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A PHASE 2, PROSPECTIVE, OPEN-LABEL STUDY (PO-MMM-PI-0011) TO DETERMINE THE SAFETY AND EFFICACY OF CC-4047 IN SUBJECTS WITH PRIMARY, POST POLYCYTHEMIA VERA, OR POST ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS (PMF; post-PV MF, or post-ET MF)

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1. BACKGROUND AND RATIONALE

1.1. Myelofibrosis with Myeloid Metaplasia

Myelofibrosis with myeloid metaplasia (MMM) is a rare (0.4-1.3 per 100,000 in Europe, Australia and USA), chronic, malignant disorder that was first described in 1879 by Henck who called it osteosclerosis. MMM was classified as a myeloproliferative disorder (1951) and further characterized as a clonal proliferative disorder of a pluripotent stem cell (1978).

There is some evidence of genetic transmission evidenced by a higher incidence rate in the Ashkenazi Jewish population in Northern Israel. It is also theorized that exposure to Thorotrast, industrial solvents (benzene and toluene) and the atomic bomb predisposes people to development of the disorder.

The primary pathogenetic mechanism of proliferation of a pluripotent stem cell clone leads to ineffective erythropoiesis, dysplastic-megakaryocyte hyperplasia, and an increase in the ratio of immature granulocytes to total granulocytes. This clonal myeloproliferation is characteristically accompanied by reactive myelofibrosis (bone marrow fibrosis) and by extramedullary hematopoiesis in the spleen or in multiple organs. The diagnosis is often suspected when teardrop-shaped red cells and myeloid precursors are detected in the peripheral blood. The typical clinical features include marked splenomegaly, progressive anemia, and constitutional symptoms. The terms “myeloid metaplasia” and “extramedullary hematopoiesis” are used interchangeably to describe a pathologic process of ectopic hematopoietic activity that may occur in any organ system but that affects primarily the liver and spleen.

1.1.1. Differential Diagnosis

The term “myelofibrosis with myeloid metaplasia” is usually reserved for subjects with agnogenic myeloid metaplasia (AMMM, also known as idiopathic myelofibrosis) and for those with a history of Polycythemia Vera (PV; 25-50% of subjects) or Essential Thrombocythemia (ET; 2-3% of subjects). Fibrosis can also be observed in Philadelphia-positive chronic myelogenous leukemia (CML). These three disease states are part of the differential diagnosis in the early cellular phase of MMM with minimal marrow fibrosis. These must be distinguished based on cytogenetics and clinicopathologic features. Other entities that must be included in the differential diagnosis include acute megakaryocytic leukemia (AML), primary thrombocytopenia, lymphoma, Hodgkin’s disease, metastatic malignancies (e.g., breast and colon cancer), tuberculosis (TB), histoplasmosis, Myelodysplastic syndrome (MDS), Hairy Cell Leukemia and plasma cell dyscrasias. While the diagnosis is often one of exclusion, there are some discriminating findings.

1.1.2. Prognosis

At the molecular level, a JAK2 tyrosine kinase mutation ($JAK2^{V617F}$) has recently been described in MMM with the reported mutational frequency ranging from 35% to 57% with 9-29% homozygosity. To date, however, the presence of $JAK2^{V617F}$ in MMM has

not been shown to have prognostic relevance. Presence of this mutation, change in its prevalence during the course of treatment, and associations with outcomes may provide further insight into its potential use as a biologic marker to track the effectiveness of therapies for MMM.

Adverse prognostic factors for survival include older age and anemia (hemoglobin < 10 gm/dL). The etiology for the latter finding is usually multifactorial and related both to marrow failure and hypersplenism. Poor prognosis has also been correlated with leukocytosis, leukopenia, circulating blasts, increased numbers of granulocyte precursors, thrombocytopenia, abnormal karyotype, and hypercatabolic symptoms.

