



Protocol Page

Phase II Study of Eltrombopag With or Without Continuation of Hypomethylating Agent After Hypomethylating Agent Failure For Patients with MDS
2013-0225

Core Protocol Information

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- The Clinical Research Committee - (CRC)

Protocol Body



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Phase II Study of Eltrombopag With or Without Continuation of Hypomethylating Agent after Hypomethylating Agent Failure for Patients with MDS

MDACC Protocol #: 2013-0225

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1. OBJECTIVES

1.1 Primary

The primary objectives of this study are to evaluate the safety and efficacy of eltrombopag for the treatment of MDS patients after experiencing hypomethylating agent (HMA) failure. The primary efficacy endpoint is the overall response rate (ORR) based on the IWG-2006 criteria, which includes complete remission (CR), partial remission (PR), and major hematologic improvement (HI). Safety will be assessed by the overall incidence and severity of all study-treatment related adverse events and clinically thrombocytopenic events per CTC v 4

1.2 Secondary

The secondary objectives of the study are:

- Incidence of transformation from MDS to AML during treatment period and follow-up
- Incidence and severity of bone marrow fibrosis during treatment period and follow-up
- Proportion of patients achieving a platelet response during treatment per IWG-2006 criteria
- Proportion of patients achieving a durable platelet response during treatment per IWG-2006 criteria

1.3 Exploratory

The exploratory objectives of the study are:

- Correlative laboratory studies of subjects including detailed mutation analysis of 53-genes known to be affected in myelodysplastic syndromes and acute leukemias will be performed
- Proportion of subjects achieving a major or minor cytogenetic response will be obtained per IWG-2006 criteria
- To evaluate efficacy of eltrombopag based on IPSS risk classification at diagnosis
- The number and frequency of platelet transfusions during the treatment period will be assessed.
- To examine the relationship between clinical response with ferritin level and other markers of iron burden at study start.

2. BACKGROUND AND SCIENTIFIC RATIONALE

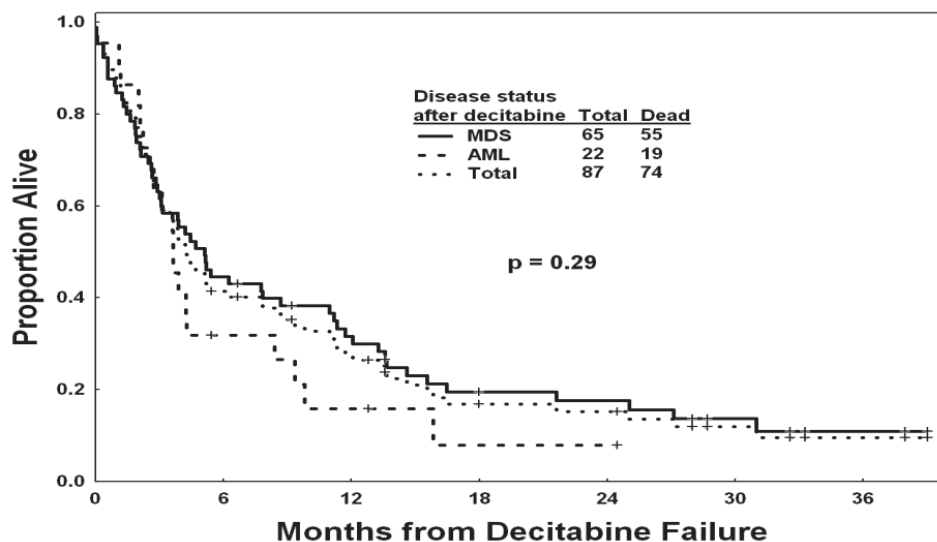
2.1 Background

Myelodysplastic syndromes (MDS) are malignant clonal disorders characterized by ineffective hematopoiesis, bone marrow dysplasia, peripheral cytopenias including thrombocytopenia, and a propensity to transform into acute myeloid leukemia (AML).^{1,2} Classically, MDS is associated with apoptosis and excessive proliferation, resulting in a paradoxical combination of a hyper-cellular marrow and peripheral cytopenias.³ The incidence of MDS in the United States is rising, with approximately 20,000 to 30,000 new cases of MDS diagnosed annually, and a median age at diagnosis of 70 years.³⁻⁶

The therapeutic options for MDS remain limited. A small percentage of patients are candidates for curative therapies such as allogeneic stem cell transplant. For the vast majority of patients the lack of acceptable donors, advanced age, and/or serious comorbid medical conditions and organ dysfunction prevent access to this option. For essentially the same reasons, AML-like chemotherapy regimens represent an unacceptable benefit/risk ratio for many of these patients. In fact, the standard of care in MDS has generally been accepted as supportive in nature.

Over the past decade, clinical use of the hypomethylating agents (HMA) azacitidine and decitabine have been shown to improve patient quality of life, decrease transfusion requirements, and improve outcome parameters in MDS patients, and are now the standard of care for MDS patients requiring therapy. However, not all patients respond to HMAs, and unfortunately most patients initially responding to HMAs will ultimately progress on therapy. Current evidence suggests ORRs of 28-48% and CR rates of 6-34% in all patients treated with HMAs, with a median length of response in HMA-responders of only 8 to 10 months.^{6,7} Myelosuppression, including severe thrombocytopenia, is commonly seen in HMA-treated patients, and is the most frequent cause of dose reduction, delay and discontinuation of HMA agents in up to 80% of patients.⁸ Currently there are no thrombopoietic agents indicated for use in MDS.

Prognosis in HMA-failure patients is extremely poor. Jabbour et al⁹ report a median survival of merely 4 months in MDS patients with progressive disease after decitabine (Figure 1), and Prebet et al⁷ identified a similar median survival of 5.6 months in MDS patients with progressive disease after 5-azacytidine. There are no currently approved agents in the setting of HMA-failure MDS patients, and there are limited therapeutic options, particularly given the increased age and frequent comorbidities of this population.



As alluded to above, the platelet count in MDS patients is critically important, and impacts both treatment decisions and overall survival in the majority of MDS patients. Among 2410 patients with MDS referred to the MD Anderson Cancer Center, 67% had a platelet count $<100 \times 10^9/L$ at the time of their initial consultation, and even within the lower-risk MDS categories, over 10% of patients experience life-threatening thrombocytopenia ($<20 \times 10^9/L$) at presentation.¹⁰ Thrombocytopenia has been identified as an independent and adverse prognostic factor for overall survival in MDS at all stages.¹¹ An analysis of 892 primary MDS subjects identified a median survival in patients with platelet counts $< 100 \times 10^9/L$ of 27 months, compared to 60 months for patients with platelet counts $\geq 100 \times 10^9/L$.¹² Furthermore, the mainstay of treatment for thrombocytopenia in MDS patients, transfusions, are short-lived, and associated with transfusion reactions, allo-immunization, transmission of bacterial and viral infections, and have no impact on the underlying disease biology.

