THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Phase II Study of Eltrombopag in Combination with Decitabine in Subjects with Advanced Myelodysplastic Syndrome
2013-0590

Core Protocol Information

Short Title	Eltrombopag with decitabine in advanced MDS
Study Chair:	Courtney DiNardo
Additional Contact:	Tawana Heiskell Vicky H. Zoeller Leukemia Protocol Review Group
Department:	Leukemia
Phone:	713-794-1141
Unit:	428
Full Title:	Phase II Study of Eltrombopag in Combination with Decitabine in Subjects with Advanced Myelodysplastic Syndrome
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Terminated 01/03/2019
Version:	11
Submitted by:	Tawana Heiskell--11/11/2015 4:03:01 PM
OPR Action:	Accepted by: Debbie D. Stroughter -- 12/1/2015 3:05:44 PM

Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

Frontline Phase II Epag + Dacogen 4 14 15 - final .pdf

Phase II study of eltrombopag in combination with decitabine in subjects with advanced myelodysplastic syndrome

MDACC Protocol #: 2013-0590

Principal Investigator: Courtney DiNardo, M.D., M.S.C.E.

Address: 1515 Holcombe Blvd, Unit 428
Houston, TX 77030

Phone: 713) 794-1141

Fax: 713) 792-0319

Email: cdinardo@mdanderson.org

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of eltrombopag in combination with decitabine for the front-line treatment of Intermediate-2 or High-Risk Myelodysplastic Syndrome (MDS). The primary endpoint is the overall response rate (ORR) based on the IWG-2006 criteria, which includes complete remission (CR), partial remission (PR), and hematologic improvement (HI).

1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of the combination of eltrombopag and decitabine. Safety will be assessed by the overall incidence and severity of all study-treatment related adverse events per CTCAE v 4.0

- To evaluate the incidence of dose reductions and delays of decitabine therapy

- To evaluate the effect of eltrombopag on medically significant hemorrhagic events (defined as Grade 3 or 4 hemorrhagic events on CTCAE v 4.0)

- To evaluate the effect of eltrombopag on platelet and RBC transfusion independence per IWG-2006 criteria

- Incidence of transformation to AML per FAB criteria (>30% blasts) during treatment period and follow-up

- Incidence and severity of bone marrow fibrosis during treatment period and follow-up

- To examine the relationship between clinical response with ferritin level and other markers of iron burden at study start

1.3 Exploratory Objectives

- Correlative laboratory studies of subjects including gene expression profiling and molecular analysis to determine the in vivo mechanism of action and the molecular and biological effects of the combination of decitabine and eltrombopag will be performed.

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]

Over the past decade, clinical use of the hypomethylating agent decitabine has been shown to improve patient quality of life, decrease transfusion requirements, and improve outcome parameters in MDS patients, and is now a standard of care for MDS patients requiring therapy. However, myelosuppression including severe thrombocytopenia is commonly seen in decitabine-treated patients, and is the most frequent cause of dose reduction, delay and discontinuation of the HMA agents (including both decitabine and 5-azacitidine) in up to 80% of patients.[7] With current HMA regimens, achievement of an ORR is estimated at 28-70%, with a CR rate of only 6-34% in patients treated with front-line HMA therapy, and with a median length of response in the HMA-responders of only 8 to 10 months.[6,8-11]

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 x 10^9/L at the time of their initial consultation, with over 10% of patients presenting with life-threatening thrombocytopenia (<20x10^9/L). The frequency of hemorrhagic deaths within this population ranged from 14 to 24%.[12]

Thrombocytopenia has been identified as an independent and adverse prognostic factor for overall survival in MDS at all stages.[13] An analysis of 892 primary MDS subjects identified a median survival in patients with platelet counts < 100 x 10^9/L of 27 months, compared to 60 months for patients with platelet counts $\geq$ 100 x 10^9/L.[14] 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.

Given the high rate of thrombocytopenia both prior to and during decitabine therapy, which can result in inadequate treatment due to dose reductions and therapy delay, as well as the risks of hemorrhagic complications, the addition of eltrombopag to improve thrombocytopenia in MDS patients is justified. Furthermore, the anti-leukemia properties of eltrombopag seen both *in vitro* and in early clinical studies, identify eltrombopag as an excellent candidate agent for this purpose.

