ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY

MONTEFIORE MEDICAL CENTER

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Protocol Title: PHASE II STUDY OF LENALIDOMIDE AND ELTROMBOPAG IN PATIENTS WITH SYMPTOMATIC ANEMIA IN LOW OR INTERMEDIATE I MYELODYSPLASTIC SYNDROME (MDS)

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator	Date
Printed Name of Investigator	

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

STUDY PERSONNEL

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1 PROTOCOL SYNOPSIS

PROTOCOL TITLE:PHASE II STUDY OF LENALIDOMIDE AND ELTROMBOPAG IN PATIENTS WITH SYMPTOMATIC ANEMIA IN LOW OR INTERMEDIATE I MYELODYSPLASTIC SYNDROME (MDS)	
DATE PROTOCOL FINAL:	***08 JULY 2011***
INDICATION:	MDS
STUDY PHASE:	Phase II

BACKGROUND AND RATIONALE: The rationale for this studyis that combined treatment with eltrombopag (PROMACTA) and lenalidomide (REVLIMID) will reduce the incidence of lenalidomide induced thrombocytopenia thus enabling patients to tolerate the required duration of lenalidomide therapy leading to higher rates of response to lenalidomide. A major reason why lenalidomide cannot be used for the treatment of MDS is because of the occurrence of thrombocytopenia. The use of eltrombopag will potentially raise platelet counts in these patientsand enable a longer exposure to lenalidomide. Secondly, thrombocytopenia in the first 2 months after lenolidomide therapy predicts the subsequent response to lenalidomide treatment in patients with low risk MDS Thus raising platelet counts to enable continuation of Lenalidomide therapy is important in these patients. Lastly, an increase in blasts has been a potential concern with the use of thrombopoietin mimetics. Preclinical studies have indicated that eltrombopag is less likely to increase blasts thus making it a possible potential therapeutic candidate in low risk MDS.

STUDY OBJECTIVES:

Primary Objectives:

To evaluate the rate of hematologic improvement of the eltrombopag/lenalidomide combination as defined by the IWG 2006 criteria
To evaluate the safety and tolerability of the eltrombopag/lenalidomide combination in patients with low –intermediate risk MDS

Secondary Objectives

To compare the time to hematologic improvement
To evaluate the duration of hematologic improvement
To evaluate the effect of combination treatment on platelet counts, platelet transfusions.and bleeding events.
To evaluate the frequency of bone marrow response (CR+PR) and cytogenetic response.
To evaluate the relationship between mutations in bone marrow stem cells and response
To evaluate the relationship between various stem and progenitor alterations and response

STUDY DESIGN:

This is a multicenter, phase II study evaluating the efficacy and safety of the combination of lenalidomide and eltrombopag in low risk MDS.

Patients will be treated based on their baseline platelet counts:

Arm A: Patients with platelet counts >=50k at baseline:
These patients will start Len at 10mg/d for 3 weeks/month, and will not start eltrombopag until the platelet counts drop below 50,000. If platelets drop less than 50,000, Len will be stopped and eltrombopag will be started at a dose of 100mg initially (50 mg for subjects of East Asian heritage) and titrated up to a maximum dose of 300 mg (150 mg for subjects of East Asian heritage) to achieve a platelet count above 50,000/L. Once a platelet count above 50,000 is achieved, the same dose of eltrombopag will be continued for an additional two weeks. Once a platelet count > 50,000 is maintained for two weeks, eltrombopag will be discontinued and Len will be started as a single agent. If the platelets again fall below 50,000 then Len will stopped and eltrombopag will be re-initiated at the dose that was last given to the patient. Once the platelets are increased to above 50,000 and maintained at this level for 2 weeks, Len will be started again and this time will be given concurrently with eltrombopag. These agents will subsequently be used concurrently for all subsequent cycles.

Arm B: Patients with Plts <50k at baseline
These patients will not receive Len initially. Eltrombopag will be started alone at a dose of 100mg initially and titrated up (Table 4) to achieve a platelet count above 50,000. Once the platelet count above 50,000 is achieved, the same dose of eltrombopag will be continued for an additional two weeks. Once the plt count > 50,000 is maintained for two weeks, the patients will discontinue eltrombopag and follow the treatment algorithm described for patients in arm A.

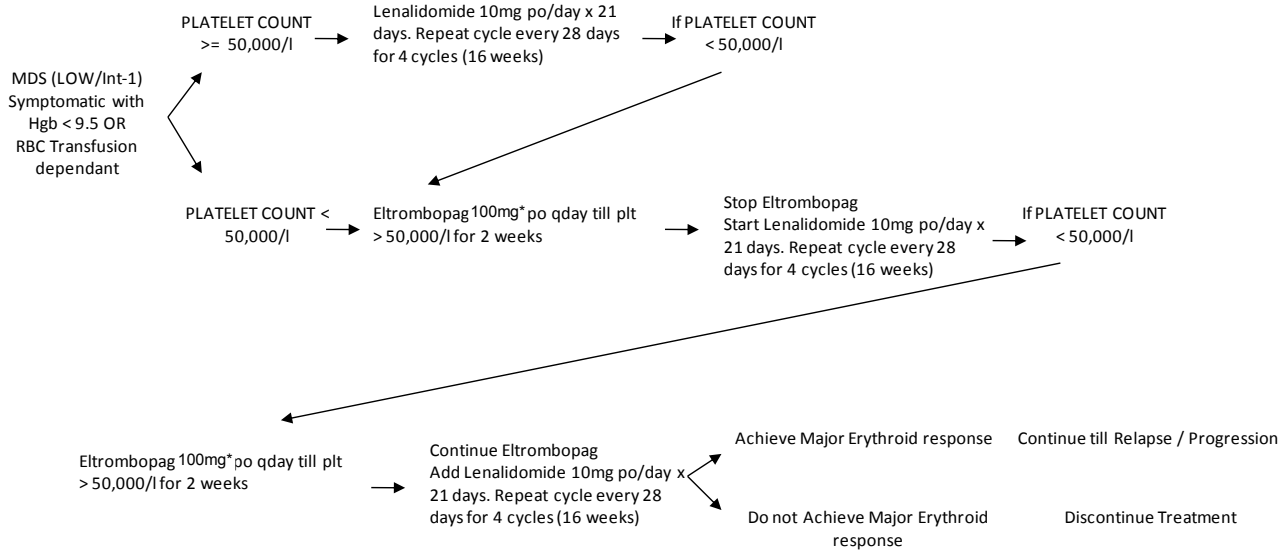


Figure 1: Schema of the study (* starting dose of Eltrombopag for Asian subjects is 50mg)

STUDY ENDPOINTS

Primary:

Hematologic improvement

Secondary: Time to attain and duration of hematologic improvement Bone marrow morphologic and cytogenetic response Platelet counts and Bleeding events	
STUDY DURATION:2 years	**TOTAL SAMPLE SIZE:**52patients
DOSING REGIMEN(S): The lenalidomide starting dose will be based on baseline calculated creatinine clearance (see Appendix 3). Eltrombopag starting dose will be 100mg (50mg for patients with east Asian descent) and dosing will be based on regimen as detailed in protocol.	**DRUG SUPPLIES:** For study participants, Celgene Corporation will provide lenalidomide at no charge through the Revlimid REMS™program. GSK will provide eltrombopag at no charge.

2 SCHEDULE OF STUDY ASSESSMENTS

	Screening Assessment (30 days prior to initiation)	Weekly	Every 28 days (Day 1 of each cycle)	Week 16 and treatment discontinuation	Follow up [11]
Medical History	x				
Prior MDSTreatment	x				
ECOG Performance Status	x	X[8]	x		
Pregnancy test [1]	x [2]		x[3]	X	
Serum ferritin level	x			X	
Serum erythropoietin	x				
Thyroid function tests [4]	x			X	
aaPT/PTT/INR	x				
Serum chemistry [5]	x	X[8]	x	X	
Hematology, peripheral blood smear and RBC transfusion history [6]	x [7]	x[8]	x	X	x
Physical examination	x		x	x	**x**
ECG	x	x [12]			
Review medication log			x		
Response				x	

assessment [9]					
Bone marrow aspirate & biopsy[10]	x			x	
Cheek swab and toe nail clipping	x				

1. Women of childbearing potential only. Serum or urine pregnancy testing for β-HCG with a sensitivity of at least 50 mIU/mL. For further requirements for pregnancy testing and birth control, please see Appendix 1.

2. Within 7 days prior to the first day of study therapy.

3. Every 4 weeks while on study drug.

4. TSH (thyroid-stimulating hormone), T3, and T4 levels. Repeat thyroid function tests every three months.

5. Includes sodium, potassium, chloride, CO2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate transaminase (SGOT/AST) or glutamic pyruvic transaminase (SGPT/ALT), lactate dehydrogenase (LDH), and uric acid.

6. Red blood cell (RBC) count, reticulocyte count, hemoglobin, hematocrit, white blood cell (WBC) count and differential, absolute neutrophil count (ANC), and platelet count required for protocol therapy must be done < 24 hours prior to the treatment cycle. Pretreatment CBC with differential and LFT's should be done < 1 week before randomization.

7. If not obtained within 7 days of the first day of study therapy, repeat the CBC on Day 0 of study treatment prior to start of study therapy.

8. Perform weekly for 4 weeks, then every 2 weeks for 5 to 8 weeks and monthly thereafter. Weekly CBC should be done when titrating or starting eltrombopag dosing until a stable platelet count is achieved.

9. Hematologic, pathologic, and cytogenetic response will be assessed according to criteria outlined in Section 6.1.2.

10. Bone marrow aspirate and biopsy with cytogenetic analysis and iron stains will be performed pre-study, and after 16 weeks of study treatment, and at the time of final response analysis. Additional biological studies obtained with bone marrow aspiration

are summarized in Section 14.
11. Every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, every 12 months if patient is 5-10 years from study entry. No specific requirements if patient is more than 10 years from study entry.
12. Only for patients receiving 300 mg eltrombopag dose or higher, resting 12-lead ECG will be obtained pre-dose on Day 1. A post-dose ECG should be obtained at Tmax (3 hours); if assessment cannot be performed at 3 hours, record actual time ECG was performed within a 2-6 hour window post-dose. A pre- and post-dose ECG as described above is required Week 2, week 4, 8 and 16.

