relevant information and eCRF forms. The Database Manager will periodically run reports across all studies to ensure timely and accurate entry of accrual data.

Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Novartis (changes are to be submitted by CCF) and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The CCF Principal Investigator will submit all protocol modifications to Novartis and the regulatory authority(ies) in accordance with the governing regulations. All participating subsite(s) will contact the CCF study coordinator. Any departures from the protocol must be fully documented in the source documents.

On-site Audits

Regulatory authorities, the IEC/IRB, and/or Novartis may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

Drug Accountability

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Novartis or disposal of the drug (if applicable and if approved by Novartis) will be maintained by the clinical site. Accountability records will include drug receipt/destruction dates, quantities, lot numbers, expiration dates (if applicable), and corresponding registered patient numbers. All material containing eltrombopag will be treated and disposed of as hazardous waste in accordance with governing regulations.

Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Novartis, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Novartis by the terminating party. Circumstances that may warrant termination include, but are not limited to:

1. Determination of unexpected, significant, or unacceptable risk to patients
2. Failure to enter patients at an acceptable rate
3. Insufficient adherence to protocol requirements
4. Insufficient complete and/or evaluable data
5. Plans to modify, suspend or discontinue the development of the drug
6. Should the study be closed prematurely, all study materials must be returned to Novartis

Record Retention

The sponsor-investigator will maintain all study records according to applicable Cleveland Clinic Foundation regulatory requirement(s).

Patient Consent and Peer Judgment

All institutional, NCI, FDA, state and Federal regulations concerning informed consent and peer judgment will be fulfilled.

14.0 REFERENCES

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Appendix I: WHO Bleeding Scale

	Modified Response Criteria
Grade 0	No bleeding
Grade 1	Petechiae
Grade 2	Mild blood loss
Grade 3	Gross blood loss
Grade 4	Debilitating blood loss

Appendix II: ECOG Performance Status

	Modified Response Criteria
PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix III: AML IWG Response Criteria *(Cheson, 2003)*

	Modified Response Criteria
Morphologic leukemia-free state	Bone marrow blasts <5% No extramedullary disease
Morphologic CR	Bone marrow blasts <5%; Neutrophils >1Gi/L; HI-P a b No extramedullary disease
Cytogenetic CR	As morphologic CR and normal cytogenetics No extramedullary disease
Molecular CR	As morphologic CR and no molecular mutations No extramedullary disease
Partial remission	Bone marrow blasts >50% or decrease to 5-25% (<5% if Auer rod positive) Neutrophils >1Gi/L; HI-P a b

Modification to Cheson 2003.
HI-P : Baseline <20Gi/L: >20 Gi/L and 2x baseline; Baseline ≥20 Gi/L: ≥50 Gi/L and 2x baseline