The course of the disease is highly variable. Median survival from time of diagnosis ranges from 3 to 6 years; survival rates are 68% at 2 and 40% at 5 years. The usual causes of death are progressive marrow failure, transformation into a nonlymphoblastic leukemia, and portal hypertension.

1.1.3. Signs and Symptoms

The clinical picture of MMM involves constitutional symptoms (e.g., cachexia, night sweats, bone pain, fatigue, fever—present in 40% of subjects), splenomegaly, anisopoikilocytosis with teardrop erythrocytes, progressive anemia, immature myeloid and erythroid precursors in the peripheral blood (in one-third of the subjects), elevated lactate dehydrogenase (LDH) levels, and fibrosis of the marrow (as evaluated by reticulin and trichrome [collagen] stains). The leukoerythoblastic picture is postulated to be related to both the intramedullary sinusoidal marrow and splenic hematopoiesis.

The disease generally occurs in adults, 70% of the subjects are over the age of 50 years and the median age ranges from 54 to 62 years. Anemia is apparent in 50% to 70% at diagnosis and 25% will have severe anemia with hemoglobin level < 8.0 gm/dL. Splenomegaly is present in 85% to 100% of the subjects at diagnosis, and is massive in 10%. Approximately half of the subjects present with an elevated white cell count (WBC), 28% with thrombocytosis (platelet count > 500 x 10^9/L, and 37% with thrombocytopenia (platelet count < 150 x 10^9/L).

Growth factor and cytokine variations are multiple. It is unclear whether the aberrations in cytokine production and in the vasculature are pathogenic or whether they represent a nonspecific reaction associated with the underlying clonal activity. Increased levels of basic fibroblast growth factor (bFGF) have been reported in subjects with MMM. Both transforming growth factor–beta (TGF-beta) and bFGF regulate cell growth and differentiation. In addition to their potent fibrogenic activity, TGF-beta and bFGF regulate hematopoiesis by selective actions on primitive stem cells. Basic FGF has been shown to augment the activity of stem cell factor (SCF), interleukin-3 (IL-3), granulocyte-macrophage colony stimulating factor (GM-CSF), or erythropoietin on committed progenitor cells. Serum interleukin-6 (IL-6) has multiple biological effects, including the regulation of hematopoiesis, immune responses, and acute phase reactions. IL-6 appears to be a potent megakaryocytic maturation factor. Other cytokines/proteins that are disregulated in MMM include; tumor necrosis factor-alpha (TNF-alpha) and angiogenic agents like vascular endothelial growth factor (VEGF).

1.1.4. Treatment of MMM

No standard therapy exists for MMM. Hydroxyurea is the most commonly used agent in the proliferative phases of the disease. Interferon-alpha had yielded hematologic responses and reductions in splenomegaly in 30% to 50% of subjects, especially those in a proliferative phase; however, it tends to be poorly tolerated. Therapies for anemia management include androgens and/or erythropoietin. Splenectomy and/or splenic irradiation have been used to manage symptomatic splenomegaly. Splenectomy has been associated with risk of leukemic transformation in some series, and splenic irradiation can result in severe myelosuppression.

No medical therapy has been proven to prolong overall survival for these subjects. Subjects with an intact quality of life and no threatening hematologic abnormalities, such as erythrocytosis or thrombocytosis, have usually been observed without any therapy; however, new therapeutic modalities are currently being considered in determining treatment indications.

Advances in the pathogenesis of MMM are expected to facilitate the development of molecularly targeted therapy. In the meantime, current management strategies include observation for low risk cases, participation in experimental drug therapy at the intermediate risk level and allogeneic stem cell transplantation for high-risk disease. From a therapeutic standpoint, benefit to a subset of subjects has been demonstrated for both allogeneic stem cell transplantation and novel drugs, including the thalidomide-derived immunomodulatory analogs known as immunomodulatory drugs.