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.[15] It is currently FDA-approved for the treatment of immune thrombocytopenic purpura (ITP) and hepatitis C (HCV) associated thrombocytopenia.[16-18] 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.[19] 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,[20-22] and has also been associated with multilineage clinical responses in patients with severe and refractory aplastic anemia.[23]

This study will enroll patients with advanced MDS, defined as IPSS Int-2 or high-risk MDS, or IPSS-R high or very-high MDS and with thrombocytopenia with a platelet count < 100K. The study will explore the supportive care and disease-modifying effects of eltrombopag in addition to decitabine standard of care treatment for advanced MDS. In patients with advanced MDS receiving decitabine, the consequences of low platelet counts, namely platelet transfusions and hemorrhage, form the basis of clinical outcomes which provide clinically meaningful benefit.

Optimal dosing of eltrombopag is adjusted, based upon platelet count response in individual patients. The starting dose of eltrombopag selected for this study is 100mg (50mg for East Asian patients). Dose modifications will be permitted, from a minimum dose of 25mg to a maximum dose of 300mg in order to maintain platelet counts at a safe and effective level. This is based upon the observed efficacy, safety and pharmacokinetics of studies including PMA112509 (NCT009034) and TRC114968 (NCT014403). In both studies, the majority of subjects were escalated to the maximum dose of 300mg (150mg for East Asian patients). The safety profile of eltrombopag at these doses was similar to prior studies at lower doses (i.e. 50mg in ITP registry studies). No new safety signals were identified, and the frequency and intensity of AEs known to be associated with eltrombopag (e.g. elevation in liver enzymes) were not increased despite the higher doses. 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.[24-26]

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 (≤Grade 3).

In 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, ALT or AST ≥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 ≥1.5 X ULN was reported in 76% and 50% of patients receiving eltrombopag and placebo, respectively.

Measure 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 ≥3X (ULN) in patients with normal liver function or ≥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 may increase the risk for development or progression of reticulin fiber deposition within the bone marrow. In the extension trial in chronic ITP, 151 patients have had bone marrow biopsies evaluated for increased reticulin and collagen fiber deposition. Bone marrow biopsies taken after 1 year of therapy showed predominantly myelofibrosis (MF) Grade 1 or less in 140/151 (93%) of patients. There were 11/151 (7%) of patients with MF Grade 2. Four patients had collagen deposition reported. One patient with a pre-existing MF Grade 1 developed a MF Grade 2 and subsequently discontinued treatment with eltrombopag. Clinical trials have not excluded a risk of bone marrow fibrosis with demonstrated clinical consequences to date. If new or worsening blood morphological abnormalities or cytopenias occur, consider a bone marrow biopsy including staining for fibrosis.

2.3.3. Thrombotic/Thromboembolic Complications

In 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, (31/955) treated with eltrombopag experienced a thrombotic event compared to 1% (5/484) on placebo. The majority of events were of the portal venous system (1% in patients treated with eltrombopag versus <1% for placebo).

Thrombotic/thromboembolic complications may result from increases in platelet counts with eltrombopag. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts.

Consider the potential for an increased risk of thromboembolism when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for thrombotic/thromboembolic complications, do not use eltrombopag in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve and maintain a target platelet count.

In a controlled trial in non-ITP thrombocytopenic patients with chronic liver disease undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased in patients treated with 75 mg eltrombopag once daily. Seven thrombotic complications (six patients) were reported in the group that received eltrombopag and three thrombotic complications were reported in the placebo group (two patients). All of the thrombotic complications reported in the group that received eltrombopag were portal vein thrombosis (PVT). Symptoms of PVT included abdominal pain, nausea, vomiting, and diarrhea. Five of the six patients in the group that received eltrombopag experienced a thrombotic complication within 30 days of completing treatment with eltrombopag and at a platelet count above 200 x 109/L. The risk of portal venous thrombosis was increased in thrombocytopenic patients with chronic liver disease treated with 75 mg eltrombopag once daily for 2 weeks in preparation for invasive procedures.

2.3.4 Cataracts

In the 3 controlled clinical trials in chronic ITP, cataracts developed or worsened in 15 (7%) patients who received 50 mg eltrombopag daily and 8 (7%) placebo-group patients. In the extension trial, cataracts developed or worsened in 4% of patients who underwent ocular examination prior to therapy with eltrombopag. In the 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, cataracts developed or worsened in 8% patients treated with eltrombopag and 5% patients treated with placebo. Patients treated with eltrombopag who experience visual difficulties should have an appropriate ophthalmologic examination including evaluation for cataract formation.