2.2 Rationale for Use of Eltrombopag and Dose Selection

Eltrombopag (Promacta), a second-generation thrombopoietin-receptor agonist (TPO-RA), is a synthetic small-molecule oral thrombopoietin mimetic that binds to c-MPL, promoting megakaryopoiesis and release of platelets from mature megakaryocytes.¹³ It is currently FDA-approved for the treatment of immune thrombocytopenic purpura (ITP) and hepatitis C (HCV) associated thrombocytopenia.¹⁴⁻¹⁶ Eltrombopag has a unique mechanism of action compared to the other TPO-RAs, and functions through binding to a transmembrane domain of the TPO-receptor, activating the JAK/STAT pathway but producing much less activation of the STAT family, and without activation of the Akt pathway.¹⁷ Intriguingly, in cell lines and in Phase I clinical studies, eltrombopag has shown anti-leukemia activity unrelated to the TPO-RA pathway, leading to a modest inhibition of leukemia or MDS cell growth, while continuing to simulate normal megakaryopoiesis in bone marrow samples,¹⁸⁻²⁰ and has also been associated with multilineage clinical responses in patients with severe and refractory aplastic anemia.²¹

The dose of eltrombopag selected is 200mg (100mg for East Asian patients). This is based on the encouraging results of a recent Phase I clinical study of eltrombopag monotherapy for elderly patients with relapsed or refractory AML.²² Eltrombopag monotherapy revealed no platelet responses in the 50mg or 100mg eltrombopag cohorts (n=7). Two of the seven patients treated at the 200mg dose level and two of the nine patients treated at the 300mg dose level achieved platelet response and platelet transfusion independence. Interestingly, one patient with primary refractory AML associated with monosomy 7 obtained a CR with a complete cytogenetic response with eltrombopag monotherapy. Overall eltrombopag was well tolerated at all doses studied and a maximally tolerated dose (MTD) was not reached. Additional trials of lower-risk and higher-risk MDS patients with thrombocytopenia have shown daily eltrombopag, dosed from 50mg to up to 300mg daily, is safe and effective in the MDS population.^{23,24}

Furthermore, the combination of eltrombopag in addition to a hypomethylating agent is currently being evaluated in two ongoing studies (NCT02488565 and NCT01481220) of MDS patients with thrombocytopenia with eltrombopag doses ranging from 50-300mg in both studies, with promising efficacy results, and without new identified safety signals.

Interim results from the first clinical trial (NCT02488565) are available in abstract form from the EHA 2013 meeting. In this trial, n=17 patients have been started on 50mg of eltrombopag and dose-escalated every 2 weeks up to 300mg daily. One patient developed reversible grade III LFT abnormalities, and 4 patients developed thrombocytosis requiring eltrombopag cessation. Activity was seen in 76% (4 CR, 3 marrow CR, 3 HI-P, 1 HI-E, 2 with >50% bone marrow blast reduction) and platelet improvement was seen in 8/15 (53%) patients with baseline platelets <100K. One patient had an improvement in platelet count during the lead-in 2-week 50mg eltrombopag phase. Treatment with the combination of eltrombopag and azacitidine at doses up to 300mg were well-tolerated, with encouraging response and AE events.

Interim results from the second trial (NCT01481220) are also available from the EHA meeting. This pilot study explores eltrombopag with increasing doses of eltrombopag (from 50mg to 300mg in a 3+3 dose-escalation fashion) in conjunction with standard azacitidine dosing, and reports on n=11 patients. Reported SAEs were one case of fatal pneumonia with E. coli septicemia, erysipelas (occurring twice in n=1 patient), and bronchitis (n=1). One patient developed DLT with an extremity DVT, elevated liver enzymes and progressive disease at the n=300mg dose. The combination of eltrombopag with azacitidine was summarized as feasible and well-tolerated.

Additionally, in a Phase II study of 25 patients with refractory aplastic anemia²¹, eltrombopag monotherapy was administered to all patients at a dose of 50mg, with dose escalation to a maximum dose of 150mg daily possible. All but one patient in this study received the maximum dose of 150mg per day, and 11 of 25 patients obtained a platelet response. Serious adverse events in this cohort included abdominal pain and orthostatic hypotension in a patient with diabetic gastroparesis, a severe rash that was temporally related to the initiation of cephalosporin, severe gingival bleeding associated with thrombocytopenia, and episodes of fever with neutropenia. One patient acquired

Hepatitis B virus infection during the study and eltrombopag was discontinued. Diagnosis of a cataract in one patient at week 9, during examination for a “floater”, prompted the discontinuation of eltrombopag, although the patient met hematologic response criteria. The cataract could not be confirmed on subsequent examinations.

Given this scientific rationale, we propose to evaluate the safety and efficacy of eltrombopag in MDS patients with HMA-failure (as defined by persistent cytopenias or rising blast percentage on HMAs). The use of a parallel two-arm Phase II design will allow the evaluation of disease response with the addition of single-agent eltrombopag after HMA failure, as well as to the addition of eltrombopag with *continuation* of the hypomethylating agent to evaluate for additive or synergistic responses, as have been reported with lenalidomide in combination with azacitidine in MDS-azacitidine failures.²⁵ As thrombocytopenia $<100,000 \times 10^9/L$ is an independent and adverse prognostic factor for overall survival in MDS at all stages and given the primary eltrombopag mechanism of augmented megakaryopoiesis, this study will evaluate HMA-failure patients with a platelet count of $<100 \times 10^9/L$.

2.3. Eltrombopag Safety Profile:

2.3.1. Hepatotoxicity:

Eltrombopag may cause hepatotoxicity. In the controlled clinical trials in chronic ITP, one patient experienced Grade 4 (NCI Common Terminology Criteria for Adverse Events [NCI CTCAE] toxicity scale) elevations in serum liver test values during therapy with eltrombopag, worsening of underlying cardiopulmonary disease, and death. One patient in the placebo group experienced a Grade 4 liver test abnormality. Overall, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 11% and 7% of the eltrombopag and placebo groups, respectively. In the 3 controlled chronic ITP trials, four patients (1%) treated with eltrombopag and three patients in the placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seven of the patients treated with eltrombopag in the controlled trials with hepatobiliary laboratory abnormalities were re-exposed to eltrombopag in the extension trial. Six of these patients again experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of eltrombopag in one patient. In the extension study chronic ITP trial, one additional patient had eltrombopag discontinued due to liver test abnormalities (\leq Grade 3).

In 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, ALT or AST $\geq 3X$ ULN was reported in 34% and 38% of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon/ribavirin therapy will experience indirect hyperbilirubinemia. Overall, total bilirubin $\geq 1.5 X$ ULN was reported in 76% and 50% of patients receiving eltrombopag and placebo, respectively.

Current guidelines include measurement of serum ALT, AST, and bilirubin prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels. Discontinue eltrombopag if ALT levels increase to $\geq 3X$ (ULN) in patients with normal liver function or $\geq 3X$ baseline in patients with pre-treatment elevations in transaminases and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

Reinitiating treatment with eltrombopag is not recommended. If the potential benefit for reinitiating treatment with eltrombopag is considered to outweigh the risk for hepatotoxicity, then cautiously reintroduce eltrombopag and measure serum liver tests weekly during the dose adjustment phase. If liver tests abnormalities persist, worsen or recur, then permanently discontinue eltrombopag.

2.3.2. Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis:

Eltrombopag is a thrombopoietin (TPO) receptor agonist and TPO-receptor agonists may increase the risk for the development or progression of reticulin fiber deposition within the bone marrow.

In the ITP extension study, seven patients had reticulin fiber deposition reported in bone marrow biopsies, including two patients who also had collagen fiber deposition. The fiber deposition was not associated with cytopenias and did not necessitate discontinuation of eltrombopag. However, clinical studies have not yet excluded a risk of bone marrow fibrosis with cytopenias.