3 BACKGROUND AND RATIONALE

3.1 Hypothesis

Combined treatment with eltrombopag (EP) and lenalidomide (CC-5013;REVLIMID) will reduce the incidence of thrombocytopenia due to Lenalidomide and enable patients to tolerate duration of therapy leading to higher rates of response.

3.2 Treatment of Thrombocytopenia in MDS or sAML/MDS

In a review of patients with MDS referred to the M. D. Anderson Cancer Center, the incidence of life-threatening thrombocytopenia was 16-40% depending on the MDS risk status, with a median survival of only 6 to 12 months. The incidence of thrombocytopenia increases with disease progression, and without effective therapies, some patients may experience life-threatening bleeding(1)
In MDS, the disease clone includes the megakaryocytic lineage. Megakaryocytes from patients with MDS show impaired proliferation and differentiation, thus causing thrombocytopenia (2). Additional aspects potentially contributing to thrombocytopenia in MDS are premature cell death of megakaryocytes and decreased platelet life span(3). Interestingly, these aspects can be observed in both patients with MDS, and patients with Idiopathic Thrombocytopenic Purpura (ITP). In MDS, the megakaryocytic proliferation is unresponsive to recombinant thrombopoietin (TPO), possibly due to deregulated TPO-receptor-mediated signaling(4) . In addition to the qualitative disturbance of the TPO-receptor, there is also a quantitative disturbance in terms of the number of TPO receptors, which show a reduced expression by 50% on MDS platelets, as well as on CD41+ and CD34+ cells as compared to normal cells. However, an in vitro study showed that CD61+ cells in suspension cultures increased with PEG-rHuMGDF (pegylated recombinant human MGDF)alone in 31 out of 39 patient samples from MDS patients (5). The clinical development of PEG-rHuMGDF was aborted owing to the development of cross-reacting autoantibodies against endogenous TPO. More recently, Phase II data were presented for another TPO-R agonist, romiplostim, which showed efficacy in 41% of the patients with low- or intermediate-1 risk MDS (6) However, few patients showed some direct or indirect evidence for disease progression [FDA Oncology Drug Advisory Committee Meeting, March 2008].

3.3 Treatment of Thrombocytopenia in MDS or sAML/MDS with Eltrombopag

Eltrombopag is an orally available, non-peptide TPO-receptor (TPO-R) agonist that stimulates platelet production by a mechanism similar, but not identical to endogenous TPO. Eltrombopag has been investigated at dose ranges of up to 200 mg daily for 5 days in healthy volunteers, and a dose-platelet response relationship was observed. In ITP, patients received up to 75 mg daily, and response rates were 28% with 30 mg, 67% with 50 mg, and 86% with 75 mg (response defined as a platelet count >50 Gi/L; the studied patients had platelet counts <30 Gi/L). The safety profile was similar to placebo (7). The positive results with eltrombopag in ITP are encouraging but the required dose and response in MDS are unknown. A phase I/II study in high risk MDS is presently evaluating the efficacy of eltrombopag at different doses with dose escalations of up to 300 mg.

It is theoretically possible that eltrombopag could worsen the disease in patients with MDS. However, in vitro preclinical studies in leukemia and lymphoma cell lines indicate that eltrombopag does not stimulate leukemia cell growth. In contrast to TPO, it may in fact suppress leukemic cell growth, as evidenced by the fact that 12 out of 14 leukemic/lymphoid cell lines tested demonstrated decreased proliferation when treated with eltrombopag, with an IC_{50} of 0.5 to 15 μg/mL. This effect occurs even in the presence hematopoietic cytokines. (8-11). There is additional evidence from an ex vivo study indicating that eltrombopag does not stimulate leukemic cell growth. In 7 out of 7 BM specimens taken from patients with MDS or AML secondary to MDS, no increase in proliferation due to co-incubation with eltrombopag was seen (12).

3.4 Lenalidomide can result in transfusion independence in MDS but leads to a high rate of thrombocytopenia

Ineffective erythropoiesis remains the hallmark of myelodysplastic syndromes (MDS) forwhich few treatments offer sustained erythropoietic improvement (13). Lenalidomide) (CC-5013; REVLIMID⁄) is an oral 4-amino glutarimide derivative of thalidomide that lacks the neurological toxicities of the parent compound. In a safety and efficacy study (MDS-001) investigating erythroid response to CC-5013 (lenalidomide) monotherapy in 43 patients with MDS, CC-5013 (lenalidomide) yielded a high frequency of major erythroid response (MER) in patients that had either failed prior treatment with erythropoietin or had high endogenous levels and high transfusion burden (14). Patients received treatment with one of three CC-5013 (lenalidomide) dose schedules, 25 or 10 mg daily, or 10 mg/day x 21 days every 4 weeks. Neutropenia (67%) and thrombocytopenia (57%) > grade 3 NCI-CTC version 2.0 were dose limiting, necessitating treatment interruption and dose-reduction in 25 (61%) patients. Other adverse effects were infrequent and of mild to moderate severity including pruritus, fatigue, diarrhea, edema,thyroid dysfunction and joint discomfort. Among the 36 patients completing more than one cycle of treatment, 24 (67%) experienced an erythroid response according to International Working Group (IWG) criteria. MER defined by sustained transfusion-independence (> 8 weeks) or a rise in hemoglobin >2 g/dl was achieved in 21 patients and 3 patients experienced a >50% reduction in red blood cell

(RBC) transfusions. Response rate was highest among evaluable patients with a chromosome 5q31.1 deletion (91%) compared tothose with a normal karyotype (68%) or other chromosome abnormality (17%) [P=0.009],and response rate was higher in patients with lower (Low-/Intermediate-1) InternationalPrognostic Scoring System (IPSS) risk categories (72% vs. 25%) [*P*=0.098] (15). Eleven of17 (65%) patients with karyotypic abnormalities had a 50% or greater reduction in abnormalmetaphases, including ten (57%) complete cytogenetic remissions. After a median follow-upof 109 weeks in November 2004, median duration of transfusion-independence had notbeen reached (81+; range, 19 to >128 weeks) with a median sustained hemoglobin (Hgb) of13.4 g/dL (range, 11.5-15.8 g/dL) and median Hgb rise of 5.6 g/dL. The results of this studyindicate that CC-5013 (lenalidomide) has significant and sustained erythropoietic andcytogenetic remitting activity in patients with Low/Intermediate-1 IPSS risk MDS that havefailed or are unlikely to benefit from conventional cytokine therapy.Two phase II multicenter trials were completed in the past year, evaluating the frequency ofMER to lenalidomide in patients with transfusion-dependent Low/Int-1 risk MDSwith (MDS-003; N=148) or without a chromosome 5q31.1 deletion (MDS-002; N=215).Intent-to-treat analysis of the data confirm the high response rate in patients with del 5q31.1(MER 66%, MER + Minor erythroid response 75%, cytogenetic response 70%) compared toa MER rate of 27% and Minor + MER rate of 44% in the MDS-002 results (15, 16). Grade 3or greater neutropenia or thrombocytopenia were the principal reasons for treatment interruption and dose-reduction.

3.5 Rationale for combining lenalidomide and eltrombopag:

The rationale for combination is based on the following:

1. A major reason why lenalidomide cannot be used in MDS is because of the occurrence of thrombocytopenia. The use of EP will potentially raise platelet counts in these patients.

2. Thrombocytopenia in the first 2 months after Len therapypredicts the subsequent response to lenalidomide treatment in patients with low risk MDS (17)Thus raising platelet counts to enable continuation of lenalidomide therapy is important in these patients.

3. An increase in blasts has been a potential concern with the use of thrombopoietin mimetics and has been reported in a study with romiplostim (6) Preclinical studies have indicated that eltrombopag is less likely to increase blasts thus making it a possible potential therapeutic candidate in low risk MDS(12).

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objectives

- To evaluate the rate of hematologic improvement of the eltrombopag/lenalidomide combination (as per Modified IWG criteria)
- To evaluate the safety and tolerability of the combination

4.1.2 Secondary Objectives

- To compare the time to hematologic improvement
- To evaluate the duration of hematologic improvement
- To evaluate the effect of combination treatment on platelet counts, platelet transfusions.and bleeding events.
- To evaluate the frequency of bone marrow response (CR+PR) and cytogenetic response.
- To evaluate the relationship between mutations in bone marrow stem cells and response
- To evaluate the relationship between various stem and progenitor alterations and response

5 INVESTIGATIONAL PLAN

5.1 Overall design

This is a multicenter, Phase II study evaluating the efficacy and safety of the combination of lenalidomide and eltrombopag in low risk MDS. This study will include patients with low risk MDS (IPSS low and Int-1) with symptomatic anemia or transfusion dependence. Patients will be treated in 2 separate arms based on their baseline platelet counts:

Arm A : Patients with platelet counts >=50k at baseline:
These patients will start Len at 10mg/d for 3 weeks/month, and will not start Eltrombopag until the platelet counts drop below 50,000. If platelets drop less than 50,000, Len will be stopped and Eltrombopag will be started at a dose of 100mg initially and titrated up (similar schema to 509 study) to achieve a platelet count above 50,000. Once the platelet count above 50,000 is achieved, the same dose of Eltrombopag will be continued for an additional two weeks. Once a platelet count > 50,000 is maintained for two weeks, Eltrombopag will be discontinued and Len will be started as a single agent. If the plts again fall below 50k then Len will stopped and Eltrombopag will be re-initiated at the dose that was last given to the patient. Once the platelets are increased to above 50,000 and maintained at this level for 2 weeks, Len will be started again and this time will be given concurrently with Eltrombopag. These agents will now be used concurrently for all subsequent cycles.

Arm B: Patients with Plts <50k at baseline
These patients will not receive Len initially. Eltrombopag will be started alone at a dose of 100mg initially and titrated up (similar schema to 509 study) to achieve a

platelet count above 50,000. Once the platelet count above 50,000 is achieved, the same dose of eltrombopag will be continued to additional two weeks. Once the plt count > 50,000 is maintained for two weeks, the patients will discontinue eltrombopag and follow the treatment algorithm described for patients in arm A. Patients that never drop their platelet counts below 50,000 will not receive any additional eltrombopag. (Figure 1)

Treatment with myeloid growth factors is permittedfor the management of neutropenia atthe discretion of the treating investigator.

Study drugs will be continued until disease progression or unacceptable toxicities.