2.4. Decitabine

Decitabine is supplied as a lyophilized white to almost white, finely crystalline, odorless powder for injection in 20 mL glass vials, containing 50 mg of decitabine, monobasic potassium phosphate, and sodium hydroxide. When reconstituted with 10 mL of sterile water for injection each mL will contain 5 mg of decitabine, 6.8mg of KH2PO4, and approximately 1.1 mg NaOH. The pH of teh resulting solution is 6.5-7.5. The reconstituted solution can be further diluted to a concentration of 1 mg/mL or 0.1 mg/mL in cold infusion fluids (0.9% Sodium Chloride Injection USP, 5% Dextrose in Water Injection, USP, or Lactated Ringer's Injection USP).

The intact vials should be stored under refrigeration (2-8°C; 36-46°F) in the original package. Shelf life surveillance of the intact vials is on-going. The intact vials are stable for at least 1 year at room temperature (22-25°C), 2 years at 2-8°C or 6 months at 40°C. Reconstiution and dilution of the powder for injection (with 10 mL of sterile water for injection) results in a rapidly decomposing solution. The concentration of decitabine in the reconstituted and diluted solution decreases about 10% after 4 hours at 25°C or

about 10% after 24 hours at 4°C. Since 10% is the maximum allowable decomposition, and the solution will also decompose during administration (infusion), the solution should be prepared just prior to administration. If this is not possible the solution should be prepared at least twice a day and be kept in a refrigerator (2-8°C) until administration. Furthermore, the solution should be prepared only with cold infusion fluids at a temperature of 2-8°C (36-45°F). The solution can be infused over a maximum period of 3 hours.

Drug handling precautions will be strictly followed. Skin contact with the solution should be avoided and protective gloves should be worn. Spilt drug can be inactivated by 2 M sodium hydroxide solution.

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) and chronic myelomonocytic leukemia (CMML) with at least 10% bone marrow blasts by World Health Organization (WHO) classification are eligible.

3. Advanced MDS by virtue of intermediate-2 or high-risk MDS by IPSS score, or high or very-high risk by IPSS-R.

4. Platelet count ≤ 100 x 10^9/L at baseline

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

6. 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.

7. Serum creatinine $\leq$ 2.5x upper limit of normal

8. Subjects must be $\geq$ 18 years of age at the time of informed consent

9. 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).

3.2 Exclusion Criteria

1. Subjects with any prior exposure to a thrombopoietin-receptor agonist

2. Prior hypomethylating agent treatment for MDS

3. 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

4. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary study procedures

5. Active uncontrolled serious infection or sepsis at study enrollment

6. Clinically significant gastrointestinal disorders that may interfere with absorption of drug.

7. History of arterial thrombosis (i.e. stroke) in the past year

8. History of venous thrombosis currently requiring anti-coagulation therapy

9. 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

10. Subjects with a QTc > 480 msec (QTc > 510 msec for subjects with Bundle Branch Block) at baseline

11. Pregnant or breast-feeding

12. 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.

13. Subjects with liver cirrhosis (as determined by the investigator)

14. Subjects with hypersensitivity to study drugs or their excipients.

4. TREATMENT PLAN

4.1 Study Design

This is a single arm phase II study of eltrombopag in combination with decitabine in subjects with thrombocytopenia and higher risk (advanced) myelodysplastic syndromes (MDS). The purpose of this study is to explore the supportive care and disease-modifying effects of eltrombopag in combination with decitabine standard of care for patients with advanced MDS. The primary objective will be the overall response rate (ORR) based on the IWG-2006 criteria, which includes complete remission (CR), partial remission (PR), and hematologic improvement (HI).

The primary endpoint will be evaluated for each 28-day cycle of decitabine treatment during the first four cycles, and these 4 cycles will be used for the primary analysis. Four cycles of the primary endpoint was chosen since the median duration to decitabine response is 3.3 cycles, and the occurrence or worsening of thrombocytopenia in patients treated with hypomethylating agents is most commonly observed in the initial cycles of treatment. Adverse events, bleeding events, and concomitant medications will be assessed continually throughout the study; specific information will be requested at every study visit.

A total of 40 patients will be accrued from M. D. Anderson Cancer Center (MDACC).

4.1.1. Study Replacement:

All patients who receive at least one dose of the study drug will be included in the efficacy and safety analysis. For efficacy analysis, patients who drop out of the study early (i.e. before the end of cycle 1) due to treatment-related toxicities will be counted as treatment failures (i.e. non-responders). Patients will be replaced if they drop out of the study before receiving any dose of the study drug.