Prior to initiation of eltrombopag, the screening bone marrow biopsy should be examined closely to establish a baseline level of fibrosis. The presence and degree of reticulin fiber fibrosis should be evaluated on all bone marrow biopsies performed on study.

2.3.3. Worsened Thrombocytopenia After Cessation of Eltrombopag

Discontinuation of eltrombopag may result in thrombocytopenia of greater severity than was present prior to therapy with eltrombopag. This worsened thrombocytopenia may increase the patient's risk of bleeding, particularly if eltrombopag is discontinued while the patient is on anticoagulants or antiplatelet agents. In the 3 controlled ITP clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% and 8% of the eltrombopag and placebo groups, respectively. Serious hemorrhagic events requiring the use of supportive ITP medications occurred in 4 severely thrombocytopenic patients within one month following the discontinuation of eltrombopag; none were reported among the placebo group.

Following discontinuation of eltrombopag, weekly CBCs including platelet counts for at least 4 weeks should be obtained and alternative treatments for worsening thrombocytopenia, according to current treatment guidelines, considered.

2.3.4. Thrombotic/thromboembolic complications

Eltrombopag may increase the risk of thrombotic/thromboembolic events. In the controlled ITP clinical studies, four thrombotic/thromboembolic complications were reported within the groups that received eltrombopag and none within the placebo groups. Thrombotic/thromboembolic complications have also been reported in the ITP extension study.

In a placebo-controlled double-blind study (ELEVATE) of 292 patients with chronic liver disease who were undergoing an elective surgical procedure, the risk of thrombotic events was increased in patients treated with 75mg eltrombopag. Six thrombotic complications were reported within the group that received eltrombopag and two within the placebo group. All of the thrombotic complications reported within the eltrombopag group were of the portal venous system. Malignancy is known to increase the risk for developing a thrombotic event. Four of the 6 subjects receiving eltrombopag either had a diagnosis or suspicion of malignancy (2 hepatocellular carcinoma; 1 possible lymphoma and 1 brain tumor). The ELEVATE study was terminated in November 2009 and a Dear Health Care Professional Letter (DHCPL) was sent to all physicians enrolled in *Promacta* Cares in May 2010. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome and portal hypertension).

2.3.5. Cataracts

Cataracts were observed in toxicology studies of eltrombopag in rodents (see Non-clinical Information). To date, however, there is no evidence that eltrombopag increases

the incidence nor progression of cataracts in patients who have received eltrombopag. In the three placebo-controlled ITP studies, 7% of patients in both the placebo and eltrombopag treatment groups had a report of cataract. A significant proportion of patients in the ITP clinical studies were also exposed to chronic corticosteroid administration. Patients treated with eltrombopag who experience visual difficulties should have an appropriate ophthalmologic evaluation including evaluation for cataract formation.

3. STUDY ELIGIBILITY

3.1 Inclusion Criteria

1. Signed, informed consent must be obtained prior to any study specific procedures.
2. Subjects with a histologically confirmed diagnosis of MDS by FAB criteria, including both MDS and RAEB-T (AML with 20-30% blasts and multilineage dysplasia) by World Health Organization (WHO) classification are eligible.
3. Patients must have completed at least 4 cycles of hypomethylating agent therapy (e.g azacitidine or decitabine) with failure to achieve at least a partial response, or with the presence of ongoing cytopenias per IWG (platelet count $< 100 \times 10^9/L$, hemoglobin $< 11g/L$ or ANC $< 1 \times 10^9/L$). Patients with progressive disease on HMA-therapy prior to this time point are also eligible at the time of documented progression. Therapy with decitabine analogs (i.e. SGI-110) will be considered as decitabine for the purposes of this study.
4. Platelet count $< 100 \times 10^9/L$
5. Low, intermediate-1, intermediate-2 or High-risk category by IPSS
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
7. Adequate liver function, as evidenced by a serum bilirubin $\leq 2x$ the ULN (except for patients with a confirmed diagnosis of Gilbert's Disease) and an ALT or AST $\leq 3x$ the laboratory ULN.
8. Serum creatinine $\leq 2x$ upper limit of normal
9. Subjects must be ≥ 18 years of age at the time of informed consent, because no dosing or adverse event data are currently available on the use of eltrombopag in children.

10. Subject is practicing an acceptable method of contraception (documented in chart). Female subjects (or female partners of male subject) must either be of non-childbearing potential (hysterectomy, bilateral oophorectomy, bilateral tubal ligation or post-menopausal > 1 year), or of childbearing potential and use one of the following highly effective methods of contraception (i.e. Pearl index < 1.0%) from 2 weeks prior to administration of study medication, throughout the study, and 28 days after completion or premature discontinuation from the study:

- Complete abstinence from intercourse;
- Intrauterine device (IUD);
- Two forms of barrier contraception (diaphragm plus spermicide, and for males condom plus spermicide);
- Male partner is sterile prior to entry into the study and is the only partner of the female;
- Systemic contraceptives (combined or progesterone only).

11. Patients must have recovered from acute toxicity (to grade 1 or less) of all previous therapy prior to enrollment. Treatment may start earlier if necessitated by the patient's medical condition (e.g. progressive disease) following discussion with the Investigator.

3.2 Exclusion Criteria

1. Subjects with any prior exposure to a thrombopoietin-receptor agonist
2. Any prior or co-existing medical condition that in the investigator's judgment will substantially increase the risk associated with the subject's participation in the study
3. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary study procedures
4. Active uncontrolled serious infection or sepsis at study enrollment
5. Clinically significant gastrointestinal disorders that may interfere with absorption of drug.
6. History of arterial thrombosis (i.e. stroke) in the past year
7. History of venous thrombosis currently requiring anti-coagulation therapy
8. Unstable angina, congestive heart failure (New York Heart Association (NYHA) > Class II), uncontrolled hypertension (diastolic blood pressure > 100mmHg), or recent (within 1 year) myocardial infarction
9. Subjects with a QTc > 480 msec (QTc > 510 msec for subjects with Bundle Branch Block) at baseline

10. Pregnant or breast-feeding, because there are no adequate and well-controlled studies of eltrombopag use in pregnancy and it is unknown whether eltrombopag is excreted in human milk.

11. Subjects with known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV), because eltrombopag is hepatically cleared, and underlying hepatic impairment may lead to an increased risk of hepatotoxicity. Eltrombopag has not been evaluated with combination antiretroviral regimens.

4. TREATMENT PLAN

4.1 Study Design

This is a two arm phase II study to evaluate the safety and efficacy of high dose eltrombopag for the treatment of MDS patients with thrombocytopenia after experiencing hypomethylating agent (HMA) failure. The primary efficacy endpoint is the overall response rate (ORR) based on the IWG-2006 criteria, which includes complete remission (CR), partial remission (PR), and major hematologic improvement (HI). Patients' overall response will be assessed after at least 2 cycles of treatment and no more than after 6 cycles of treatment and each cycle is 28 days. A total of 46 patients will be enrolled into two arms: (A) eltrombopag only or (B) eltrombopag with continuation of the hypomethylating agent. All patients will be accrued from M. D. Anderson Cancer Center (MDACC).