1.2. Rationale for CC-4047 in MMM

The efficacy of thalidomide has been significantly limited by adverse effects, which include sedation, neuropathy, constipation, and deep vein thrombosis. This toxicity profile seems dose-related and duration-related, spurring the development of IMiDs, which have the potential of improved potency and reduced toxicity. By modifying thalidomide structure through the addition of an amino group at the 4 position of the phthaloyl ring (to generate CC-4047) and with the further removal of a carbonyl on the ring to form another analog (CC-5013), such analogs are up to 50,000 times more potent at inhibiting TNF-alpha than the thalidomide parent compound *in vitro* and are markedly more stable. Indeed, when CC-5013 was tested at a dose range of 5 to 50 mg/d, 25 mg/d was determined to be the maximum tolerated dose without a significant level of the side effects of constipation and neuropathy as had been typical of thalidomide. Along with the improved tolerability, impressive response rates were realized in the treatment of multiple myeloma (MM) and MDS.

In multiple myeloma IMiDs not only act to inhibit angiogenesis through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, but also block the increased secretion of myeloma cell growth, survival, and migratory factors such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), and vascular endothelial growth factor (VEGF). In addition, they expand natural killer (NK) cell and T-cell numbers and are potent co-stimulators of T-cells when activated through the T-cell receptor. CC-4047, an IMiD, enhances production of gamma interferon (INFγ) and interleukin (IL)-2, and augments IL-10 production. Many of the cytokines active in MM

are similar to those noted in MMM: increased levels of bFGF, TNF-alpha, VEGF and IL–6. Therefore, there is reason to expect that CC-4047 may have a beneficial effect in the treatment of MMM.

In vitro models of anti-TNF activity have shown that CC-4047 has an IC_{50} of 24 nM (6.55 ng/mL) and 25 nM (6.83 ng/mL) against TNF produced by Lipo-polysaccharide (LPS)-stimulated human peripheral blood mononuclear cells and LPS-stimulated human whole blood respectively. Thalidomide, by comparison, has a TNF IC_{50} in human peripheral blood mononuclear cells of approximately 194 µM (50.1 µg/mL).

There is previous human experience with the treatment of MMM by the original IMiD, thalidomide. Single-agent thalidomide at "conventional" doses (> 100 mg/d) has been evaluated in MMM based on its antiangiogenic properties and the prominent neoangiogenesis that occurs in MMM. Thalidomide monotherapy at such doses produces approximately a 20% response rate in anemia but is poorly tolerated (an adverse dropout rate of >50% in 3 months). To improve efficacy and tolerability, 21 symptomatic subjects (hemoglobin level < 10 g/dL or symptomatic splenomegaly) with MMM were treated with low-dose thalidomide (50 mg/d) along with a 3-month oral prednisone taper (beginning at 0.5 mg/kg/d). The combination therapy was well tolerated in all enrolled subjects, with 20 subjects (95%) able to complete 3 months of treatment. An objective clinical response was demonstrated in 13 (62%) subjects, all improvements in anemia. Among 10 subjects who were transfusion dependent, 7 (70%) improved and 4 (40%) became transfusion independent. Improvements in anemia correlated with lower pretherapy $CD34^+$cell counts in the peripheral blood (median, 81.2 CD34+ cells/µL versus 554 $CD34^+$ cells/µL [nonresponders]; $P = 0.03$) as well as lower numbers of circulating blasts (median, 0.8% versus 4.7% in nonresponders; $P = 0.03$). Among 8 subjects with thrombocytopenia (platelet count <100 x 10^9/L), 6 (75%) experienced a 50% or higher increase in their platelet count. In 4 of 21 subjects (19%), spleen size decreased by more than 50%. Responses observed were mostly durable after discontinuation of the prednisone. The dose of thalidomide in this study (50 mg/d) was better tolerated than the higher doses used in previous studies. Adverse events associated with corticosteroid therapy were mild and transient. Clinical responses did not correlate with improvements in either intramedullary fibrosis or angiogenesis. The thalidomide-prednisone combination was well tolerated and appeared to be a promising drug regimen for treating cytopenias in subjects with MMM.