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. Treatment will continue until discontinuation due to relapse, unacceptable toxicity, or disease progression as defined by the IWG 2006 criteria for MDS. This includes:

- clinically significant progressive disease at any time, or

- a lack of clinical benefit after 4 cycles of treatment at the highest dose of study medication, or

- Possibility of undergoing allogeneic stem cell transplantation

- 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 that render the patient unacceptable for further treatment in the judgement of the investigator

4.2.3. Study cycles will be administered every 28 days $\pm$ 5 days or upon resolution of any clinically significant study drug related AE to grade 0-1, whichever occurs first. If a subsequent cycle is delayed due to adverse events related to decitabine, or if it is considered in the best interest of the patient to delay administration of decitabine (e.g. because of concern for an infection), administration of the eltrombopag may continue as planned.

4.2.4. Administration of subsequent cycles should be administered when neutrophils recover to $\geq$ 1 x 10^9/L and platelets to $\geq$30 x 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.

4.2.5. 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 $\geq$ 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. Decitabine Administration

Decitabine may be administered by local doctor or at MD Anderson, inclusive of the Regional Cancer Centers (RCC). Commercial supplies of decitabine and will be used and records will be obtained from the local physician as indicated in the Dear Doctor Letter (Appendix E).

4.4 Eltrombopag Administration

4.4.1. Eltrombopag should be taken on an empty stomach (1 hour before or 2 hours after a meal) or with food containing little (<50 mg) or preferably no calcium or dairy products. 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.

4.4.2. Eltrombopag will be self-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.

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

4.4.4 Subjects will be permitted to use HMG-CoA reductase inhibitors (statins) 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 as well as efficacy. Preclinical data showed that eltrombopag is an inhibitor of the organic anion transporters OATP1B1 and BCRP. 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 and identified increased plasma rosuvastatin Cmax and AUC.[27,28]

4.4.5. Subjects of East Asian ancestry exhibit higher eltrombopag drug exposure and will be initiated at a 50% reduced initial dose.

4.5. Non-MDACC Physician Participation

4.5.1. 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. 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.

4.5.2. Changes in decitabine 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. All decisions for dose adjustments of eltrombopag will be made by the MD Anderson treating physician.

4.5.3. All serious adverse events (SAEs) that occur will be reported to the research nurse and will be evaluated by the PI within 48 hours of observing or learning of the event for reportability to the FDA (Appendix E). Fax and/or email will be dated and signed by the MDACC physician.

4.6. Identity of Investigational Product

International Non-proprietary name	eltrombopag
Manufacturer	Novartis Oncology
Dose	100mg daily
Route of Administration	oral
Formulation	12.5mg, 50mg, 75mg and 100mg capsules; in bottle

Eltrombopag will be provided by Novartis Oncology.

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

4.7. Supportive Care Guidelines

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

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

4.7.3. 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 Procrit or Neupogen, or for one month after receipt of Neulasta or Darbopoetin.

4.7.4. 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 10^9/L (i.e. severe thrombocytopenia)
- Signs of hemorrhage
- Subject with a high fever and platelet count < 20 x 10^9/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

4.8 Dosing Delays and Dose Modifications

4.8.1. Dose Adjustments for Toxicity:

The doses of eltrombopag and decitabine 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 4.8.4 for 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 4.8.4 for additional liver chemistry stopping and follow-up criteria

4.8.2 Decitabine Dosing, Delays and Dose Modifications

4.8.2.1. Decitabine 20mg/m2 IV on Days 1-5 will be administered for each 28-day cycle.

4.8.2.2. Standard dose reductions for decitabine are described in the following table. Patients with drug-related toxicities that are manageable with supportive therapy may not require dose reductions.

Dose level	Decitabine (in mg/m2 for 5 days)
0	20
-1	15
-2	10
-3	10 for 4 days

4.8.2.3. Administration of subsequent cycles should be administered when neutrophils recover to $\geq$ 1 x 10^9/L and platelets to $\geq$30 x 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. Patients with delayed recovery of neutrophils to 1x10^9/L and/or platelets to 75x10^9/L in the absence of residual disease may have dose reductions by 1 dose level in subsequent cycles.

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

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

4.8.3 Eltrombopag Dosing Delays and Dose Modifications

Dose modifications for eltrombopag:

Dose level	eltrombopag (mg/day)
+2	300
+1	200
0	100
-1	50
-2	25

4.8.3.1. Starting Dose

The starting dose for all study patients (with the exception of East Asians, see 4.8.3.2.) will be 100mg orally daily. East Asians will start at 50mg orally daily.

4.8.3.2. Dose Adjustments for Platelet Count:

The dose of eltrombopag can be increased every 2 weeks by 100mg until a maximum of 300mg per day has been attained. Dose adjustments will be dependent on each subject's platelet counts; adjusted to maintain an un-transfused platelet count >100 x 10^9/L. Laboratory work including a CBC with differential and blood chemistries must be evaluated weekly for 4 weeks after any change in eltrombopag dosing.