Bone marrow examinations will be performed at baseline, at every 4 months and at study discontinuation.

52 evaluable adult subjects with MDS will be evaluated.

5.2 Protocol Therapy

5.2.1 Lenalidomide Description

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide

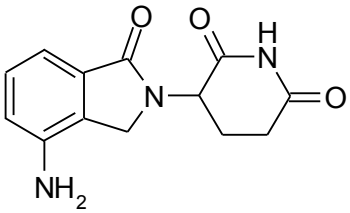


Figure 2: Structure of lenalidomide: 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions.(18, 19) Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

Pharmacokinetics and Drug Metabolism:

Absorption: Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). No plasma accumulation was observed with multiple daily dosing. Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters:

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

As the majority of lenalidomide is excreted unchanged by the kidney (where OATP1B1 and BCRP are not involved in xenobiotic excretion), no pharmacokinetic interactions between lenalidomide and eltrombopag are expected.

Supplier(s)

Celgene Corporation will supply Revlimid®(lenalidomide) to study participants at no charge through the Revlimid REMS™program.

Dosage form

Lenalidomide will be supplied as capsules for oral administration.

Packaging

Lenalidomide will be shipped to the clinic site for IND studies. Bottles will contain a sufficient number of capsules for one cycle of dosing**.**

Storage

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

Prescribing Information

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Revlimid REMS™program of Celgene Corporation. Per standard Revlimid REMS™requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS™program.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle**.

Pregnancy Testing

Must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.

5.2.2 Eltrombopag Description

Promacta® (Eltrombopag),is an agonist of the thrompoietin receptor that stimulates platelet production. The chemical name is 3'-(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo- 1,5-dihydro-4H-pyrazol-4-ylidene] hydrazino-2'-hydroxy-3-biphenylcarboxylic acid -2-aminoethanol and it has the following chemical structure:

Chemical Structure of Eltrombopag

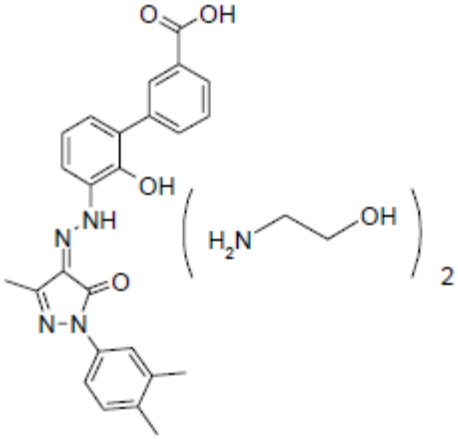


Figure 3: Eltrombopag (3'-(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene] hydrazino-2'-hydroxy-3-biphenylcarboxylic acid -2-aminoethanol)

The empirical formula for eltrombopag is C25 H22 N4 O4 . 2 (C2 H7 N O) and its molecular weight is 564.65.

Eltrombopag is ared/brown solid and is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Eltrombopag olamine, the bis-monoethanolamine salt form of eltrombopag, is an orallybioavailable, small molecule thrombopoietin receptor (TPO-R) agonist. Eltrombopagfunctions in a similar manner to endogenous thrombopoietin (TPO), inducingproliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

Pharmacokinetics and Drug Metabolism:

Absorption and Bioavailability
Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oraladministration. Administration of eltrombopag concomitantly with antacids and otherproducts containing polyvalent cations such as dairy products and mineral supplementssignificantly reduces eltrombopag exposure.The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52 %.

Distribution
Eltrombopag is highly bound to human plasma proteins (> 99.9 %). Eltrombopag is asubstrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Metabolism

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation withglucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopagaccounted for approximately 64 % of plasma radiocarbon AUC0-∞. Minor metabolites,each accounting for < 10 % of the plasma radioactivity, arising from glucuronidation andoxidation were also detected. Based on a human study with radiolabel eltrombopag, it isestimated that approximately 20 % of a dose is metabolised by oxidation. *In vitro* studiesidentified CYP1A2 and CYP2C8 as the isoenzymes responsible for oxidativemetabolism, uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 as theisozymes responsible for glucuronidation, and that bacteria in the lower gastrointestinaltract may be responsible for the cleavage pathways.

Elimination

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59 %) with 31 % of the dose found in the urine asmetabolites. Unchanged parent compound (eltrombopag) is not detected in urine.Unchanged eltrombopag excreted in faeces accounts for approximately 20 % of the dose.The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Special Patient Populations

Renal Impairment

The pharmacokinetics of eltrombopag has been studied after administration ofeltrombopag to adult patients with renal impairment. Following administration of a single50 mg-dose, the AUC0-∞of eltrombopag was decreased by 32 % (90 % CI: 63 %decrease, 26 % increase) in patients with mild renal impairment, 36 % (90 % CI: 66 %decrease, 19 % increase) in patients with moderate renal impairment, and 60 % (90 % CI:18 % decrease, 80 % decrease) in patients with severe renal impairment compared withhealthy volunteers. There was a trend for reduced plasma eltrombopag exposure inpatients with renal impairment, but there was substantial variability and significantoverlap in exposures between patients with renal impairment and healthy volunteers.Patients with impaired renal function should use eltrombopag with caution and closemonitoring.

Hepatic Impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with liver cirrhosis (hepatic impairment). Following theadministration of a single 50 mg dose, the AUC0-∞of eltrombopag was increased by 41 %(90 % CI: 13 % decrease, 128 % increase)in subjects with mild hepatic impairment, 93 %(90 % CI: 19 %, 213 %) in subjects with moderate hepatic impairment, and 80 % (90 %CI: 11 %, 192 %) in subjects with severe hepatic impairment compared with healthyvolunteers. There was substantial variability and significant overlap in exposures betweensubjects with hepatic impairment and healthy volunteers.The influence of hepatic impairment on the pharmacokinetics of eltrombopag followingrepeat administration was evaluated using a population pharmacokinetic analysis in 28healthy adults and 79

patients with chronic liver disease. Based on estimates from thepopulation pharmacokinetic analysis, patients with liver cirrhosis (hepatic impairment)had higher plasma eltrombopag AUC(0-τ) values as compared to healthy volunteers, andAUC(0-τ) increased with increasing Child-Pugh score. Compared to healthy volunteers,patients with mild hepatic impairment had approximately 87 % to 110 % higher plasmaeltrombopag AUC(0-τ) values and patients with moderate hepatic impairment hadapproximately 141 % to 240 % higher plasma eltrombopag AUC(0τ) values.Patients with liver cirrhosis (hepatic impairment) should use eltrombopag with cautionand close monitoring.

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag wasevaluated using a population pharmacokinetic analysis in 111 healthy adults (31 EastAsians) and 88 patients with ITP (18 East Asians). Based on estimates from thepopulation pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese andKorean) ITP patients had approximately 87 % higher plasma eltrombopag AUC(0-τ)values as compared to non-East Asian patients who were predominantly Caucasian,without adjustment for body weight differences.

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using apopulation pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patientswith ITP (57 females). Based on estimates from the population pharmacokineticanalysis, female ITP patients had approximately 50 % higher plasma eltrombopagAUC(0-τ) as compared to male patients, without adjustment for body weight differences.

Supplier(s)

GSK will supply eltrombopag for study participants at no charge.

Dosage form

Eltrombopag will be supplied as tablets for oral administration.

Packaging and Labeling

The tablets will be packaged in white opaque, HDPE bottles with child resistantclosures. The contents of the label will be in accordance with all applicable regulatory requirements.
Tablets will be provided to the sponsor-investigator by GSK. The tablets provided would be as follows: 25mg, 50mg, 75mg and 100mg SB497115: A white to off-white 13/32" standard round tablet

Pharmaceutical Information

GlaxoSmithKline Document Number UM2005/00217/05. Clinical Investigator’s

Brochure for SB496115-GR. Version 07. Effective date March 03, 2010.

6 SCREENING AND ELIGIBILITY

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Schedule of Study Assessments and unless otherwise specified, must take place within 28 days prior to initiation of therapy.

Approximately 52 subjects with Low / Int-1 MDS will be screened for enrollment and must meet the eligibility criteria below.

6.1 Inclusion Criteria

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

1 Age ≥ 18 years.

2. Patient must have a documented diagnosis of MDS according to World Health Organization (WHO) criteria (see Appendix IV) or non-proliferative chronic myelomonocytic leukemia (CMML) (WBC ≤ 12,000/ul).

3. Patients must have International Prognostic Scoring System (IPSS) categories ofLow- or Intermediate-1-risk disease (see Appendix 4).

4.Patients must have symptomatic anemia untransfused with hemoglobin ≤ 10.0g/dLwithin 8 weeks of registration or with RBC transfusion-dependence (i.e., ≥ 2 units/month) confirmed for a minimum of 8 weeks before randomization. Or patients have platelet <50,000/uL with hemoglobin > 10.0 g/dL.

5. Patients must have IPSS score determined by cytogenetic analysis prior to randomization. Patients with cytogenetic failure and ≤ 10% marrow blasts will be eligible.

6. Patients must be off all disease modifying therapy for MDS for 28 days prior to initiation of study treatment. Patients may receive hydrocortisone prophylactically to prevent transfusion reactions.

7. Patients must not have documented iron deficiency. All patients must havedocumented marrow iron stores. If marrow iron stain is not available, thetransferrin saturation must be ≥ 20% or a serum ferritin ≥ 100 ng/100 mL or soluble transferring receptor < 5mg/L.

8. Women must not be pregnant or breastfeeding. Females of childbearing potentialshould have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL). The

firsttest should be performed within 10-14 days, and the second test within 24 hoursprior to prescribing lenalidomide.

9.Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).

10. Women of childbearing potential and sexually active males must agree to use 2methods of an accepted and effective method of contraception and counseled onthe potential teratogenic effects of lenalidomide. Effective contraceptionmust be used by patients for at least 4 weeks before beginning lenalidomide therapy, during lenalidomide therapy, during doseinterruptions and for 4 weeks following discontinuation of lenalidomidetherapy. Reliable contraception is indicated even where there has been a history ofinfertility, unless due to hysterectomy or because the patient has beenpostmenopausal naturally for at least 24 consecutive months. Two reliable forms ofcontraception must be used simultaneously unless continuous abstinence fromheterosexual sexual contact is the chosen method. Females of childbearingpotential should be referred to a qualified provider of contraceptive methods, ifneeded. Sexually mature females who have not undergone a hysterectomy or whohave not been postmenopausal naturally for at least 24 consecutive months (i.e.,who have had menses at some time in the preceding 24 consecutive months) areconsidered to be females of childbearing potential.It is not known whether CC-5013 (lenalidomide) is present in the semen of patientsreceiving the drug. Therefore, males receiving CC-5013 (lenalidomide) must alwaysuse a latex condom during any sexual contact with females of childbearing potentialeven if they have undergone a successful vasectomy.