Ten of the MMM subjects completed an additional 3 month thalidomide-only treatment phase of the study. After discontinuation of the prednisone, clinical responses were maintained in 62% in terms of anemia, 66% in terms of thrombocytopenia, and 50% of the splenomegaly responses. (Mesa, 2003)

In 2006, results of 2 similarly designed but separate phase 2 studies involving single-agent lenalidomide (CC-5013, Revlimid) have been published, involving in a total of 68 patients with symptomatic myelofibrosis with myeloid metaplasia (MMM). Protocol treatment consisted of oral lenalidomide at 10 mg/d (5 mg/d if baseline platelet count < 100 x 10(9)/L) for 3 to 4 months with a plan to continue treatment for either 3 or 24 additional months, in case of response. Overall response rates were 22% for anemia, 33% for splenomegaly, and 50% for thrombocytopenia. Response in anemia was deemed

impressive in 8 patients whose hemoglobin level normalized from a baseline of either transfusion dependency or hemoglobin level lower than 100 g/L. Additional treatment effects in these patients included resolution of leukoerythroblastosis (4 patients), a decrease in medullary fibrosis and angiogenesis (2 patients). Grade 3 or 4 adverse events included neutropenia (31%) and thrombocytopenia (19%). The authors (Tefferi, 2006) concluded that lenalidomide engendered an intriguing treatment activity in a subset of patients with MMM that includeed an unprecedented effect on peripheral blood and bone marrow abnormalities. Interestingly, some patients previously treated with thalidomide responded to lenalidomide.

Prompted by the activity of single-agent oral lenalidomide (LEN) in primary or secondary (post-essential thrombocythemia or post-polycythemia vera) myelofibrosis (MF), Quintas-Cardama and colleagues (2008) sought to evaluate the safety and efficacy of the combination of LEN and prednisone (LEN+PRD) in a phase II study for patients with MF. The rationale was that the potent antiangiogenic and cytokine-modulating activity of LEN may be enhanced by PRD to reduce marrow fibrosis and improve hematopoiesis in MF. Therapy consisted of LEN 10mg/d PO (dose level [DL] 0) on days 1–21 of a 28-day cycle in combination with PRD 30mg/d PO during cycle 1, 15mg/d during cycle 2, and 15 mg/d every other day during cycle 3. LEN was to be given for a minimum of 6 cycles and continued indefinitely in responders. LEN dose could be reduced to 5 mg/d (DL –1) or to 5 mg/d every other day (DL –2), or increased to 15 mg/d (DL +1) or 20 mg/d (DL +2) according to toxicity or lack of response. Forty patients (23 male) have been treated. Median age was 62 years (range, 41–86), time from MF diagnosis to LEN+PRD therapy 10 months (range, 0–122), WBC count $87x10^9$/L (range, 1.1–89), hemoglobin 9.8 g/dL (range, 7.8–17.3), and palpable splenomegaly 10cm (range, 0–25). Patients had received a median of 1 prior therapy (range 0–4), including hydroxyurea (n=14), azacitidine (n=6), thalidomide (n=4), and IFN-α (n=3). Ten (25%) patients were treatment-naïve. The $JAK2^{V617F}$ mutation was detected in 18 (50%) of 36 tested patients and 20 (50%) of 40 had abnormal cytogenetics. 341 cycles have been administered. Patients have received therapy for a median of 18 months (range, 6–24.5). According to the International Working Group for Myelofibrosis Research and Therapy (IWG-MRT) criteria, 12 (30%) patients responded, including 8 $JAK2^{V617F}$-positive, 3 previously untreated, and 2 who had failed prior thalidomide-based therapy. Three (7.5%) partial response (PR), and 9 (22.5%) clinical improvement (CI) were seen. Anemia improved in 7 (30%; 3 PR and 4 CI) of 23 patients with pretreatment Hb <10g/dL or transfusion dependency. Splenomegaly significantly decreased in 10 (42%; 2 PR and 8 CI) of 24 patients. Again, few patients previously exposed to thalidomide responded to lenalidomide therapy. Responses occurred after a median of 12 weeks (range, 2–32), have been sustained for a median of 15 months (range, 4.1–20), and are ongoing in 10 of 12 responders still receiving LEN. After 12 months of therapy, a significant decrease was observed in the $JAK2^{V617F}$ allele burden among the 8 $JAK2^{V617F}$ positive responders (p=0.03). Four of the 8 $JAK2^{V617F}$-positive responders had >50% reduction of the mutant allele burden, becoming undetectable in 1. Serial histopathology analyses revealed significant reductions in bone marrow cellularity (p=0.01) and reticulin fibrosis (p=0.02) after 12 months of therapy in 8 assessable responders. The most frequent grade 3–4 toxicities were neutropenia (65%), anemia (50%), fatigue (30%), and thrombocytopenia (20%). Twenty-