All decisions for dose adjustments of eltrombopag will be made by the MD Anderson treating physician. If needed, additional supplies of eltrombopag may be mailed by the MD Anderson research pharmacy to the patient.

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

4.8.3.3. Dose Adjustments for Subjects of East Asian Ancestry:

The starting dose for patients of East Asian ancestry will be 50mg orally daily. East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) subjects exhibited 50-55% higher eltrombopag plasma concentrations compared to non-East Asian subjects. Dose adjustments for platelet counts will proceed as per 4.8.3.1. regardless of ethnicity.

Dose reductions 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.

4.8.4. Liver Chemistry Stopping and Follow-Up Criteria:

Treatment should be held for any of the following liver chemistry criteria:
1. ALT $\geq$ 5x ULN and bilirubin $\geq$ 2.7x ULN (>35% direct bilirubin)

2. ALT ≥ 8x ULN
3. ALT ≥ 5x ULN but < 8x ULN and persists for ≥ 2 weeks
4. ALT ≥ 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 ≥ 5x ULN but < 8x ULN and cannot be monitored weekly for ≥ 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 ≥ 5x ULN and bilirubin ≥ 2.7x ULN (>35% direct bilirubin), modified Hy's Law for oncology clinical trials[29], must be reported as an SAE.

  NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 5x ULN and bilirubin ≥ 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.

5. STUDY PROCEDURES

5.1 Screening (Visit 1)

The following procedures are performed during screening, staging and workup. 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	History – present illness, prior surgeries, other medical illnesses, review of systems, allergies, prior therapy for cancer and concurrent meds; 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
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
Disease status (IPSS classification and WHO disease classification) Note: Bone marrow aspirate and/or biopsy within 4 weeks prior to first dose of drug in all patients. *Cytogenetics and*	Staging with bone marrow aspiration and/or biopsy for disease assessment.

immunohistochemistries performed as indicated.	
Serum chemistries and iron studies (repeat if screening chemistries completed greater than 72 hours prior to the first dose)	Sodium, potassium, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST and/or ALT, total bilirubin, alkaline phosphatase, uric acid, serum iron, transferrin, transferrin saturation, total iron binding capacity and ferritin.
CBC with differential (repeat if screening test completed greater than 72 hours prior to the first dose)	Differential may be omitted if WBC ≤0.5 $x10^9$/L

5.2 On-Study Procedures

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 (+/- 5 days)	End of Treatment Visit (+/- 5 days)	Safety Visit 28 days after last dose (+/- 28 days)
Informed Consent	X							
Eligibility	X	X						
Medical History	X							
Patient Weight	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	X	X	X	X
CBC with differential	X*	X	X	X	X	X[1]	X	X[2]
Blood Chemistries (AST, ALT, bilirubin)	X*^	X	X	X	X	X[1]	X	X
12-lead EKG	X[a]							
Bone marrow aspiration and/or biopsy	X					X[3]	X	
IPSS score & WHO disease classification	X					X[3]	X	
Pregnancy Test	X†							
Investigational Drug Dispensement		X				X		
AE and SAE assessment	X	X	X	X	X	X	X	X
Optional: Correlative studies[4]	X							

[o]Screening 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, transferrin saturation, total iron binding capacity and ferritiin) must be performed within 72 hours of Cycle 1 Day 1

^Serum iron, transferrin, transferrin saturation, total iron binding capacity and ferritin are required only on Cycle 1 Day 1 and do not need to be repeated
[a]EKG, including QTc intervals, at screening or baseline. A follow-up EKG will be performed if a subject experiences a clinically relevant abnormality.
†Within 7 days of Day 1 in females of child-bearing potential
[1]Weekly CBC with differential and blood chemistries required until stable counts, and weekly x4 weeks after any change in eltrombopag dosing
[2]Weely CBC with differential should be performed weekly for the 4 weeks after discontinuation of eltrombopag
[3]Bone marrow aspiration and/or biopsy with cytogenetics required for study entry, and every cycle for the first 4 cycles for primary outcome, and then every 3 cycles as clinically indicated. Cytogenetics do not need to be repeated if normal at study start.
[4]Optional correlative studies will be performed on bone marrow sample taken at screening. The studies will include an analysis of mutational status of up to 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.

5.3. End of Study Visit:

Subjects will undergo an End of Treatment Visit at the time of discontinuation of eltrombopag. 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 diploid at study start.

5.4. 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.

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 detailed below. Responses must last at least 4 weeks per definition.