11. Patients must not have received prior therapy with lenalidomide (for more than 2 months) nor eltrombopag.

12. Patients must not have uncontrolled hypertension

13. ECOG Performance 0-3 (ECOG).

14. Subject is able to understand and comply with protocol requirements and instructions.

15. Patient has signed and dated informed consent.

16. Prothrombin time (PT/INR) and activated partial thromboplastin time (aPTT) must be within 80 to 120% of the normal range at baseline.

17. All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.

6.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Pre-existing cardiovascular disease (including congestive heart failure, New York Heart Association [NYHA] Grade III/IV), or arrhythmia known to increase the risk of thromboembolic events (e.g. atrial fibrillation), or subjects with a QTc >450 msec (Male) and QTc > 470 msec (Female). Patients with history of atrial fibrillations or arrhythmias may be considered if in normal sinus rhythm at the time of registration and if cardiac echocardiogram shows no evidence of any cardiac thrombus.

2. Patients determined to be at increased risk of arterial or venous thrombosis by the investigator

3. Bone marrow fibrosis that leads to a dry tap.

4. Female subjects who are nursing or pregnant (positive serum or urine β-human chorionic gonadotropin (β-hCG) pregnancy test) at screening or pre-dose on Day 1.

5. Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication.

6. Patients with documented liver cirrhosis

7. Patients with known Splenic Vein Thrombosis.

6.3 Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Section 2 Table of Study Assessments.

At treatment discontinuation, subjects will undergo off study evaluations per the Schedule of Assessments, Section 2. In addition, a safety assessment will be done approximately 28 days post the last dose of protocol therapy.

7 PATIENT REGISTRATION

Central registration for this study will take place at the Montefiore-Einstein Center Monday through Friday 9:00am – 5:00pm Eastern Standard Time. Eligibility Checklist with supporting documentation, On Study Form and the signed Patient Consent Form must be faxed to the clinical trials office at the Montefiore-Einstein Center, Fax: 718-822 -0335, at the time of registration and prior to patient treatment.

At the time of registration, all eligibility criteria must be checked. Patients must meet all of the eligibility requirements listed in the Eligibility Checklist. Patients must not start protocol treatment prior to registration.

It is the treating physician's responsibility to review all data submitted to the Clinical Trials Office for accuracy and completeness and he/she must sign the off study form.

8 DRUG ADMINISTRATION

8.1.1 Dosing regimen

All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (NCI CTC ver4.03). For patients who experience treatment delays due to toxicity, finalresponse assessment will be delayed according to the number of 28 day cycles off of studytreatment.

Subjects will be evaluated for adverse events (AEs) at each visit.

8.1.2 Dose Modifications

Dose Reductions for lenalidomide
Table 1 gives the dose levels for the dose reduction steps for adverse events.

Table 1: Dose Reduction Steps for lenalidomide

Starting dose 10 mg/day on days 1-21, followed by 7 days of no therapy
Dose level -1 5 mg daily
Dose level -2 5 mg every other day (qod)

Patients who experience limiting neutropenia after prolonged treatment with 5 mg every other day may resume treatment at the same dose upon hematologic recovery.

Dose Modifications for Neutropenia
Hold lenalidomide for a decline in neutrophil count to < 500/μL that does not respond to myeloid growth factor administration. Lenalidomide should be resumed at thenext dose

reduction step when neutrophil count is > 500/µL.**Dose Modifications for Thrombocytopenia**

For patients with a baseline platelet count<50,000/uL;
Start eltrombopag when the platelet count is < 50,000/uL. Start Lenalidomide (AND STOP eltrombopag) only after platelet count > 50,000 (non transfused) for atleast 2 weeks. If platelet fall <50,000/uL after resuming lenalidomide again then again hold dose and start Eltrombopag again. Once plt count > 50,000 for two weeks, then start lenalidomide and give eltrombopag concomitantly.

For patients with a baseline platelet count =>50,000/uL;
Start Lenalidomide alone. If plt count falls below 50,000/L then follow algorithm as above.

Patients who do not experience platelet recovery within 8weeks of starting Eltrombopag should be removed from study and complete all offstudyevaluations.

Dose modifications for hemoglobin levels:
For those patients experiencing arise in hemoglobin > 14 g/dL, Lenalidomide should be withhelduntil the hemoglobin is < 12 g/dL, at which time treatment can be resumed accordingto the dose adjustment recommendations in Table 1. For thosepatients previously adjusted to the lowest CC-5013 (lenalidomide) dose, the CC-5013 (lenalidomide) schedule should be changed to a 2 week treatment scheduleevery 4 weeks.

Dose Modifications for Other Adverse Events
Dose interruption and modification guidelines for other adverse events are in Table 2.
Lenalidomide should be held for any > grade 3 adverse events withsuspected drug association until resolution to < grade 2. For any patients who doesnot experience resolution to < grade 2 within 4 weeks should be removed from studyand complete all off-study evaluations. For patients with thromboembolic events,both agents should be discontinued and not resumed until resolution with properprophylaxis according to the discretion of the treating investigator.
NOTE: Patients will be removed from study if lenalidomide is held forlonger than 8 weeks for treatment-related toxicity.

Table 1: Dose Modifications for CC-5013 (lenalidomide)

System	NCI CTCAE Grade	Action
Coagulation	Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) dose and start anticoagulation; resume CC-5013 (lenalidomide) at investigator's discretion (maintain dose level).
Skin	Desquamating (blistering) rash	• Discontinue study treatment.
	Non- desquamating rash Grade 2	• If Grade 2, interrupt CC-5013 (lenalidomide) therapy. Resume CC-5013 (lenalidomide) when the rash resolves to ≤ Grade 1 (decrease one dose level).
	Grade ≥ 3	• Discontinue CC-5013 (lenalidomide) study drug.
Neurology	Neuropathy Grade 3	• If Grade 3, interrupt CC-5013 (lenalidomide) 3 therapy. Resume CC-5013 (lenalidomide) when the neuropathy resolves to ≤ Grade 1 (decrease one dose level).
	Grade 4	• Discontinue CC-5013 (lenalidomide) study drug.

System	NCI CTCAE Grade	Action
Allergy	Allergic reaction Grade 2	• If Grade 2, interrupt CC-5013 (lenalidomide) therapy. Resume CC-5013 (lenalidomide) when symptoms resolve to ≤ Grade 1 (decrease one dose level).
	≥ Grade 3	• Discontinue CC-5013 (lenalidomide) study drug.
Gastrointestinal	Constipation ≥ Grade 3	• Hold (interrupt) dose. Initiate bowel regimen, and resume CC-5013 (lenalidomide) when constipation resolves to ≤ grade 2 (decrease one dose level).
Endocrine	Hyperthyroidism or hypothyroidism	• Interrupt CC-5013 (lenalidomide) and initiate appropriate medical therapy. Resume CC-5013 (lenalidomide) at investigator's discretion (maintain dose level).
Cardiac Arrythmias	Sinus bradycardia/other cardiac arrhythmia Grade 2	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1resume at next lower dose level.
	≥ Grade 3	• Discontinue CC-5013 (lenalidomide) study drug.
Other Toxicity	Other non-hematologic toxicity assessed as CC-5013 (lenalidomide)-related ≥ Grade 3	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 resume at next lower dose level.

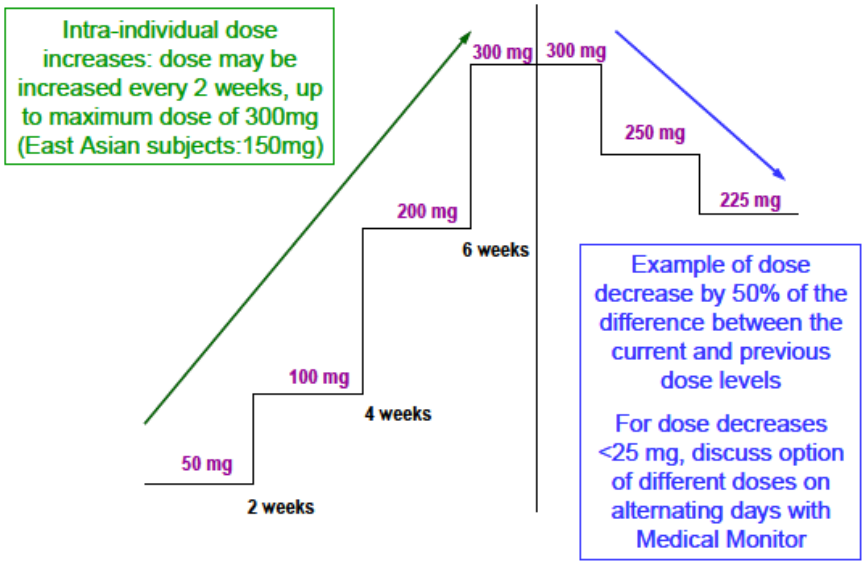
Dosing for Eltrombopag

Patients will initially be started on 100 mg eltrombopag (50 mg for subjects of East Asian heritage). Thereafter, dependent on the platelet response (see Table 3 below), the dose of study medication can be increased every 2 weeks, up to a maximum dose of 300 mg/day (150 mg/day for subjects of East Asian heritage).

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

Intra-individual dose adjustments will be made in a stepwise fashion, by sequentially increasing to dose levels of 100 mg, 200 mg or 300 mg as needed (50, 100, 150 mg for subjects of East Asian heritage). Titration of study medication with different dosages on different days will be permitted where needed in order to maintain a stable platelet count in the safe range without exceeding platelet counts >400 Gi/L.The dosing regimen of eltrombopag must be individualized based on platelet counts. Use the lowest effective dosing regimen to maintain platelet response.