four (60%) patients required one dose level reduction (5 required further reduction to dose level -2), 1 (2.5%) had the dose escalated, and 15 (25%) remained at the initial dose level. Thirty (75%) patients discontinued therapy due to lack of response (n=15), pt's decision (n=3), grade 3–4 toxicity (n=9), allogeneic stem cell transplant (n=1), loss of response (n=1), and poor compliance (n=1). No transformation to acute myeloid leukemia has been observed. In summary, prolonged administration of LEN is generally well-tolerated, and yields long-lasting clinical, histopathological, and molecular responses in patients with MF when administered in a continuous manner.

Very recently, a dose-escalation trial to determine whether CC-4047 can be given safely to MMM patients has been concluded (Mesa 2009). A classic phase-I 3 x 3 trial was done in persons with symptomatic MMM (anemia and/or symptomatic splenomegaly). The starting dose was 2.5 mg/d d 1-21 every 28 d. Dose-escalation at increments of 0.5 mg/d was done if no subject had a DLT (≥grade-4 hematologic toxicity, ≥grade-3 febrile neutropenia or ≥grade-3 non-hematologic toxicity) in cycle-1. Subsequent cohorts were treated until the maximum tolerated dose (MTD) was reached (dose level before that resulting in DLT in >1 of 6 subjects). 12 subjects with MMM were enrolled 06/08-12/08. 8 had primary MMM, 3, post-polycythemia vera MMM and 1, post-essential thrombocythemia MMM. Median age was 67 years (range, 51-83), 7 were female. 9 had a JAK2-V617F mutation. 11 were RBC-transfusion–dependent and 1 had a hemoglobin <10 g/dL. Median WBC was 4.5 x 10e9/L (range, 2–64 x 10e9/L). Median platelets were 111 x 10e9/L (range, 52-538 x 10e9/L). 10 subjects had splenomegaly, median size of 12 cm below the LCM (range, 4-26 cm). 3 subjects were enrolled in each of the 2.5, 3.0, and 3.5 mg dose cohorts. DLTs were observed at the 3.5 mg level: 2 of 3 subjects had grade-4 neutropenia and 1, grade-3 thrombocytopenia. 3 more subjects were enrolled at the 3.0 mg level cohort confirmed this dose as the MTD. 4 of 9 subjects receiving ≥3.0 mg/d had grade-3 neutropenia and 1 had grade-3 thrombocytopenia. Other toxicities were <grade-3 including fatigue, dyspnea, rash, lymphadenopathy and headaches. Subjects received a median of 3 cycles (range, 2-6 cycles). 8 subjects remain on-study; reasons for discontinuation were progression (N=2) and no response (N=2). Therefore, data indicate the dose of CC-4047 can be increased to 3.0 mg/d for 21 d of a 28 d cycle. The DLT at higher doses is neutropenia.