Complete Remission:

- Bone marrow: $\leq$ 5% myeloblasts with normal maturation of all cell lines
- Persistent dysplasia will be noted
- Peripheral blood
    - Hemoglobin $\geq$ 11g/dL
    - Platelets $\geq$ 100x10^9/L

- Neutrophils ≥ 1.0x10^9/L
- Blasts 0%

Partial Remission:

- All CR criteria if abnormal before treatment except:
  - Bone marrow blasts decreased by ≥ 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 < 11g/dL)
  - Hemoglobin increase by ≥ 1.5g/dL
  - 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 < 100x10^9/L)
  - Absolute increase of ≥ 30x10^9/L for patients starting with > 20x10^9/L platelets
  - Increase from <20x10^9/L to >20x10^9/L and by at least 100%
- **Neutrophil response** (if pretreatment <1.0 x 10^9/L)
  - At least 100% increase and an absolute increase of >0.5 x 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:
    - At least 50% decrement form maximum response levels in granulocytes or platelets
    - Reduction in hemoglobin by ≥ 1.5g/dL
    - 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
    - Return to pretreatment bone marrow blast percentage
    - Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
    - Reduction in hemoglobin concentration by ≥ 1.5g/dL or transfusion dependence

Cytogenetic Response:

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

Disease Progression:

For patients with:

- Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
- 5-10% blasts: ≥ 50% increase to > 10% blasts
- 10-20% blasts: ≥ 50% increase to >20% blasts
- 20-30% blasts: ≥ 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 $\geq$ 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 events (AEs) will be collected using the Leukemia AE guidelines.

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 Devices". 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).

Only unexpected AEs will be recorded in the Case Report Form (CRF). The Principal Investigator will sign and date the PDMS or CORE Case Report Form toxicity pages per each patient at the completion of each course. Following signature, the Case Report Form will be used as source documentation for the adverse events for attribution.

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. MDACC.

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-threating 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 (Novartis Oncology)

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:

- To evaluate the safety and tolerability of the combination of eltrombopag and decitabine. Safety will be assessed by the overall incidence and severity of all study-treatment related adverse events per CTCAE v 4.0

- To evaluate the incidence of dose reductions and delays of decitabine therapy

- To evaluate the effect of eltrombopag on medically significant hemorrhagic events (defined as Grade 3 or 4 hemorrhagic events on CTCAE v 4.0)

- To evaluate the effect of eltrombopag on platelet and RBC transfusion independence per IWG-2006 criteria
    - Platelet IWG-2006: A complete response is defined as a platelet count > 100 x 10^9/L; and a major response defined as an increase of platelet count by higher than 30 x 10^9/L.
    - Durable platelet count: in which a hematologic improvement in platelets (HI-P) defined as either an increase $\geq$30 x 10^9/L from patients with a baseline platelet count $\geq$20 x 10^9/L, or an increase from <20 x 10^9/L to $\geq$20 x 10^9/L and by at least 100%, present for $\geq$8 weeks.

- Incidence of transformation to AML per FAB criteria (>30% blasts) during treatment period and follow-up

- Incidence and severity of bone marrow fibrosis during treatment period and follow-up

- To examine the relationship between clinical response with ferritin level and other markers of iron burden at study start

6.2.4. Exploratory Endpoints

The following exploratory endpoints and correlative laboratory studies will be examined to determine the in vivo mechanism of action of the therapeutic combination, the biological effects of the combination of decitabine and eltrombopag, as well as to detect whether certain molecular or other genetic patterns can predict response to this combination:

- Genetic analysis of the mutational status of up to 53 genes known to be affected in myelodysplastic syndromes and acute leukemias prior to study start, performed through the molecular diagnostics laboratory of MD Anderson. Any remaining sample may be banked for additional future scientific research.

- Gene expression profiling and gene-specific DNA methylation may be performed in the pretreatment samples. DNA methylation is assessed using bisulfite PCR assays (i.e. COBRA or pyrosequencing analysis) and gene expression profiling by real-time PCR analysis.

6.3 Subsets

6.3.1. Full Analysis Set

The full analysis set will consist of all enrolled subjects. 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 28-day 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 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 Oncologybefore 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 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 documents submitted to Novartis Oncology, subjects should be identified by their 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 "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to , 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

This is an open label, phase II clinical trial to evaluate the efficacy of eltrombopag in combination with decitabine as a frontline therapy in patients with Intermediate-2 or High-Risk Myelodysplastic Syndrome (MDS). A total of 40 patients will be accrued from M.D. Anderson Cancer Center (MDACC), at a rate of 2-3 patients per month.