4.1.1 Arm A: Eltrombopag monotherapy in 28-day cycles.

4.1.2. Arm B: Eltrombopag in combination with continuation of hypomethylating agent in 28-day cycles. The choice of HMA agent (e.g. azacitidine or decitabine) will be the HMA the patient has received prior to enrollment on study. Eltrombopag should be initiated at the start of the next HMA cycle whenever possible so the start date of both agents is consistent. Subsequent cycles will begin on the first day of Decitabine or Azacitidine therapy, and in the absence of toxicity, Eltrombopag administration will not be interrupted. HMA dosing and dosing adjustments should be performed according to the approved package insert, or alternatively at a dose of decitabine 20mg/m² IV over 1 hour for 5 days every 4 weeks and/or according to the institution's standard of care (see Section 4.7.2 for rules of dose reduction or delay).

4.1.2.1. For patients on Arm B, discontinuation of the hypomethylating agent and continued therapy with eltrombopag monotherapy after cycle 2 of combination therapy may be considered at the discretion of the investigator.

4.1.3. Study Replacement: Study patients that discontinue during cycle 1 of the study for reasons other than toxicity or progressive disease will be replaced.

4.1.4. Treatment Extension: After 12 cycles, subjects experiencing continued clinical benefit and no clinically significant study-drug related grade ≥ 3 toxicity may be eligible to continue therapy after discussion with the PI, and the discussion documented in the patient's medical record.

4.1.5 General

Adverse events, bleeding events, and concomitant medications will be assessed continually throughout the study; specific information will be requested at every study visit.

4.2. Study Duration

4.2.1. All subjects must complete a screening visit, day 1 visits for each new cycle, an end of treatment visit and whenever possible, an end of study safety visit 28 days after the last dose of eltrombopag.

4.2.2. Patients may remain on study for up to 12 cycles if the patient demonstrates clinical benefit and no excessive toxicity (i.e. no clinically significant study-drug related grade ≥ 3 toxicity). Patients who are experiencing clinical benefit and have not experienced excessive toxicity may be eligible to continue therapy after discussion with the PI and the discussion documented in the patient's medical record.

4.3. Administration of eltrombopag, +/- decitabine and azacitidine

4.3.1. Decitabine and azacitidine may be administered by local doctor or at MD Anderson, inclusive of the Regional Cancer Centers (RCC). Commercial supplies of decitabine and azacitidine will be used and records will be obtained from the local physician as indicated in the Dear Doctor letter (Appendix F). Eltrombopag is self-administered.

4.3.2. Eltrombopag should be taken on an empty stomach (1 hour before or 2 hours after a meal). Allow a 2-hour interval before or a 4 hour interval after eltrombopag and other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc.

4.3.3. Outside physician participation during treatment is acceptable. Documentation of MDACC physician communication with the outside physician will be required. Protocol required evaluations outside MDACC will be documented by telephone, fax or email. All serious adverse events (SAEs) that occur will be reported to the research nurse and will be evaluated by the Principle Investigator within 48 hours of observing or learning of the

event for reportability to the FDA (Appendix F). Fax and/or email will be dated and signed by the MDACC physician. For protocol required labs that are completed outside MDACC, the PI or treating physician must review results for clinical significance and sign and date results. The screening visit, start of treatment visit (Cycle 1 Day 1), and the end of treatment assessment must be performed at MDACC. MDACC visits must occur at least every 3 months on study, and all study bone marrow assessments should be performed at MDACC.

4.3.4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC PI, or their representative prior to initiation, and will be documented in the patient record.

4.3.5. Eltrombopag will be administered primarily on an outpatient basis; but may be administered as an inpatient. Vomited doses will not be made up on the same day. If the patient misses the dose of eltrombopag in the morning they can take the daily dose no later than 5pm on the same day. Destruction of unused study drug will be in accordance with the institution's drug destruction policy.

4.3.6. Patient compliance will be documented using the MDACC Research Medication Diary and will be assessed at each study visit.

4.3.7. Study cycles will be administered every 28 days ± 7 days or upon resolution of any clinically significant study drug related AE to grade 0-1, whichever occurs first. Subsequent cycles will begin on the first day of Decitabine or Azacitidine therapy, and in the absence of toxicity, Eltrombopag administration will not be interrupted. If a subsequent cycle is delayed due to adverse events related to HMA-agent in Arm B, or if it is considered in the best interest of the patient to delay administration of HMA (e.g. because of concern for an infection), administration of the eltrombopag may continue as planned.

4.3.8. Administration of subsequent cycles may be administered when neutrophils recover to $\geq 1 \times 10^9/L$ and platelets to $\geq 30 \times 10^9/L$ or to baseline levels prior to the start of the last cycle of therapy. Patients with residual disease may start the next cycle with neutrophil and/or platelet counts lower than these if judged to be in the best interest of the patient to start the next cycle. The decision to treat should be documented in the patient's medical record.

4.3.9. Variations from the described doses and sequence may be considered on an individual basis after discussion with the PI and sponsor on a case-by-case basis.

4.4. Identity of Investigational Product

International Non-proprietary name	eltrombopag
Manufacturer	GlaxoSmithKline (GSK)

Dose 200mg daily
Route of Administration oral
Formulation 50mg and 100mg tablets; in bottle

Eltrombopag will be provided by GSK

For oral administration only
Bottle containing 60 tablets of 100mg eltrombopag.
Store below 30 ⁰ C (86 ⁰ F). Do not refrigerate or freeze. Keep bottle tightly closed.
The Expiry date will provided via Certificate of Analysis prepared by GSK

4.5. Supportive Care Guidelines

4.5.1. Supportive measures including blood and platelet transfusions, antimicrobials, and analgesics are permitted.

4.5.2. The administration of anticancer therapies, other investigational cytotoxic agents, or prophylactic use of hematopoietic colony stimulating factors are not permitted.

4.5.3. Erythropoietin or hematopoietic colony stimulating factors for treatment of cytopenias are discouraged. If administered, the subject will not be eligible for a HI response assessment within one week of the receipt of epoetin alfa, filgrastim, or sargramostim, or for one month after receipt of pegfilgrastim or darbopoetin.

4.5.4. Platelet Transfusions: Platelet transfusion data must be captured on the case report form during the screening, treatment and extension periods. A unit of platelets is defined as a single unit of platelet-rich plasma or buffy-coat concentrate or 1 apheresis (single donor) concentrate. The number of units transfused must be recorded.

ASCO guidelines suggest platelet transfusion criteria of:

- Platelet count < 10 x 10⁹/L
- Signs of hemorrhage
- Subject with a high fever and platelet count < 20 x 10⁹/L
- Subject has a hyperleukocytosis
- There has been a rapid fall in platelet count and transfusions will not be readily available in case of emergencies

4.6. Duration of Therapy

Treatment is expected to continue until one of the following criteria applies:

- Lack of objective response after 2 cycles of therapy unless eltrombopag is considered to be of clinical benefit to the patient, or
- Clinically significant progressive disease, or
- Discontinuation of study drug for more than 6 weeks, or
- Intercurrent illness that prevents further administration of treatment, or
- Unacceptable adverse event(s), or
- Patient decision for study withdrawal, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Continuation of therapy beyond 12 months will be considered on a case-by-case basis for patients deriving clinical benefit after discussion with the PI and the discussion documented in the patient's medical record.