Figure 4: Schema of dose adjustments for eltrombopag



Eltrombopag must be taken either in a fasted state (i.e., 1 hour before or 2 hours after food) or taken with food low in calcium (no dairy products). There must be at least a 4-hour interval between eltrombopag and other medications, food, or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc, including dairy products. After any eltrombopag dose adjustment, monitor platelet counts at least weekly for 2-3 weeks.

At eltrombopag dose levels 200 mg and above, subjects who have discontinued other drugs known to prolong QT and who still have a QTc >480 msec will be excluded

Table 2:Guidelines for Eltrombopag Dose Adjustments

Platelet Counts	Dose Adjustments
No platelet response	Increase daily dose to the next dose level If platelet counts do not stabilize at desired levels, consider dosing regimens such as different dose levels on alternating days. Wait for 2 weeks to see the effect of the dose increase on platelet response before another dose increase is considered.
200-400 k/uL	**<u>If no post-baseline BM examination has been performed:</u>** Decrease daily dose considering dosing regimens such as different dose levels on alternating days. If platelet counts remain between 200-400 k/uL, wait for 2 weeks to see the effect of the dose decrease on platelet response before another dose decrease is considered.
	<u>If BM blasts have decreased:</u> Maintain dose level and monitor platelet counts weekly.
	<u>If BM blasts have increased:</u> Decrease daily dose considering dosing regimens such as different dose levels on alternating days. If platelet counts remain between 200-400 k/uL, wait for 2 weeks to see the effect of the dose decrease on platelet response before another dose decrease is considered

>400k/uL	Interrupt treatment and monitor platelets twice a week until platelet counts fall below 150 k/uL and restart treatment by reducing the daily dose to the next dose level considering dosing regimens such as different dose levels on alternating days.

During eltrombopag therapy, CBCs, including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count has been achieved. CBCs including platelet counts and peripheral blood smears, should be obtained monthly thereafter. Blasts will be monitored as indicated in flowchart:

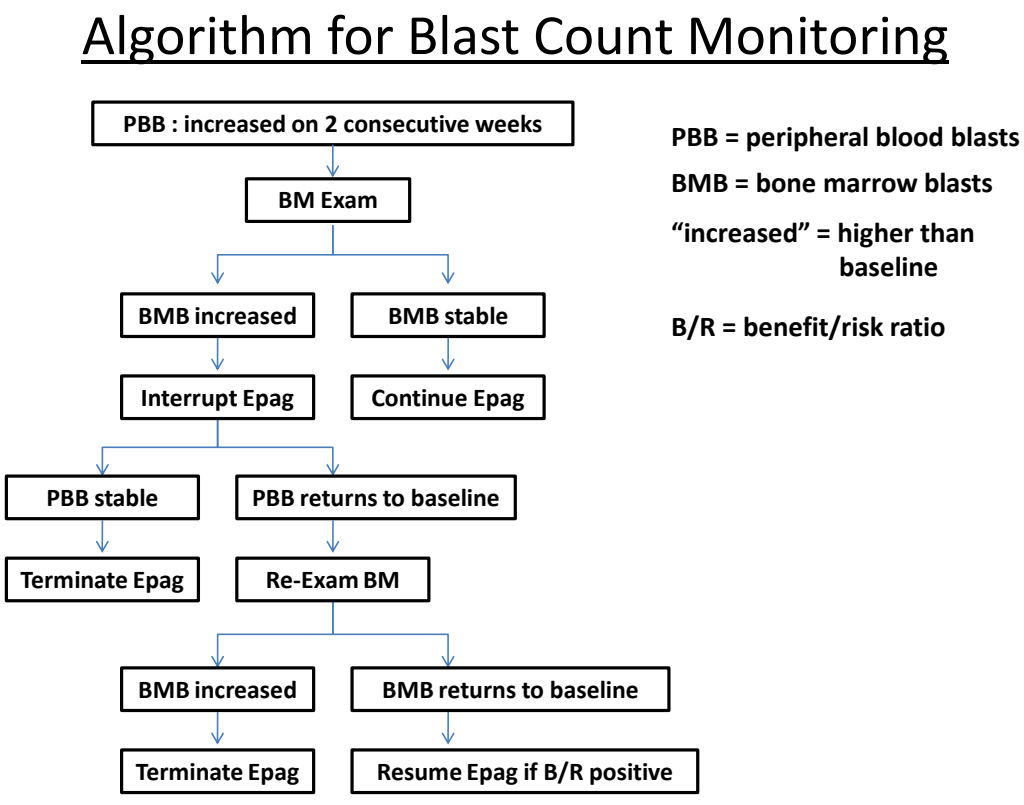


Figure 5: Schema for blast count monitoring

Special Handling Instructions

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

8.2 SUPPORTIVE CARE

1. All supportive measures consistent with optimal patient care will be given throughoutthe study.

2. Therapies considered necessary for the patient's well being may be administered atthe discretion of the Investigator. These therapies include antibiotics, analgesics,antihistamines, or other medications, and transfusions of red blood cells, platelets,or fresh frozen plasma given to assist in the management of complicationsassociated with MDS or study treatment.

3.Packed RBCs: Transfusions of two units of packed RBCs should be considered fordecline in hematocrit (HCT) to < 25% or symptoms of cardiovascular compromise.
The following **transfusion thresholds and guidelines** are recommended for studyparticipants: HCT < 25%, two units of packed RBCs; HCT < 21%, three units ofpacked RBCs; HCT < 18%, four units of packed RBCs.

4 Platelets: Eight to ten units of random donor platelets or one cytopheresis unit ofsingle donor platelets should be administered to all subjects with signs of hemostaticfailure (i.e., bleeding or petechiae) or life threatening thrombocytopenia (i.e., plateletcount < 10,000/µL).

5 Patients should not receive androgens or steroids for supportive treatment of their anemia or thrombocytopenia

6 Patients may receive hydrocortisone prophylactically to prevent transfusion reactions. Steroids given for adrenal failure, hormones administered for non-cancerrelatedconditions (e.g. insulin for diabetes), and intermittent uses of dexamethasoneas an antiemetic are permitted concomitantly with study drug. Short courses ofsteroids to treat study drug-induced skin rashes are also permitted.

8.3 DURATION OF THERAPY

Patients will receive protocol therapy unless:
1. Extraordinary Medical Circumstances: If at any time the constraints of this protocolare detrimental to the patient's health, protocol treatment should be discontinued
2. Patient withdraws consent.

3. Adverse event(s) (AEs) occur that, in the judgment of the Investigator, may causesevere or permanent harm or which rule out continuation of study drug.
4. Lack of therapeutic effect
5. Patient's disease converts to acute myeloid leukemia or disease progression.
6. Patient is lost to follow-up.
7. if a patient has a QTc >500 msec or QT >600 msec;
8. if a patient meets any of the following liver chemistry threshold criteria:

ALT ≥3xULN and bilirubin ≥1.5xULN (>35% direct).ALT ≥5xULN.

ALT ≥3xULN if associated with the appearance or worsening of hepatitis symptoms or rash.

All subjects who discontinue study medication should continue to participate in the follow-up visits.

8.4 DURATION OF FOLLOW-UP

For this protocol, all patients, including those who discontinue protocol therapy early,will be followed for response until progression and for survival for 10 years from thedate of registration. All patients must be followed through completion of protocoltherapy.

8.5 CONCOMITANT MEDICATIONSAND NON-DRUG THERAPIES

Permitted Medications and Non-Drug Therapies

A reasonable effort will be made to document any medications the subject receivedwithin 30 days prior to Day 1. Any medication taken within 7 days of study medicationadministration must be recorded in the eCRF as a prior medication.All concomitant medications taken during the study will be recorded in the eCRF withindication, dose information, including any changes in dose, as well as start and stopdates and frequency of administration. The minimum requirement is that drug name,dose, and the dates of administration are to be recorded.If any medication is required at any time within 7 days before study medicationadministration until completion of last follow-up procedures, subjects should consult theinvestigator and details should be recorded in the eCRF.

Antacids, Cations and Vitamin/Mineral Supplements

Administration of eltrombopag with a polyvalent cation-containing antacid decreasedplasma eltrombopag exposure by 70%, and a similar reduction was observed wheneltrombopag was administered with a high-calcium meal. Therefore, every effort must bemade to educate subjects on how to take study medication with medications or foodscontaining these polyvalent cations. Details of these and all concomitant medicationsshould be recorded in the eCRF.

Eltrombopag should be taken on an empty stomach (1 hour before or 2 hours aftera meal) or taken with food low in calcium (no dairy products). Allow at least a 4 hour interval between eltrombopag and othermedications, foods, or products containing polyvalent cations (e.g. calcium, magnesium,aluminium, zinc, selenium or iron) such

as antacids, dairy products, and mineralsupplements to avoid significant reduction in eltrombopag absorption due tochelation.

Antacids
Subjects requiring routine (e.g. daily) acid suppression should be encouraged to take H2antagonists like ranitidine, famotidine or nizatidine, or proton pump inhibitors likeomeprazole, esomeprazole or lansoprazole.
Subjects requiring occasional acid suppression may take liquid or chewable antacids(calcium carbonate, aluminum hydroxide or magnesium hydroxide), provided studymedication is taken at least 4 hours before and 4 hours after consumption of cationcontainingantacids.

Mineral Supplements and Dairy Products
Mineral supplements (such as calcium, magnesium, aluminium, zinc, selenium or iron)are permitted during the study but study medication must be taken at least 4 hours beforeand 4 hours after consumption of these supplements. Similarly, eltrombopag must betaken at least 4 hours before and 4 hours after consumption of dairy products (such asmilk, yogurt, and cheese).

HMG-CoA Reductase Inhibitors (statins)
Subjects will be permitted to use HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA) inhibitors during the study, but these drugs should be used with caution and a 50% dose reduction of the HMG-CoA reductase inhibitor is recommended, with close monitoring for safety, such as liver chemistry and signs and symptoms of myolysis, and efficacy, such as cholesterol and triglycerides (refer to individual product information for monitoring recommendations).
Preclinical data showed that eltrombopag is an inhibitor of the transporters OATP1B1 and BCRP. Therefore, a clinical drug interaction study to evaluate the impact of eltrombopag on the PK of rosuvastatin, an OATP1B1 and BCRP substrate, was conducted in healthy subjects. Co-administration of eltrombopag 75 mg once daily for 5 days with a single 10mg dose of rosuvastatin administered on Day 5 increased plasma rosuvastatin Cmax 2.03-fold and AUC(0-∞) 55%. Concomitant administration of eltrombopag and other OATP1B1 or BCRP substrates should be used with caution.