The primary endpoint is the overall response rate (ORR) based on the IWG-2006 criteria, which includes complete remission (CR), partial remission (PR), and hematologic improvement (HI). Patients' overall response will be assessed during the first four 28-day cycles of treatment. Patients who drop off the study early due to treatment-related toxicities will be counted as treatment failures (i.e., non-responders).

The method of Thall, Simon and Estey [1995] will be used for futility and toxicity monitoring for this study. The target overall response rate is 60% and the following futility stopping rule will be applied in cohort size of 10, starting from the 10^{th} patient: prob{p(ORR)< 0.6) > 0.95, where p(ORR) denotes the overall response rate. That is, the trial will be stopped early due to futility, if during the study we determine that there is more than 95% chance that the ORR is less than 60%. Assuming that the prior distribution of p(ORR) is beta (1.2, 0.8), the stopping boundaries corresponding to this futility monitoring rule are shown below in Table 1. The operating characteristics (OCs) for this futility stopping rule are summarized in Table 2. The design software Multc Lean Desktop (version 1.2.0) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the futility stopping boundaries and the

OC table. In order to utilize the software for the design, a highly informative beta (600, 400) prior was assumed to approximate the target 60% overall response rate.

Table 1. Futility stopping boundaries in cohort size of 10.

Number of patients	Stop the trial if there are this many patients achieving overall response
10	0-3
20	0-8
30	0-13

Table 2. Operating characteristics for futility monitoring in cohort size of 10 (max sample size = 40).

True ORR	Prob(stop the trial early due to futility)	Average sample size
0.3	0.971	14.8
0.4	0.775	22.0
0.5	0.391	31.3
0.6	0.105	37.5
0.7	0.015	39.6

Toxicity monitoring will be conducted in cohort size of 5, starting from the 5th patient. Denote the probability of toxicity by p(T), where toxicity is defined as any grade 3-4 clinically relevant non-hematologic toxicity or a serious adverse event that is felt to be drug related (Common Terminology Criteria for Adverse Events CTCAE version 4.0). We assume as a priori, p(T) ~ beta (0.6, 1.4). The trial will be stopped if Pr(p(T)> 0.30 | data) >0.90. That is, we will stop the trial for new patient enrollment if at any time during the study we determine that there is more than 90% chance that the toxicity rate is more than 30%. Stopping boundaries corresponding to this toxicity monitoring rule are shown in Table 3 below. The operating characteristics for toxicity monitoring are summarized in Table 4. Again, Multc Lean Desktop (version 1.2.0) was used to generate the toxicity stopping boundaries and the OC table and a highly informative beta (300,700) prior was assumed to approximate the fixed 30% toxicity rate.

Table 3. Toxicity stopping boundaries in cohort size of 5.

Number of patients	Stop the trial if there are this many patients having toxicities
5	4-5
10	6-10
15	8-15
20	9-20
25	11-25
30	13-30
35	15-35

Table 4. Operating characteristics for toxicity monitoring in cohort size of 5 (max sample size = 40).

True toxicity rate	Prob(stop the trial early)	Average sample size
0.10	0.0006	40.0
0.20	0.020	39.4
0.30	0.186	35.8
0.40	0.583	26.8
0.50	0.905	17.3

The PI and the study statistician will review the efficacy and toxicity data quarterly in order to determine whether the stopping boundaries have been crossed.

8.1 Analysis Plan

The primary endpoint is overall response rate (ORR). The ORR will be estimated along with the exact 95% confidence interval. Secondary endpoints include incidence of dose reductions and delays of decitabine therapy, hemorrhagic events (defined as Grade 3 or 4 hemorrhagic events on CTCAE v 4.0), platelet and RBC transfusion independence per IWG-2006 criteria, transformation from MDS to AML, Incidence and severity of bone marrow fibrosis. Descriptive statistics will be used to summarize all secondary endpoints. The incidence rates of binary secondary endpoints will be estimated, along with the exact 95% confidence intervals.

The probabilities of time-to-event outcomes (such as time to transformation from MDS to AML and time to developing BM fibrosis) will be estimated using the method of

Kaplan and Meier. Log-rank tests will be used to compare the time-to-event outcomes among subgroups of patients.

8.2. 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.

8.3. Analysis of Key Study Endpoints

The primary endpoint is overall response rate (ORR). The ORR will be evaluated along with the exact 95% confidence interval. 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 7 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. 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.