4.7 Dosing Delays/Dose Modifications

4.7.1 Dose adjustments for eltrombopag

The dose of eltrombopag will be adjusted according to the guidelines shown in the following tables for study drug-related clinically significant toxicity. If toxicity is not covered in the table, doses may be reduced or held at the discretion of the investigator for the patient's safety. See section 4.7.1.1. for additional liver chemistry stopping and follow-up criteria.

Patients will be withdrawn from the study if they fail to recover to CTCAE grade 0 to 1 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a clinically significant non-hematologic treatment-related toxicity within 6 weeks (leading to treatment delay of > 4 weeks) unless the investigator feels that the patient should remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment. Such instances will be discussed with the principal investigator on a case by case basis and the discussion documented in the medical record.

Patients with study-drug related toxicities that are manageable with supportive therapy may not require dose reductions. For patients with other drug-related toxicities, the following dose adjustment rules apply:

NCI CTCAE Grade	Action
Grade 0-2 non-hematological toxicity	No dose reduction. For grade 2 toxicities that are persistent and/or intolerable (e.g. stomatitis) patients may have a treatment interruption or dose reductions to the next lower dose level.
Grade 3-4 clinically significant non-hematological toxicity†	Hold until recover to NCI CTC AE grade 0-1 If recovery occurs within 2 weeks after treatment has been held, dose should be reduced to -1 dose level, if applicable.

† see 4.7.1.1. for additional liver chemistry stopping and follow-up criteria

Dose modifications for eltrombopag:

Dose level	eltrombopag (mg/day)
+1	300
0	200
-1	100
-2	50

4.7.1.1. Additional Liver Chemistry Stopping and Follow-Up Criteria:

If ALT $\geq 3x$ ULN and/or bilirubin $\geq 2x$ ULN, systematic evaluation for possible causes of hepatotoxicity must be initiated, with discontinuation of any potentially offending concomitant medications (in particular statins, antifungal agents, herbal supplements) and consideration of hepatobiliary imaging as appropriate. Subjects should return to clinic for repeat liver chemistries within 24-72 hours, and then at least weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve or stabilize.

Treatment should be held for any of the following liver chemistry criteria (all of which confer Grade III non-hematologic toxicity per NCI CTCAE):

1. ALT \geq 5x ULN and bilirubin \geq 2.7x ULN (>35% direct bilirubin)
2. ALT \geq 8x ULN
3. ALT \geq 5x ULN but < 8x ULN and persists for \geq 2 weeks
4. ALT \geq 5x ULN if associated with the appearance or worsening of symptoms of hepatitis such as nausea, vomiting, right upper quadrant pain or tenderness.
5. ALT \geq 5x ULN but < 8x ULN and cannot be monitored weekly for \geq 2 weeks.

When any of the above criteria is met, do the following:

- Immediately withdraw investigational product
- Report the event to Novartis Oncology within 24 hours of learning of its occurrence
- Complete the SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT \geq 5x ULN and bilirubin \geq 2.7x ULN (>35% direct bilirubin), modified Hy's Law for oncology clinical trials²⁶, must be reported as an SAE.

NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT \geq 5x ULN and bilirubin \geq 2.7x ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record the presence of detectable urinary bilirubin on dipstick, indicating bilirubin elevation and suggesting liver injury.

- Hold eltrombopag until recovery to NCI CTC AE grade 0-1 and restart at next lower dose level regardless of recovery time.

In addition, for #1:

- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow-up assessments (see below) and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For #2, 3, 4, 5:

- Make every reasonable attempt to have subjects return to clinic within 24-72 hours for repeat liver chemistries and liver event follow-up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For all Criteria 1-5, make every attempt to carry out the liver event follow-up assessments described below as clinically appropriate:

- Viral hepatitis serology (Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B core antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody; Hepatitis E IgM antibody if subject resides outside the USA or Canada or has travelled outside the USA or Canada in the past 3 months).
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Obtain complete blood count with differential to assess eosinophilia
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins.
- Record alcohol use
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

4.7.1.2. Dose Adjustments Related to Platelet Count:

The starting dose for all study patients (with the exception of East Asians, see 4.7.1.3) will be 200mg orally daily. East Asians will start at 100mg orally daily. The eltrombopag dose can be increased by 100mg (to maximum of 300mg daily) after 2 weeks if the untransfused platelet count has not increased to $> 100 \times 10^9/L$ and the patient has not experienced any grade ≥ 3 study drug related toxicity. Laboratory work including a CBC with differential and blood chemistries including ALT, AST and bilirubin must be evaluated bi-weekly for 4 weeks after any change in eltrombopag dosing.

Eltrombopag will be held if platelet counts exceed $400 \times 10^9/L$, and will be resumed the next scheduled day that platelet counts have decreased to $\leq 100 \times 10^9/L$. Dose should be reduced to the next lower dose level, if appropriate.

Dose reductions or delays different than the dose described above are acceptable after discussion with the sponsor and the PI, and will require documentation of the rationale for such action.

4.7.1.3. Dose Adjustments for Subjects of East Asian Ancestry:

The starting dose for patients of East Asian ancestry will be 100mg orally daily. East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) subjects exhibited 50-55% higher eltrombopag concentrations compared to non-East Asian subjects. Dose adjustments for platelet counts will proceed as per 4.7.1.2., regardless of ethnicity.

4.7.2. Dosing for azacitidine and decitabine-related toxicities

Patients with drug-related toxicities that are manageable with supportive therapy may not require dose reductions. For patients with other drug-related toxicities, the following dose adjustment rules apply:

NCI CTCAE Grade	Action
Grade 0-2 non-hematological toxicity	No dose reduction. Grade 2 toxicities that are persistent and intolerable (e.g. stomatitis) can result in dose delays or dose reductions to the next lower dose level in Cycle 2 or beyond.

Grade 3-4 clinically significant non-hematological toxicity	Hold until recover to NCI CTCAE grade 0-1 If recovery occurs within 2 weeks after treatment has been held, dose should be reduced to –1 dose level, if applicable.
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Standard dose reductions for azacitidine and decitabine are described in the following table (please note patients should start at the dose level they were receiving prior to study enrollment):

Dose level	Decitabine (in mg/m ² for 5 days)	Azacitidine (in mg/m ² for 7 days)
0	20	75
-1	15	50
-2	10	25
-3	10 for 4 days	25 for 5 days

Patients with delayed recovery of neutrophils to $1 \times 10^9/L$ and/or platelets to $75 \times 10^9/L$ in the absence of residual disease may have dose reductions by 1 dose level in subsequent cycles.

Patients with serious infectious complications in prior cycles may have the subsequent cycles administered at one dose level reduction in subsequent cycles.

Dose reductions or delays different than those described above are acceptable after discussion with the sponsor and the PI, and will require documentation of the rationale for such action.

4.7.3. For patients with adverse events that are due to one of the two agents, dose adjustments to only one of the study drugs may be adjusted as per the guidelines mentioned above.

4.7.4. For patients on Arm B, discontinuation of the hypomethylating agent and continued therapy with eltrombopag monotherapy after cycle 2 may be considered at the discretion of the investigator.

5. STUDY PROCEDURES

5.1 Screening (Visit 1)

The following procedures are performed during screening, staging and workup (see also Table 5.3). These procedures are to be performed within 4 weeks prior to study drug administration, except where indicated.

A signed and dated IEC/IRB approved informed consent form must be obtained before any study specific procedures are performed. Procedures that are part of routine care are not considered study specific procedures. All subjects will be screened for eligibility before enrollment. Once the subject has met all inclusion criteria, they will be enrolled onto the study.