Concomitant MDS Therapy
G-CSF is allowed during the study for subjects with severe neutropenia and recurrentinfections. Subjects who enter the study on G-CSF should continue at the same doseschedule until the optimal dose of study medication has been established.
Any change in dosage of any concomitant medication (change in dose or frequency)MUST be recorded in the eCRF, to include: drug name, dose, frequency ofadministration, start and stop dates and indication.

Prohibited Medications and Non-Drug Therapies
Subjects must abstain from using prohibited prescription or non-prescription drugs within7 days or 5 half-lives (whichever is longer) prior to the first dose of study

medication anduntil completion of follow-up procedures (Section 5.3, Exclusion Criteria).
The following medications are prohibited during the study:
• Any other TPO-R agonists
• Treatment with deferasirox. Deferasirox shares some aspects of the safety profile ofeltrombopag, and should therefore not be combined with eltrombopag to allow for abetter identification of potential, eltrombopag-related events.
• Drugs that affect platelet function (including, but not limited to, aspirin, clopidogreland/or NSAIDS) may also affect the results of the bleeding scale assessments duringthe study and are therefore prohibited. In the event their use is clinically indicated,those drugs will be permitted, but the subject(s) will be excluded from bleedinganalyses.
• Anticoagulants (e.g. warfarin, heparin) may also affect results of the bleeding scaleassessments during the study unless and therefore are prohibited. In the event theiruse is clinically indicated, those drugs will be permitted, but the subject(s) will beexcluded from bleeding analyses.

9 ADVERSE EVENTS

9.1 Comprehensive Adverse Events and Potential Risks List (CAEPR) for lenalidomide (NSC #703813)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single,complete list of reported and/or potential adverse events (AE) associated with an agentusing a uniform presentation of events by body system. In addition to the comprehensive list,a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column andis identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events thatare considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCIGuidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/reporting/adeers.html for further clarification. The CAEPR does notprovide frequency data; refer to the Investigator's Brochure for this information. Below is theCAEPR forLenalidomide.

Version 1.3, February 23, 20061
Category(BodySystem)Adverse Events with PossibleRelationship to CC-5013 (Lenalidomide)(CTCAE v3.0 Term)
'Agent Specific Adverse Event List'(ASAEL)

ALLERGY/IMMUNOLOGY
Allergic reaction/hypersensitivity (including drugfever)
Allergic rhinitis (including sneezing, nasalstuffiness, postnasal drip)

AUDITORY/EAR
Tinnitus

BLOOD/BONE MARROW
Blood/Bone Marrow - Other (Eosinophilia)
Hemoglobin ***Hemoglobin***
Hemolysis (e.g., immune hemolytic anemia, drugrelatedhemolysis)
Leukocytes (total WBC) ***Leukocytes (total WBC)***
Lymphopenia ***Lymphopenia***
Neutrophils/granulocytes (ANC/AGC) ***Neutrophils/granulocytes (ANC/AGC)***
Platelets ***Platelets***

CARDIAC ARRHYTHMIA
Atrial fibrillation
Palpitations
Prolonged QTc interval
Sinus bradycardia
Supraventricular tachycardia
Ventricular tachycardia

CARDIAC GENERAL
Cardiac ischemia/infarction
Hypertension
Hypotension

COAGULATION
DIC (disseminated intravascular coagulation)
INR (International normalized ratio of prothrombintime)

CONSTITUTIONAL SYMPTOMS
Fatigue (asthenia, lethargy, malaise) ***Fatigue (asthenia, lethargy, malaise)***
Fever (in the absence of neutropenia, whereneutropenia is defined as ANC <109/L)
Fever (in the absence of neutropenia,where neutropenia is defined as ANC<109/L)
Insomnia
Rigors/chills
Sweating (diaphoresis)
Weight loss ***Weight loss***

DERMATOLOGY/SKIN
Dermatology/Skin - Other (Sweet's syndrome)
Dry skin
Hair loss/alopecia (scalp or body)
Photosensitivity
Pruritus/itching ***Pruritus/itching***
Rash/desquamation ***Rash/desquamation***
Rash: acne/acneiform
Urticaria (hives, welts, wheals)

ENDOCRINE
Endocrine - Other (Low testosterone)
Thyroid function, high (hyperthyroidism,thyrotoxicosis)
Thyroid function, low (hypothyroidism)

GASTROINTESTINAL
Anorexia
Constipation ***Constipation***
Dehydration
Diarrhea
Distension/bloating, abdominal
Dry mouth/salivary gland (xerostomia)
Dysphagia (difficulty swallowing)
Flatulence
Gastritis (including bile reflux gastritis)
Heartburn/dyspepsia
Ileus, GI (functional obstruction of bowel, i.e.,neuroconstipation)
Mucositis/stomatitis (functional/symptomatic)
Nausea ***Nausea***
Perforation, GI: colon
Taste alteration (dysgeusia)
Vomiting ***Vomiting***

HEMORRHAGE/BLEEDING
Hemorrhage GU - Select
Hemorrhage, CNSHemorrhage, pulmonary/upper respiratory:respiratory tract NOS

HEPATOBILIARY/PANCREAS
Hepatobiliary/Pancreas - Other (Cholelithiasis)
Pancreatitis

INFECTION
Febrile neutropenia (fever of unknown originwithout clinically or microbiologically documented
infection)(ANC <109/L, fever $38.5°C)
Infection with Grade 3 or 4 neutrophils
Infection with normal ANC or Grade 1 or 2neutrophils
Opportunistic infection associated with Grade 2Lymphopenia

LYMPHATICS
Edema: limb

METABOLIC/LABORATORY
ALT, SGPT (serum glutamic pyruvictransaminase)
AST, SGOT (serum glutamic oxaloacetictransaminase)
Bilirubin (hyperbilirubinemia)

Calcium, serum-low (hypocalcemia)
Cholesterol, serum-high (hypercholesteremia)
Creatinine
Glucose, serum-high (hyperglycemia)
Magnesium, serum-low (hypomagnesemia)
Lipase
Potassium, serum-low (hypokalemia)
Sodium, serum-low (hyponatremia)
Uric acid, serum-high (hyperuricemia)

MUSCULOSKELETAL/SOFT TISSUE
Arthritis (non-septic)
Muscle weakness (not due to neuropathy)
Muscle weakness (not due to neuropathy): wholebody/generalized

NEUROLOGY
CNS cerebrovascular ischemia
Confusion
Dizziness
Encephalopathy
Mental status
Mood alteration: agitation
Mood alteration: anxiety
Mood alteration: depression
Myelitis
Neuropathy: motor
Neuropathy: sensory
Psychosis (hallucinations/delusions)
Seizure
Somnolence/depressed level of consciousness
Speech impairment (e.g., dysphasia or aphasia)
Syncope (fainting)
Tremor

OCULAR/VISUAL
Dry eye syndrome
Retinopathy
Vision-blurred vision
Vision-flashing lights/floaters
PAIN
Pain - abdomen NOS
Pain - back
Pain - bone
Pain - chest/thorax NOS
Pain - head/headache
Pain - joint

Pain - muscle
Pain - oral-gums
Pain NOS

PULMONARY/UPPER RESPIRATORY
Atelectasis
Cough
Dyspnea (shortness of breath)
Nasal cavity/paranasal sinus reactions
Pleural effusion (non-malignant)

RENAL/GENITOURINARY
Renal failure
Urinary electrolyte wasting (e.g., Fanconi'ssyndrome, renal tubular acidosis)
Urinary frequency/urgency

SYNDROMES
Tumor lysis syndrome

VASCULAR
Thrombosis/thrombus/embolism ***Thrombosis/thrombus/embolism***

Also reported on lenalidomide trials but with the relationship to lenalidome still undetermined:
NEUROLOGY - hemiparesis
PAIN - limb pain
RENAL/GENITOURINARY - urinary incontinence

9.2 Safety considerations with Eltrombopag:

The information in this section reflects the revised Prescribing Information for PROMACTA dated Feb 2011

Increased Liver Chemistries: Eltrombopag administration may cause hepatotoxicity. In the ITP controlled clinical studies, 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. In controlled studies, elevations of ALT and indirect bilirubin were observed more frequently on the eltrombopag arm than placebo. 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 three controlled studies, 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 studies with hepatobiliary laboratory abnormalities were re-exposed to eltrombopag in the ITP extension study. Six of these patients again experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of eltrombopag in one patient. In the ITP extension study, one additional patient had eltrombopag discontinued due to liver test abnormalities (all ≤Grade 3).

Serum ALT, AST, and bilirubin should be measured 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. Permanently discontinue eltrombopag if ALT levels increase to ≥3X the upper limit of normal (ULN) 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.

Pharmacokinetic evaluations in patients with hepatic impairment show that plasma eltrombopag $AUC_{(0-\tau)}$ increases with increasing degree of hepatic impairment (as measured by Child-Pugh). Exercise caution when administering eltrombopag to patients with hepatic impairment (Child-Pugh Class A, B, C) . Use a lower starting dose of eltrombopag in patients with any degree of hepatic impairment i.e. cirrhosis and monitor closely

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, 151 patients have had bone marrow biopsiesevaluated 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 studies have not yet excluded a risk of bone marrow fibrosis with cytopenias.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, peripheral blood smears and CBCs should be examined monthly for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia. If the patient

develops new or worsening morphological abnormalities or cytopenia, treatment with eltrombopag should be discontinued and a bone marrow biopsy, including staining for fibrosis considered.

Recurrence of Thrombocytopenia After Cessation of Eltrombopag
Discontinuation of eltrombopag may result in recurrence of thrombocytopenia. This recurrence of 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 patients in the placebo group.

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

Thrombotic/thromboembolic complications
Eltrombopag may increase the risk of thrombotic/thromboembolic events.. Excessive doses of eltrombopag may increase platelet counts to a level that produces thrombotic/thromboembolic complications.
In the 3 controlled ITP clinical studies, thrombotic/thromboembolic complications occurred in four patients in the groups that received eltrombopag and none in the placebo groups.Thrombotic/thromboembolic complications have also been reported in the ITP extension study. The thrombotic/thromboembolic complications in patients with chronic ITP included both venous and arterial events and were observed at low and normal platelet counts.