References:

1. Doll DC, List AF: Myelodysplastic syndromes. West J Med 151:161-7, 1989
2. Albitar M, Manshouri T, Shen Y, et al: Myelodysplastic syndrome is not merely "preleukemia". Blood 100:791-8, 2002
3. Dansey R: Myelodysplasia. Curr Opin Oncol 12:13-21, 2000
4. List AF: New agents in the treatment of MDS. Clin Adv Hematol Oncol 3:832-4, 2005
5. Ma X, Does M, Raza A, et al: Myelodysplastic syndromes: incidence and survival in the United States. Cancer 109:1536-42, 2007
6. Kadia TM, Jabbour E, Kantarjian H: Failure of hypomethylating agent-based therapy in myelodysplastic syndromes. Semin Oncol 38:682-92, 2011
7. Garcia-Manero G, Gore SD: Future directions for the use of hypomethylating agents. Semin Hematol 42:S50-9, 2005
8. Prebet T, Gore SD, Esterni B, et al: Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol 29:3322-7, 2011
9. Kantarjian H, Oki Y, Garcia-Manero G, et al: Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood 109:52-7, 2007
10. Steensma DP, Baer MR, Slack JL, et al: Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol 27:3842-8, 2009
11. Lee JH, Jang JH, Park J, et al: A prospective multicenter observational study of decitabine treatment in Korean patients with myelodysplastic syndrome. Haematologica 96:1441-7, 2011
12. Kantarjian H, Giles F, List A, et al: The incidence and impact of thrombocytopenia in myelodysplastic syndromes. Cancer 109:1705-14, 2007
13. Kantarjian H, O'Brien S, Ravandi F, et al: Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. Cancer 113:1351-61, 2008
14. Germing U, Hildebrandt B, Pfeilstocker M, et al: Refinement of the international prognostic scoring system (IPSS) by including LDH as an additional prognostic variable to improve risk assessment in patients with primary myelodysplastic syndromes (MDS). Leukemia 19:2223-31, 2005
15. Kuter DJ: Thrombopoietin and thrombopoietin mimetics in the treatment of thrombocytopenia. Annu Rev Med 60:193-206, 2009
16. Cheng G, Saleh MN, Marcher C, et al: Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 377:393-402, 2011
17. Saleh MN, Bussel JB, Cheng G, et al: Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood 121:537-45, 2013
18. McHutchison JG, Dusheiko G, Shiffman ML, et al: Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. N Engl J Med 357:2227-36, 2007
19. Kuter DJ: What is the potential for thrombopoietic agents in acute leukemia? Best Pract Res Clin Haematol 24:553-8, 2011
20. Roth M, Will B, Simkin G, et al: Eltrombopag inhibits the proliferation of leukemia cells via reduction of intracellular iron and induction of differentiation. Blood 120:386-94, 2012

21. Mavroudi I, Pyrovolaki K, Pavlaki K, et al: Effect of the nonpeptide thrombopoietin receptor agonist eltrombopag on megakaryopoiesis of patients with lower risk myelodysplastic syndrome. Leuk Res 35:323-8, 2011

22. Will B, Kawahara M, Luciano JP, et al: Effect of the nonpeptide thrombopoietin receptor agonist Eltrombopag on bone marrow cells from patients with acute myeloid leukemia and myelodysplastic syndrome. Blood 114:3899-908, 2009

23. Olnes MJ, Scheinberg P, Calvo KR, et al: Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N Engl J Med 367:11-9, 2012

24. Mittelman M, Assouline S, Briasoulis E, et al: Eltrombopag Treatment of Thrombocytopenia in Advanced Myelodysplastic Syndromes and Acute Myeloid Leukemia: Results of the 8-Week Open-Label Part of an Ongoing Study. ASH Annual Meeting Abstracts 120:3822-, 2012

25. Oliva EN, Santini V, Zini G, et al: Efficacy and Safety of Eltrombopag for the Treatment of Thrombocytopenia of Low and Intermediate-1 IPSS Risk Myelodysplastic Syndromes: Interim Analysis of a Prospective, Randomized, Single-Blind, Placebo-Controlled Trial (EQoL-MDS). ASH Annual Meeting Abstracts 120:923-, 2012

26. Frey NV, Hexner EO, Porter DL, et al: A Phase I Clinical Trial Using Eltrombopag in Patients with Acute Myelogenous Leukemia. ASH Annual Meeting Abstracts 120:3576-, 2012

27. Allred AJ, Bowen CJ, Park JW, et al: Eltrombopag increases plasma rosuvastatin exposure in healthy volunteers. Br J Clin Pharmacol 72:321-9, 2011

28. Eltrombopag Prescribing Information, 2013, pp Investigational Brochure

29. Parks D, Lin X, Painter JL, et al: A proposed modification to Hy's law and Edish criteria in oncology clinical trials using aggregated historical data. Pharmacoepidemiol Drug Saf, 2013