Table 5.1: Procedures during Screening, Staging and Workup

Procedures	Specifics
Informed consent	
Full History and Physical Examination	<p>History – present illness, prior surgeries, other medical illnesses, review of systems, allergies, prior therapy for cancer and concurrent meds;</p> <p>Physical exam – record weight, and note abnormalities in any major organ system (including but not limited to neurologic, head and neck, lymph nodes, cardiovascular, pulmonary, abdomen, extremities), note and measure sites of disease</p>
Concomitant Medications	
Vital signs (including temperature, pulse, and blood pressure)	
ECOG performance status	
Urine or blood pregnancy test (females of child-bearing potential only)	Within 7 days prior to first dose
<p>Disease status (IPSS classification and WHO disease classification)</p> <p>Note: Bone marrow biopsy or aspirate within 4 weeks prior to first dose of drug in all patients. <i>Cytogenetics and immunohistochemistries performed as indicated.</i></p>	<p>Staging with bone marrow biopsy and/or aspirates for disease assessment.</p>
Serum chemistries (repeat if screening chemistries completed greater than 72 hours prior to the first dose).	<p>Sodium, potassium, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST and/or ALT, total bilirubin, alkaline phosphatase, and uric acid.</p> <p>Note that serum iron, transferrin, transferrin saturation, total iron binding capacity and ferritin only need to be performed once and do not need to be repeated.</p>
CBC with differential (repeat if screening test completed greater than 72 hours prior	Differential may be omitted if WBC $\leq 0.5 \times 10^9/L$

to the first dose)	
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5.2 Treatment Assignment

This is a two arm, non randomized study. Selection of treatment arm will be performed by the patient and the treating physician in the best interest of the patient, based upon available space in either Arm.

5.3 On-Study Procedures

Table 5.3: Study Calendar

PROCEDURES	Pre-Study Screen ^o	Cycle 1 Day 1	Cycle 1 Day 8 (+/- 2 days)	Cycle 1 Day 15 (+/- 2 days)	Cycle 1 Day 22 (+/- 2 days)	Day 1 Cycle 2 onwards (+/- 7 days)	End of Treatment Visit (+/- 7 days)	Safety Visit 28 days after last dose (+/- 28 days)
Informed Consent	X							
Eligibility	X	X						
Medical History	X							
Vital Signs	X	X	X	X	X	X	X	X
Physical Exam and Performance Status	X	X				X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Transfusion and Supportive Care Assessment	X					X	X	X
CBC with differential	X*	X	X	X	X	X ¹	X	X ²
Blood Chemistries (AST, ALT, bilirubin)	X ^{^A}	X	X	X	X	X ¹	X	X
Bone marrow aspiration and/or biopsy	X					X ³	X	
IPSS score & WHO disease classification	X						X	
Pregnancy Test	X†							
Investigational Drug Dispense		X				X		
AE and SAE assessment	X	X	X	X	X	X	X	X
Optional: Correlative Studies	X							

^oScreening must be performed within 4 weeks prior to study drug initiation / study start unless otherwise indicated

*CBC with differential and blood chemistries including iron studies (sodium, potassium, BUN, creatinine, glucose, calcium, phosphate, magnesium, AST, ALT, total bilirubin, alkaline phosphate, uric acid, serum iron, transferrin, , total iron binding capacity and ferritin) must be performed within 72 hours of Cycle 1 Day 1

[^]Serum iron, transferrin, total iron binding capacity and ferritin are required only on Cycle 1 Day 1 and do not need to be repeated

†Within 7 days of Day 1 in females of child-bearing potential

¹Weekly CBC with differential and blood chemistries required until stable counts, and bi-weekly x4 weeks after any change in eltrombopag dosing

²Weekly CBC with differential should be performed weekly for the 4 weeks after discontinuation of eltrombopag

³Bone marrow aspiration and biopsy with cytogenetics required for study entry, at completion of cycle 2, and then every 3 cycles as clinically indicated. Cytogenetics do not need to be repeated if normal at study start.

⁴Optional correlative studies will be performed on bone marrow sample taken at screening. The studies will include an analysis of mutational status of 53 genes known to be affected in acute leukemias as well as gene expression profiling, and evaluation of any potential relationship with the presence or absence of mutations and response will be assessed.

5.4. End of Study Visit:

Subjects will undergo an End of Treatment Visit at the time of discontinuation of investigational product. A bone marrow biopsy and/or aspirate with cytogenetics for IPSS and WHO classification will be performed at this visit. Cytogenetics can be omitted if normal at study start.

5.5. Safety Visit:

Whenever possible, subjects will undergo an End of Study Safety Visit 4 weeks after his/her last dose of investigational product in the treatment period.

5.6. Criteria for Removal from Study:

Treatment is expected to continue until one of the following criteria applies:

- Lack of objective response after 2 cycles of therapy unless eltrombopag is considered to be of clinical benefit to the patient
- Unacceptable adverse event(s)
- Discontinuation of study drug for more than 6 weeks
- Clinically significant progressive disease
- Possibility of undergoing allogeneic stem cell transplantation
- Intercurrent illness that prevents further administration of treatment
- Patient request
- General or specific changes in the patient's condition that renders the patient unacceptable for further treatment in the judgment of the investigator

Continuation of therapy beyond 12 months will be considered on a case-by-case basis for patients deriving clinical benefit after discussion with the PI and sponsor.

6. RESPONSE DEFINITIONS

6.1. Patients' overall response will be assessed after at least 2 cycles of treatment but no more than after 6 cycles, and each cycle is 28 days.

6.2. Study Endpoints

6.2.1. Primary Efficacy Endpoint: The overall response rate (CR + PR + HI) based on the IWG-2006 criteria. Responses must last at least 4 weeks.

Complete Remission:

- Bone marrow: $\leq 5\%$ myeloblasts with normal maturation of all cell lines
- Persistent dysplasia will be noted
- Peripheral blood
 - o Hemoglobin $\geq 11\text{g/dL}$
 - o Platelets $\geq 100 \times 10^9/\text{L}$
 - o Neutrophils $\geq 1.0 \times 10^9/\text{L}$
 - o Blasts 0%

Partial Remission:

- All CR criteria if abnormal before treatment except:
 - o Bone marrow blasts decreased by $\geq 50\%$ over pretreatment but still $> 5\%$

Stable Disease:

- Failure to achieve at least PR, but no evidence of progression for >8 weeks

Failure:

- Death during treatment or disease progression characterized by worsening of cytopenias or significant increase in percentage of bone marrow blasts

Hematologic Improvement (HI) Response Criteria*: responses must last at least 8 weeks

- **Erythroid response** (if pretreatment hemoglobin $< 11\text{g/dL}$)
 - o Hemoglobin increase by $\geq 1.5\text{g/dL}$
 - o Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wks. Only RBC transfusions given

for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation

- **Platelet response** (if pretreatment platelets $< 100 \times 10^9/L$)
 - o Absolute increase of $\geq 30 \times 10^9/L$ for patients starting with $> 20 \times 10^9/L$ platelets
 - o Increase from $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100%
- **Neutrophil response** (if pretreatment $< 1.0 \times 10^9/L$)
 - o At least 100% increase and an absolute increase of $> 0.5 \times 10^9/L$