ADDENDUM 11/10/09:

An update of the Phase 1 trial done at the Mayo clinic (Dr. Ruben Mesa, personal communication) was provided. Nineteen MMM patients were enrolled between June, 2008 and March, 2009. Most of the subjects were intermediate-2 or high risk by the International Prognostic Scoring System for MF. Median duration of disease at enrollment was 24 months (range, 1-173 months). Most were RBC-transfusiondependent and had symptomatic splenomegaly. Three subjects enrolled into the 2.5 mg/d, 3.0 g/d, and 3.5 mg/d cohorts (given for 3 weeks, with one week break). The dose limiting toxicity (DLT) was bone marrow suppression which occurred in 2 of 3 subjects in the 3.5 mg/d cohort. 3 additional subjects received 3.0 mg/d confirming this as the MTD. 7 additional subjects were enrolled at the MTD of 3.0 mg/d. Because no efficacy was seen at 3.0 mg/d (21 of 28 days) the dose was decreased to 0.5mg/d (given continuously daily for 4 weeks; no break in therapy) after three cycles in 8 subjects. 7 subjects responded using the International Working Group for Myelofibrosis Research and Treatment criteria

for Clinical Improvement (IWGMRT CI). All responders had an IWG-MRT CI for anemia (6 previously RBC transfusion-dependent). 2 of these anemia responders also had a decrease in splenomegaly. The eligibility criteria excluded the possibility of an IWG-MRT CI for thrombocytopenia. However all 5 subjects with pre-study platelets of 50-100x109/L had an increase in their platelet number, with 3 of these achieving normal platelet levels. Responses occurred after a median of 4 months (range, 2-9 months) and only after reduction to 0.5mg/d in 5 responders including the 2 subjects with decreased spleen size. These responses occurred after 1 and 2 cycles after dose reduction, respectively (1-3 months). Responses were durable; 5 responders continue on-study.

In addition, results of randomized Phase II study have been published (Tefferi, 2009). In a phase II randomized, multicenter, double-blind, adaptive design study, four treatment arms were evaluated: pomalidomide (2 mg/day) + placebo, pomalidomide (2 mg/day) + prednisone, pomalidomide (0.5 mg/day) + prednisone, and prednisone + placebo. Pomalidomide was administered for up to twelve 28-day treatment cycles. Prednisone (30 mg/day) was given in a tapering dose schedule during the first three cycles. Response was assessed by International Working Group criteria. Eighty four patients with MMM-associated anemia were randomly assigned to the above-listed treatment arms: 22, 19, 22 and 21, respectively. All active patients have completed six cycles of treatment. Response in anemia was documented in 20 patients, including 15 who became transfusion-independent. Response rates in the four treatment arms were 23%, 16%, 36% and 19%. The corresponding figures for patients receiving ≥ 3 cycles of treatment (*n*=62) were 38%, 23%, 40% and 25%. Response to pomalidomide ± prednisone was durable (range 3.2-16.9+ months) and significantly better in the absence of leukocytosis (37% vs. 8%; p=0.01); *JAK2*V617F or cytogenetic status did not affect response. Grade ≥3 toxicities were infrequent and included (in each treatment arm) neutropenia (9%-16%-5%-5%), thrombocytopenia (14%-16%-9%-5%) and thrombosis (9%-5%-0%-0%). Pomalidomide therapy at 0.5 ± an abbreviated course of prednisone is well tolerated in patients with myelofibrosis and active in the treatment of anemia.

Finally, 20 patients have been accrued into current study so far, with starting dose of 3mg/day. After median follow up of 2 months, most patients had to interrupt the therapy due to side effects: 13 patients experienced myelosuppression, 3 had rash/swelling. The study accrual has been put on hold, pending modification of the dose to 0.5mg/day (given continuously).