Use caution when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, 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 platelet count of $\geq 50 \times 10^9$/L as necessary to decrease the risk for bleeding

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 portal venous thrombosis was increased in patients treated with 75 mg eltrombopag once daily for 2 weeks in preparation for their invasive procedure. Seven thrombotic complications (six patients) were reported within the group that received eltrombopag and three thrombotic complications were reported in the placebo group (two patients). All of the thrombotic complications reported within the eltrombopag group were of the portal venous system. 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 10^9/L. Malignancy is known to increase the risk for developing a thrombotic event and four of the 6 patients either had a diagnosis or suspicion of malignancy (2 hepatocellular carcinoma; 1 possible lymphoma and 1 brain tumor).

Caution should be exercised when administering eltrombopag to patients with hepatic impairment (Child-Pugh Class A, B, C) and a lower starting dose of eltrombopag should be used in patients with any degree of hepatic impairment. Such patients should be monitored very closely. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease.
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.

Hematologic Malignancies and Progression of Malignancies
Stimulation of the TPO receptor on the surface of hematopoietic cells by eltrombopag may increase the risk for hematologic malignancies. In the controlled clinical studies, patients were treated with eltrombopag for a maximum of 6 months. During this period no hematologic malignancies were reported in patients treated with eltrombopag. One hematologic malignancy (non-Hodgkin's lymphoma) was reported in the extension study.Eltrombopag is not indicated for the treatment of thrombocytopenia due to diseases or treatments that cause thrombocytopenia (e.g., myelodysplasia or chemotherapy) other than chronic ITP.

Cataracts Cataracts were observed in toxicology studies of eltrombopag in rodents (see Non-clinical Information). To date, there is however, 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.

Routine monitoring of patients for cataracts is recommended. Patients treated with eltrombopag who experience visual difficulties should have an appropriate ophthalmologic evaluation

10 REPORTING REQUIREMENTS

10.1 Definitions

10.1.1 Adverse Events

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse Events encompass both physical and/or psychological harms.

10.1.2 Unanticipated Problem

Any event, deviation, or problem, that meets **ALL**of the following criteria:

- Is unexpected, AND
- Is possibly, probably or definitely related to participation in the research; **AND**
- fatal, life-threatening, or serious OR suggests greater risk of harm to study participant(s)or others than was previously known or recognized.

(A) Unexpected:
An event can be categorized as unexpected ifit occurs in one or more subjects participating in a research protocol; and the nature, severity, or frequency of which is not consistent with either:

- The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in protocol-related documents such as: the IRB-approved research protocol; any applicable investigator brochure: the current IRB-approved informed consent document; or other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression ofany underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factorprofile for the adverse event.

(B) Serious Adverse Event (SAE):
A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Pregnancy

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such 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. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

10.1.3 Protocol Deviation

Any change in the processes or procedures of research that were not approved by amendment of an IRB-approved protocol.

10.1.4 Protocol Exception

A planned, one-time deviation from the IRB-approved protocol (e.g. enrollment of a subject who does not meet inclusion criteria, or one-time dose changes for a single subject).

10.1.5 Systematic Data Collection Error

Data collection errors that may affect the scientific soundness ofthe investigational plan.

10.2 Reporting Events to IRB at Montefiore-Einstein

10.2.1 Expedited Reporting

The Protocol PI will report the following events to the IRB within 5 business days of the clinical team's awareness via the reportable events form:

- All deaths
- Protocol Deviations that place subjects at greater risk
- All Unanticipated Problems
- All serious non-compliance

The PI's signature and the date it was signed are required on the completed report.

10.2.2 Continuing Review Reporting

At the time of continuing review, the IRB requires an internal log of all AE (except non-serous AEs), UP and PD events that have occurred on the protocol since the previous continuing review and in aggregate.

For additional information please refer to the IRB Reportable Events Policy located on the intranet: http://www.einstein.yu.edu/docs/administration/institutional-review-board/policies/reportable-events.pdf

10.3 Reporting Events to Study Supporters (Celgene Corporation/ GSK)

All SAEs must be reported to the Montefiore-Einstein PI or designee within 24 hours of being aware of the event. The Montefiore-Einstein Research team will inform study supporters and collaborating centers of reportable events.

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

10.3.1 GSK Reporting Requirements

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 GlaxoSmithKline. MDC - Oncology Fax: 1 610 422 2527 (make sure you include the 1 prior to the 610 as otherwise it doesn't work!)
For medical emergencies contact:
Toll Free Number: (800) 877-7074, ext. 7194
After Hours or Weekends: (800) 366-8900, ask for physician on call
GlaxoSmithKline UP4420
1250 S. Collegeville Road,
P.O. Box 5089
Collegeville, PA 19426-0989

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 GSK within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of eltrombopag and considered by the investigator to be related or possibly related to eltrombopag must be reported to GSK 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.
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	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**1**	**Documents**	**Time Frame**	**Documents**
All SAEs	1	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	1	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form

Table 3

10.3.2 Celgene Reporting Requirements

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

IND Annual Reports to Celgene

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700

Berkeley Heights, NJ 07922

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

Expedited reporting by investigator to Celgene
Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writingusing a Celgene SAE form or MEDWATCH 3500A formof any SAE within 24 hours of being aware of the event.The written report must be completed and supplied to Celgene by facsimilewithin 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene trackingnumber (RV-MDS-PI-0645)and the institutional protocol number should be included on SAE reports(or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Adverse event updates/IND safety reports
Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 11.4 for records retention information).

10.4 IND Safety Reports to the FDA (Refer to 21 CFR 312.32)

The Sponsor will notify the FDA of any unexpectedfatal or life-threateningsuspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information using the MedWatch Form 3500a.

The Sponsor is also responsible for reporting any:

- suspected adverse reaction that is both serious and unexpected
- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

to the FDA and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendars days after receiving the request.

10.4.1 FDA Annual Reports (Refer to 21 CFR 312.33)

The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

Responsibility of Participating Sites	Responsibility of Montefiore-Einstein
• Participating sites are responsible for reporting all events to their local IRB per local guidelines	• The Montefiore-Einstein Research Staff is responsible for submitting all reportable events to the IRB as specified in section 10.2
• Participating sites are responsible for reporting all SAEs (section 10.3) to the Montefiore-Einstein PI via fax or email within 24 hours of learning of the event.	• The Montefiore-Einstein PI will be responsible for reporting all drug related serious adverse events to the FDA (section 10.4) and events noted in section 10.3 to study supporters • The Montefiore-Einstein PI is responsible for informing all participating sites about unanticipated problems and fatalities within 30 days of receiving the stamped reportable events form from the IRB.

11 RESPONSE CRITERIA

MDS Response Criteria: Modified International MDS Working Group (IWG) Criteria forMeasurement of Response/Treatment Effect in MDS (20) will be used to assess response.

Complete Remission (CR)
Bone marrow evaluation (>4 weeks): Bone marrow showing =< 5% myeloblastswith normal maturation of all cell lines. When erythroid precursors constitute < 50% of bonemarrow nucleated cells, the percent of blasts is based on allnucleated cells; when there are > 50% erythroid cells, the percentblasts should be based on the non-erythroid cells. This response should last for atleast 4 weeks. Dysplasia if present will be noted.

Peripheral Blood Counts (Absolute values must last >4 weeks)
o Hemoglobin greater than 11 g/dL (untransfused, patientnot on erythropoietin).
o Neutrophils 1000/mm3 or more (not on a myeloid growthfactor)
o Platelets 100 000/mm3 or more (not on a thrombopoeticagent)
o Blasts – 0%
o Hematologic improvement should be obtained.

Marrow CR: Bone marrow: < 5% myeloblasts and decrease by > 50% over pretreatment marrow. Peripheral blood: if hematologic improvement occurs, it will be noted in addition to marrow CR

Partial Remission (PR)
All of the CR criteria (if abnormal prior to treatment), except
o Bone marrow evaluation: Blasts decreased by 50% overpretreatment, b

Stable Disease
Failure to achieve at least a PR, but with no evidence ofprogression for >8 weeks.

Failure
Death during treatment or disease progression characterizedby worsening of cytopenias, increase in the percent of bonemarrow blasts, or progressionto an MDS FAB subtype more advanced than pretreatment.

Relapse (following a CR or PR)
One or more of the following:
o Return to pretreatment bone marrow blast percentage.
o Decrement of > 50% from maximum remission responselevels in neutrophils or platelets.
o RBC transfusion dependence (> 2 unites RBCtransfusions over an 8 week period) or a reduction inhemoglobin concentration by >1.5 g/dL in the absence ofacute infection, gastrointestinal bleeding, hemolysis,treatment hiatus etc.

6. **Disease Progression**
A 50 % increase in blasts, depending on baseline blastpercent, if confirmed by subsequent BM examination (Fig 5).
o For patients with < 5% blasts: increase to > 10% blasts
o For patients with 5% to 10% blasts: > 50% increase to> 10% blasts
o For patients with 10% to 20% blasts: > 50% increase to20% blasts
o For patients with 20% to 30% blasts: > 50% increase to30% blasts

Any of the following:
At least 50% decrement from maximum remission/response in granulocytes or platelets
Reduction in Hgb by 2 g/dL
Transfusion dependence

7. **Disease Transformation**
Transformation to AML (> 30% blasts).

Cytogenetic Response
Requires 20 analyzable metaphases when using conventionaltechniques. Analysis of data will require 20 metaphases before andafter treatment. Fluorescent *in situ* hybridization (FISH) may be used asa supplement to follow a specifically defined cytogenetic abnormality,but it is not a substitute for conventional cytogenetic studies.

Cytogenetic response is defined as follows:

Complete response: Restoration of a normal karyotype in patientswith a documented pre-existing clonal (>2 metaphases abnormal)chromosome abnormalities.
Partial response: > 50% reduction in the percentage of bone marrowmetaphases with only clonal abnormality.

Hematologic Improvement
Improvements must last >**8 consecutive weeks**.

1.Erythroid Response
Hgb increase by 1.5 g/dL if not transfusion dependent 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 wk. Only RBC transfusions given for a Hgb of 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation

2. **Platelet Response**
For patients with a pretreatmentcount < 100,000/mm3, an absolute increase of > 30,000/mm3 (for patients with pretreatment counts >20,000).
For patients with pretreatment counts < 20,000, an increase to absolute count above 20,000 by at least 100% increase will be considered as response.