*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) for at least one week

Progression or relapse after HI‡:

- At least 1 of the following:
 - o At least 50% decrement from maximum response levels in granulocytes or platelets
 - o Reduction in hemoglobin by ≥ 1.5 g/dL
 - o Transfusion dependence
- ‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Relapse after CR or PR:

- At least 1 of the following
 - o Return to pretreatment bone marrow blast percentage
 - o Decrement of $\geq 50\%$ from maximum remission/response levels in granulocytes or platelets
 - o Reduction in hemoglobin concentration by ≥ 1.5 g/dL or transfusion dependence

Cytogenetic Response:

- Complete: Disappearance of the known chromosomal abnormality without appearance of new abnormalities
- Partial: At least 50% reduction of the chromosomal abnormality in 20 metaphases

Disease Progression:

For patients with:

- Less than 5% blasts: $\geq 50\%$ increase in blasts to $> 5\%$ blasts
- 5-10% blasts: $\geq 50\%$ increase to $> 10\%$ blasts
- 10-20% blasts: $\geq 50\%$ increase to $> 20\%$ blasts
- 20-30% blasts: $\geq 50\%$ increase to $> 30\%$ blasts

Any of the following:

- At least 50% decrement from maximum remission/response in granulocytes or platelets
- Reduction in hemoglobin by ≥ 2 g/dL
- Transfusion dependence

Survival Endpoints:

- Overall: death from any cause
- Event free: failure or death from any cause
- PFS: disease progression or death from MDS
- DFS: time to relapse
- Cause specific death: death related to MDS

6.2.2. Primary Safety Endpoint and Safety Considerations

Primary safety endpoint: The overall incidence and severity of all adverse events including clinically significant thrombocytopenic events using Common Toxicity Criteria v 4.0.

An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal

relationship with this treatment. Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

All “suspected adverse reactions” (as defined in 21 CFR 312.32(a)) will be captured in the case report forms. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. Protocol specific data and adverse events will be entered into PDMS/CORe, the electronic case report form for this protocol.

6.2.2.1. Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an

SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Device. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

The following SAEs are not subject to expedited reporting, but would still be included in the annual report via the SAE log.

- a. Infection or cytopenias leading to hospitalization or prolongation of hospitalization
Disease progression leading to death, life-threatening AE, hospitalization or prolongation of hospitalization, or disability.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32
- **It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

6.2.2.2. Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 3 months from the discontinuation of dosing, the investigator should report the information to the study supporter as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information. The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth.
- "Normality" of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

6.2.2.3. SAE Reporting to Study Supporter (GSK/Novartis)

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

All serious adverse events must be reported by facsimile within 24 hours to Novartis Oncology. MDC – Oncology Fax: 1 610 422 2527 (make sure you include the 1 prior to the 610 as this is a desktop fax)

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 Oncology within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of eltromboapg and considered by the investigator to be related or possibly related to eltrombopag must be reported to Novartis Oncology 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.

6.2.3. Secondary Efficacy Endpoints

The key secondary endpoints for this study are:

- The incidence of transformation to AML by FAB during treatment period and follow-up
- The incidence and severity of bone marrow fibrosis during treatment period and follow-up
- Proportion of patients achieving a platelet response during treatment; and proportion of patients achieving a durable platelet response.
 - o Platelet IWG-2006: A complete response is defined as a platelet count $> 100 \times 10^9/L$; and a major response defined as an increase of platelet count by higher than $30 \times 10^9/L$.
 - o Durable platelet count: in which a hematologic improvement in platelets (HI-P) defined as either an increase $\geq 30 \times 10^9/L$ from patients with a baseline platelet count $\geq 20 \times 10^9/L$, or an increase from $< 20 \times 10^9/L$ to $\geq 20 \times 10^9/L$ and by at least 100%, present for ≥ 8 weeks.

6.2.4. Exploratory Endpoints

The following exploratory endpoints will be examined by descriptive statistics:

- Correlative laboratory studies of subjects including an analysis of mutational status of at least 53 genes known to be affected in acute leukemias will be performed, and evaluation of any potential relationship with the presence or absence of mutations and response will be assessed. This panel has been validated using a next generation sequencing (NGS) platform for the detection of frequently reported mutations in our CLIA-certified molecular diagnostics laboratory.
- Proportion of subjects achieving a major or minor cytogenetics response during study bone marrow assessments per IWG-2006 criteria.
 - o Major: Disappearance of cytogenetic abnormality
 - o Minor: $\geq 50\%$ reduction in abnormal metaphases out of 20 analyzable metaphases
- Evaluation of the efficacy of eltrombopag (as determined by IWG-2006 criteria) based on IPSS risk classification system at diagnosis

- The number and frequency of platelet transfusions received during the treatment period will also be assessed
- To examine the relationship between clinical response with ferritin level and other markers of iron burden at study start, given recent data that the antileukemic effects of eltrombopag may be mediated through modulation of intracellular iron content.

6.3 Subsets

6.3.1. Full Analysis Set

The full analysis set will consist of all enrolled subjects. Subjects will be analyzed according to their treatment group. Analyses for demographics and baseline characteristics will utilize this analysis set.

6.3.2. Efficacy Analysis Set

The efficacy analysis set will consist of all enrolled subjects who have received at least one cycle of investigational product. Analysis for efficacy endpoints will utilize this analysis set.

6.3.3. Safety Analysis Set

The safety analysis set will consist of all enrolled subjects who received at least 1 dose of investigational product. Subjects will be analyzed according to the treatment actually received. Analysis for safety endpoints will utilize this analysis set.

7. Regulatory and Reporting Requirements

7.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form should be

retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

7.2. Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Novartis Oncology before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent form. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from GSK or Novartis Oncology, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB's continuance of approval must be sent to Novartis Oncology

7.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On all documents submitted to GSK or Novartis Oncology subjects should be identified by their initials and a subject study number only. Documents that are not for submission to Novartis Oncology (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

7.4. Protocol Amendments and Study Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of Novartis Oncology. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent form. The IEC/IRB must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IEC/IRB to

Novartis Oncology.

Both Novartis Oncology and the investigator reserve the right to terminate the study according to the study contract. The investigator should notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to Novartis Oncology.

Subjects may be eligible for continued treatment with investigational product by extension protocol or as provided for by the local country's regulatory mechanism. However, Novartis Oncology reserves the unilateral right, at its sole discretion, to determine whether to supply the investigational product, and by what mechanism after termination of the trial and before it is available commercially.

7.5. Study Documentation and Archival

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Case report form entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, case report forms calculating IPSS may be used as source documents for IPSS risk category assignment.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Novartis Oncology and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation and all correspondence to and from the IEC/IRB and Novartis Oncology
- Proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available. No study document should be destroyed without prior written agreement between Novartis Oncology and the investigator. Should

the investigator wish to assign the study records to another party or move them to another location, he/she must notify Novartis Oncology in writing of the new responsible person and/or the new location.

7.6. Serious Adverse Event Reporting (SAE):

See Section 6.2.2.1 for detailed information regarding SAE definitions.

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to Novartis Oncology, regardless of attribution (see Section 6.2.2.3). SAE reporting will be done according to 21 CFR 312.32(c)(1)(iv) ("Sponsor must report any clinically important increase in the rate of a serious adverse reaction over that listed in the protocol or investigator brochure.").