ADDENDUM 3/30/11:

Since the last amendment final results (previous amendment provided preliminary results) of the Phase I study of pomalidomide has been published (Phase1/-2 study of Pomalidomide in myelofibrosis. Mesa RA, Pardanani AD, Hussein K, Wu W, Schwager S, Litzow MR, Hogan WJ, Tefferi A. Am J Hematol. 2010 Feb;85(2):129-30.): "We conducted a dose-escalation study to see if higher doses of pomalidomide (previously shown to be safe and effective for myelofibrosis associated anemia at 0.5 mg/day [with prednisone] or 2.0 mg/day) increased anemia responses. 3.0 mg/d given for 21 of 28 consecutive days was the maximum-tolerated dose (MTD), with myelosuppression being

dose limiting. Nonresponders at the MTD had their dose decreased and the therapy interval increased to daily. Seven of 19 subjects had an anemia-response and two had a spleen response. Most responses occurred after dose-reduction to 0.5 mg/d, suggesting higher doses are associated with increasing myelosuppression without increasing (or possibly decreasing) efficacy.

Very recently, a Phase II study results were published, examining low dose pomalidomide 0.5mg/day as a single agent, without prednisone (A phase-2 trial of low-dose pomalidomide in myelofibrosis. Begna KH, Mesa RA, Pardanani A, Hogan WJ, Litzow MR, McClure RF, Tefferi A. Leukemia. 2011 Feb;25(2):301-4.): "In a previous study, we reported on the safety and efficacy of low-dose (0.5 mg) pomalidomide and prednisone and pomalidomide alone (2 mg/day), for the treatment of anemia associated with myelofibrosis (MF). The current study examined the value of low-dose pomalidomide alone. The main eligibility criterion was transfusion-dependency or hemoglobin of 10gm per 100 ml. Anemia response was assessed by International Working Group criteria. Pomalidomide (0.5 mg/day) was given to 58 patients (median age 68 years); 46 (79%) were transfusion-dependent. Anemia response was seen in 17% of patients. Grade 3 or 4 thrombocytopenia/neutropenia occurred in 2%/ 0% of patients". This experience was not as good as previously published result when pomalidomide 0.5mg/day was combined with prednisone (36% response in anemia), as explained above in the "ADDENDUM 11/10/09" (Tefferi, 2009).

Finally, preliminary interim results of this study are available, as described in section 5.5: 20 evaluable patients have been observed for at least 6 cycles on therapy with single agent CC-4047 at 0.5mg/day. We have observed 3 patients that has become transfusion independent (response rate of 15%). In terms of toxicity, the therapy with such a low dose of pomalidomide was very safe: one occurrence of neutropenic fever and one occurrence of leg DVT (both in the same patient). Therefore, we propose to study low dose pomalidomide 0.5mg/day in combination with prednisone, to extend previously noted activity of the combination (22 patients treated with 36% response rate) as reported by Tefferi (2009).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary objectives

- To determine the effect of CC-4047 and prednisone in the treatment of Primary, Post Polycythemia Vera, or Post Essential Thrombocythemia Myelofibrosis (PMF, post-PV MF, or post-ET MF).
- To determine the safety of CC-4047 and prednisone in the treatment of Primary, Post Polycythemia Vera, or Post Essential Thrombocythemia Myelofibrosis (PMF, post-PV MF, or post- ET MF).

2.1.2 Secondary study objectives

- To further explore the nature and quality of responses to CC-4047 and prednisone

2.2. Endpoints

2.2.1. Primary Endpoint

- Best overall response as determined by International Working Group Criteria over the first 6 cycles (168 days) of study treatment
- Safety (type, frequency, severity [National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0] of adverse events (AEs), and relationship of AEs to CC-4047)

2.2.2. Secondary Endpoints

- Duration of response
- Time to response
- Best overall response as determined by International Working Group Criteria over the first 12 cycles (336 days) of study treatment
- Cytogenetic response in subjects with a baseline abnormality
- Molecular response ($JAK2^{V617F}$ mutation burden) in peripheral blood in mutation positive subjects
- Bone marrow fibrosis improvement
- Quality of Life (QoL) assessments [the four components (Physical, Social/Family, Emotional and Functional Well-Being) and total of the 27-item FACT-G, together with the 13-item fatigue subscale, the total of the Additional Concerns, and a Likert Pain Scale for splenic pain.