†;for platelet transfusion-dependent patients, stabilization ofplatelet counts and platelet transfusion independence.

3. **Neutrophil Response**
At least 100% increase and an absolute increase > 0.5 x 10^9/L

4. **Progression/Relapse Following Erythroid HematologicImprovement**
At least 1 of the following:
At least 50% decrement from maximum response levels in granulocytes or platelets
Reduction in Hgb by 1.5 g/dL
Transfusion dependence

Duration of Response
Time to disease progression (as per Bone Marrow Responses above) orprogression/relapse following hematologic improvement (as perHematologic Improvement above).

12 DATA MANAGEMENT

12.1 Analyses and Reporting

Data will be analyzed and reported after 25 patients are enrolled. All subsequent data collected will be analyzed and reported in a follow-up clinical report by the PI.

12.2 Study auditing

12.2.1 Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by Celgene or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

13 DATA SAFETY AND MONITORING BOARDS

All trials initiated by Montefiore-Einstein are subject to oversight by the Albert Einstein Cancer Center Data Safety Monitoring Board (DSMB). This board meets once a month with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.

- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

14 BIOSTATISTICAL ANALYSIS

14.1 Safety evaluation

Data from all subjects who receive any protocol therapy will be included in the safety analyses. Subjects who entered the study and did not receive any protocol therapy and had this confirmed, will not be evaluated for safety.

The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible.

14.2 Sample size and power considerations

The primary outcome is major erythroid response. A maximum of 52 patients will be enrolled into the study. An early stopping rule for lack of efficacy will be implemented as follows based on Simon's optimal two-stage design. After the first 25 patients have been enrolled and evaluated for response, the trial will be terminated early if fewer than 7 patients respond to treatment. If 7 or more responses are observed, the trial will continue until a total of 52 patients have been evaluated. At the end of the trial, the treatment will be considered efficacious and worthy of further study if 17 or more patients respond out of 52 patients.

The target response rate is assumed to be 40%. (Conservative estimate) A response rate less than 25% is considered to be clinically unimportant(21). Under these assumptions, the design specified above has the following operating characteristics. The probability of accepting the treatment for further study if the response rate is unacceptably low

(<25%) is at most 10%. In contrast, there is a 80% probability of accepting the treatment for further study if the response rate is at least 40%. The expected sample size is 32.4 subjects. It is also assumed that 10-20% of patients with plts > 50,000 that receive Len may not need Eltrombopag at all as there plts will not fall below 50,000.

Furthermore, since we will accrue patients with both high and low platelet counts, it is possible that the response rates to Lenalidomide will be different in these groups. These will be analyzed by exploratory studies.

15 REGULATORY CONSIDERATIONS

15.1 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

15.2 Protocol amendments

Any amendment to this protocol must be agreed to by the Montefiore-Einstein Principal Investigator and reviewed by Celgene and GSK. Amendments should only be submitted to IRB/EC after consideration of Celgene and GSK review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

Each change to the protocol document must be first approved by the Einstein IRB. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each participating study center. A copy of the written IRB approval and corresponding documents must be provided to Montefiore-Einstein.

15.3 Continuing Review

Participating sites must submit their continuing review approval letter from their IRB of Record accompanied by the most current approved version of the consent form prior to expiration. Suspension of enrollment may be considered if receipt of this document does not occur within this time frame.Registration will be halted at any participating institution in which a current continuing approval is not on file.

15.4 Deviations and Exceptions

A protocol deviation is any change in the process or procedure of research that were not approved by amendment of an IRB approved protocol. Participating sites should report deviations to Montefiore-Einstein as soon as possible as well as maintain record the event on a deviation log that will be collected at the time of the Montefiore-Einstein's IRB continuing review.

A protocol exception on this study is defined as a planned one-time deviation from the IRB approved protocol. If a deviation from the protocol is proposed for a potential or existing participant at Montefiore-Einstein or a participating site, approval from Montefiore-Einstein IRB is required prior to the action. Participating sites should contact the Montefiore-Einstein PI who will in turn seek approval from the Montefiore-Einstein IRB.

Participating sites should report deviations and exceptions to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and exceptions should be submitted to Montefiore-Einstein as received.

15.5 Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

15.6 Subject confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene and GSK require the Investigator to permit representatives of Celgene Corporation and GlaxoSmithKline, and when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

15.7 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

15.8 Premature discontinuation of study

The Principal Investigator, institution, GSKand Celgene have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

16 CORRELATIVE STUDIES:

Correlative studies will be performed on all subjects. Specifically, we will study:

a. Whole transcriptome sequencing (RNA-Seq) of MDS bone marrow progenitors and correlation with response. Pretreatment bone marrow aspirates will be used for these studies. Bone marrow stem cells will be sorted and RNA will be isolated. Sequencing libraries will be generated and subjected to massive parallel sequencing using an Illumina

HiSeq2000 instrument.. The transcriptome patterns will be correlated with response. In addition to gene expression patterns, this study will also correlate mutations and single nucleotide polymorphisms with response to lenalidomide and eltrombopag. Somatic mutations will be identified by comparison of marrow and germline (toenail clippings or cheek swabs) samples.

b. Analysis of "MDS" stem cells pre and post treatment with the combination of eltrombopag and lenalidomide and their correlation with response (Study co-chair Dr. Ulrich Steidl is an expert in flow sorting of leukemia stem cells and their functional characterization, both in vitro and in vivo). Using high-speed multi-parameter fluorescence-activated cell sorting we will separate bone marrow progenitors into long-term and short-term hematopoietic stem cells as well as more committed myeloid, erythroid and megakaryocytic progenitors, as performed previously (22, 23). Stem cell compartments expanded in MDS as compared to normal bone marrow will be identified. Sorted cell fractions will be studied for the presence of pathogenic mutations and characteristic chromosomal lesions. Functional validation of sorted cell populations will be performed in vitro and in vivo.

Our preliminary studies indicate that primitive stem cells (LT-HSCs and ST-HSCs) are expanded in MDS and harbor initiating karyotypic abnormalities and striking alterations in DNA methylation with an accumulation of aberrantly hypermethylated loci. Furthermore, we and others observe that karyotypically abnormal stem cells persist in the bone marrow even after morphological complete remission and thus may potentially lead to relapse of MDS (24). These preliminary data lead us to hypothesize that a pool of disease-initiating stem or early progenitor cells exists in MDS that contains and progressively acquires genetic and epigenetic alterations and may persist after conventional treatments. The study of these MDS cells-of-origin and MDS-initiating cell populations will reveal fundamentally new information about early pathogenic events, which represent particularly promising targets for therapeutic intervention, as well as the modes of MDS progression.
Quantitative and cytogenetic assessment of MDS stem and progenitor cells from marrow samples of responders and non-responders to lenalidomide and eltrombopag will be performed. Karyotypic, transcriptomal, as well as methylomic analysis of these cells will be conducted for clonal genetic and epigenetic assessment. Comparison of pretreatment and post treatment samples from both subsets of patients will demonstrate whether a decrease in clonal stem cells correlates with clinical response. We will also determine whether persistence of clonal stem cells in responders correlates with a risk of future relapse.

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Appendices

Appendix 1: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory Revlimid REMS™ program, and be willing and able to comply with the requirements of Revlimid REMS™.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from

heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.

- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give lenalidomide to another person.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.

Appendix 2 – ECOG Performance Status Scale

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

Appendix 3: Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl):
(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min) (Males)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

$$\text{CrCl (mL/min) (Females)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

Appendix 4 – International Prognostic Scoring System (IPSS) for MDS

Prognostic Variable	Survival and AML Evolution Score Value				
	0	0.5	1.0	1.5	2.0
Marrow Blasts (%)	<5	5 to 10	N/a	11 to 20	21 to 30
Karyotype	Good Normal or any 1 of: -Y (del(5q) del(20q)	Intermed. Any other abnormality	Poor chromosome 7 anomalies; Complex: ≥ 3 abnormalities	n/a	n/a
Cytopenias Neutrophil Count < 1800/uL Platelets < 100,000 uL Hemoglobin < 10 g/dL	0 or 1	2 or 3	n/a	n/a	n/a

Low: total score = 0

Int-1: total score 0.5-1.0

Int-2: total score 1.5-2.0

High: total score ≥ 2.5

Appendix 5 NCI CTC Version 4.0

TOXICITY WILL BE SCORED USING NCI CTC VERSION 4.0 FOR TOXICITY AND ADVERSE EVENT REPORTING. A COPY OF THE NCI CTC VERSION 4.0 CAN BE DOWNLOADED FROM THE CTEP HOMEPAGE: (HTTP://CTEP.INFO.NIH.GOV**). ALL APPROPRIATE TREATMENT AREAS HAVE ACCESS TO A COPY OF THE CTC VERSION.**

APPENDIX 6 – CORRELATIVE STUDIES:

All specimens for correlative studies must be labeled with the patient's code number, which will be assigned by the Data Management Office, and should not bare the patient's identity. The specimens must be kept at room temperature and sent by fedex to

Amit Verma, MD
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1300 Morris Park Ave, Chanin 302B
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Bone Marrow Aspirate: 10cc of heparinized marrow aspirate will be required. We will perform flow cytometry and genome wide sequencing from these samples. RNA and DNA from patient bone marrow specimens at baseline will be sequenced to correlate expression patterns and mutational patterns with response. Three unstained slides containing bone marrow aspirate will be required for further studies

Peripheral Blood: If the bone marrow aspirate cannot be obtained then we will require 3 green top tubes, with 8 cc of blood each. Mononuclear cells from patient's peripheral blood will be purified by Ficoll-Hypaque sedimentation and these cells used for the Immunophenotyping by flow cytometry (CD33, CD34 and CD11b). These samples will also be used for possibly interphase FISH studies (if abnormal cytogenetics found at diagnosis). Cells will be frozen for future RNA extraction to perform gene expression studies.

Buccal swabs: Buccal swabs with brushes will be done at baseline and stored in RNA later solution. RNA/DNA will be isolated from these samples and compared to bone marrow samples to determine somatic mutations in MDS stem cells.

Banking of Samples: Peripheral blood, bone marrow, cell lysates, and cell products obtained from the previously mentioned samples will be stored for subsequent research related to this project.