The descriptions and grading scales found in the revised NCI Common Terminology *Criteria for Adverse Events (CTCAE) version 4.0* will be utilized for adverse event reporting. (<http://ctep.cancer.gov/reporting/ctc.html>).

8. Statistical Considerations

8.1. Design and Sample Size

This is a two arm phase II study to evaluate the safety and efficacy of high dose eltrombopag for the treatment of MDS patients after experiencing hypomethylating agent (HMA) failure. The primary efficacy endpoint is the overall response rate (ORR) based on the IWG-2006 criteria, which include complete remission (CR), partial remission (PR), and major hematologic improvement (HI). Patients' overall response will be assessed after at least 2 cycles of treatment but no more than after 6 cycles; and each cycle is 28 days. A total of 46 patients will be enrolled by patient and treating physician preference into two arms: (A) eltrombopag only or (B) eltrombopag with continuation of the hypomethylating agent. All patients will be accrued from M. D. Anderson Cancer Center (MDACC).

Currently, there is no FDA approved agent for patients who have failed on hypomethylating agent, and therapeutic options are limited, particularly given the

increased age and frequent comorbidities of this population. In this proposed study, patients will be enrolled into one of two treatment arms. Treatment arm will be determined by patient and treating physician, taking into account patient experience with prior hypomethylating agent therapy. Arm A (eltrombopag only) or Arm B (eltrombopag with continuation of HMA). We anticipate that patients treated in Arm A will achieve an ORR of 15-20%, while patients treated in Arm B will achieve an improved ORR of 25%. Given the expected small difference (5-10%) between the two arms, the sample size needed to detect such a difference with enough statistical power will be too large to be accommodated in this small phase II trial. Therefore, our focus for this study is to assess the ORR in each arm separately using Simon's Minimax two-stage design²⁷.

8.2. Futility Monitoring

8.2.1. For patients treated in Arm A (eltrombopag alone), we assume a target ORR of 18% and a response rate of 5% or lower will be considered not desirable. With a 1-sided type I error rate of 10.3% and 80% power, we will enroll 15 patients in the first stage. If none of these patients achieve OR, the trial will be stopped. If 1 or more out of the first 15 patients have OR, accrual will continue until a total of 23 patients have been enrolled. At the end of the study, if 3 or more out of these 23 patients achieve OR, the treatment of eltrombopag alone will be considered efficacious and is worth further investigation. Under this Simon's Minimax two-stage design, the probability of early termination is 46.3% if the true ORR is 5% and the expected sample size is 19 patients.

For patients treated in Arm B (eltrombopag in combination with HMA), the target ORR is 25%, and a response rate of 5% or lower will be considered not desirable. With a 1-sided type I error rate of 3% and 85% power, we will enroll 12 patients in the first stage. If none of these 12 patients achieve OR, the trial will be stopped. If 1 or more out of the first 12 patients have OR, accrual will continue until a total of 23 patients have been enrolled. At the end of the study, if 4 or more of these 23 patients achieve OR, the treatment of eltrombopag in combination with HMA will be considered efficacious and is worth further investigation. Under this Simon's Minimax two-stage design, the probability of early termination is 54% if the true ORR is 5% and the expected sample size is 17 patients.

Patient enrollment will be suspended if for an arm the first-stage patients have been enrolled and none of these first-stage patients has OR. Accrual will resume if at least one OR is observed within 2 cycles among the first-stage patients for that arm.

8.2.2. The accumulating data will be summarized at regular intervals to provide an ongoing assessment of the safety and efficacy of eltrombopag in this population. Additional summaries of data may be provided for regulatory or publication activities.

8.3. Safety Monitoring

8.3.1. The method of Thall, Simon, and Estey²⁸ will be employed for interim safety monitoring. We assume a Beta (0.6, 1.4) prior distribution for the toxicity rate which has mean of 30%. For the purpose of safety monitoring, toxicities are defined as any grade 3 or greater clinically significant non-hematologic adverse events, attributed to the study drug.

The following Bayesian monitoring rule will be applied in each arm separately, starting from the 3rd patient and up to the total of 23 patients per arm. Specifically, an arm will be stopped early if

$$\text{Pr}[\text{toxicity rate} > 30\% | \text{data}] > 0.9$$

That is, if at any time during the study we determine that there is more than a 90% chance that the toxicity rate is more than 30% in a treatment arm, we will stop enrolling patients into that arm. If one arm is stopped due to severe toxicity, we will continue enroll patients into the other arm until the total accrual of 23 patients is reached or until the toxicity stopping boundary is crossed in that arm, whichever occurs first.

Stopping boundaries corresponding to this toxicity monitoring rule are displayed in the following table:

Number of patients evaluated	Recommend stopping if \geq toxicity observed
3-4	3
5-7	4
8-9	5
10-12	6
13-14	7
15-17	8
18-20	9
21-22	10

The operating characteristics of this toxicity monitoring rule are shown in the following table

True toxicity rate	Early stopping probability	Sample size percentile		
		25%	50%	75%
0.2	0.07	23	23	23

0.3	0.25	22	23	23
0.35	0.4	9	23	23
0.4	0.57	7	17	23

8.4 Statistical Analysis Plan

8.4.1. General Approach/Considerations

The final analysis will be performed when all data has been retrieved, entered, cleaned, locked and frozen. Descriptive statistics for demographic and baseline characteristics will be summarized for all enrolled subjects. For categorical variables, the number and percentage of subjects in each category will be summarized. Continuous variables will be summarized by n, mean, standard deviation, median, Q1 (25% percentile), Q3 (75% percentile), minimum and maximum values.

8.4.2. Analysis of Key Study Endpoints

The primary endpoint is overall response rate (ORR). The ORR in each arm will be evaluated along with the exact 95% confidence interval. Given the limited sample size, no formal comparison will be made between these two arms in terms of ORR.

Secondary endpoints include platelet response, durable platelet response, transformation to AML, incidence of bone marrow fibrosis, and time-to-event outcomes such as progression-free survival (PFS) and overall survival (OS). The probabilities of PFS and OS will be estimated using the method of Kaplan and Meier. The incidence rates of other binary secondary endpoints will be estimated, along with the exact 95% confidence intervals. Subjects that discontinue the study prior to having achieved a clinical response will be considered to have not had an event.

Patients receiving growth factors other than eltrombopag (erythropoietin, GM-CSF or G-CSF) will not be considered in the HI analysis for the time periods specified in Section 4.5.3 Supportive Care Guidelines. Hemoglobin levels and platelet counts collected from patients that have received a transfusion within the last 3 days will not be considered in the analysis.

Survival or times to failure and time to progression functions will be estimated using the Kaplan-Meier method. The two-sided log-rank test will be used to assess the differences of time to events between groups.

The total number of dose administrations, the average dose (mg), and the cumulative dose administered will be summarized by eltrombopag treatment group.

Blood chemistry and complete blood counts will be summarized by treatment group at each time point.

Additional exploratory analyses of the key study endpoints will be performed as deemed appropriate.

8.4.2.1. Safety Endpoints

The incidence of adverse events will be summarized by system organ class and by preferred term according to the MedDRA dictionary for each treatment group. This summary includes all treatment-emergent adverse events recorded from the start of investigational product on this study, or any worsening of adverse events initially experienced before initiation of this study.

Narratives of “on-study” deaths, serious and significant adverse events, including early withdrawals due to adverse events, may also be provided.

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