3. INVESTIGATIONAL PLAN

3.1. Overall design

CC-4047 is a phase 2, prospective, open-label study to determine the efficacy and safety of CC-4047 at a 0.5 mg dose, in combination with prednisone, to study further in subjects with primary, post polycythemia vera, or post essential thrombocythemia myelofibrosis

Screening:

Potential subjects will enter screening and be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. The screening period will not last more than 28 days. The assessments and procedures that will be performed during screening are outlined in Appendix M: Schedule of Events. Screening assessments will include an informed consent, medical history, review of prior medications, complete physical exam, ECOG performance status assessment, complete blood count (CBC) with differential, serum chemistries, urinalysis, thyroid function tests, 12-lead ECG, bone marrow biopsy and aspirate to confirm diagnosis and for standard cytogenetics, JAK2 mutation (by quantitative polymerase chain reaction [PCR], and PCR or fluorescent in situ hybridization (FISH) for bcr/abl, spleen and/or liver (if spleen is absent) measurements, and QoL Assessments.

Females of reproductive potential[1] must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program. All study participants must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program.

Before starting study drug:

Subjects must follow pregnancy testing requirements as outlined in the POMALYST REMS™ program.

Treatment Period:

Subjects meeting all inclusion and exclusion criteria will receive 0.5mg CC-4047. Prednisone will be given during first 3 cycles of therapy. It will be dosed orally at the dose of 30 mg/day during cycle 1, 15 mg/day during cycle 2, and 15 mg every other day during cycle 3, and then it will be discontinued. Prednisone will be used from commercially available supplies.

Subjects will remain on study treatment in the Treatment Period in the absence of disease progression or toxicity warranting discontinuation of therapy. Twenty-eight days is considered one cycle of therapy. Subjects may be taken off study at 6 months if there is no response, however, they should continue to be followed until disease progression or initiation of an alternate therapy.

[1] A female of childbearing potential is a sexually mature woman 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).

Study assessments and serial measurements of safety and efficacy will be performed as outlined in Appendix M: Schedule of Assessments. All scheduled visits will have a ±3-day window unless otherwise stated. Beginning with Cycle 6 scheduled visits will have a +/-7 day window.

CBCs will be monitored weekly for the first 56 days of study treatment and then, at minimum, every 28 days. Study visits will occur at least every 28 days. Study visits should occur whether or not study drug has been interrupted for an adverse event. Repeat bone marrow aspirate, biopsy and cytogenetic studies will be performed to confirm a complete response and when clinically indicated. Cytogenetic analysis may be performed on the peripheral blood if necessary. Patients who have been on the study for at least 3 cycles and had no grade 3 or 4 toxicity, will be allowed to return to MD Anderson at the end of Cycle 6, then subsequently every 6 cycles. In this case mandatory monthly visits will be done at the local referring doctor's office, and will also include phone contact by the study staff.

Pregnancy Testing

Patients must follow pregnancy testing requirements as outlined in the POMALYST REMS™ program.

3.1.1. Investigational Drug

3.1.1.1. Supplier(s)

Celgene Corporation will supply POMALYST® (CC-4047) to study participants at no charge through Celgene's Pomalidomide Risk Evaluation and Mitigation Strategy (POMALYST REMS™).

3.1.1.2. Dosage form

CC-4047 will be supplied as 0.5mg capsules for oral administration.

3.1.1.3. Packaging

CC-4407 will be shipped directly to the pharmacy at the study site. Bottles will contain a sufficient number of capsules for one cycle of dosing.

3.1.1.4. Labeling

CC-4047 investigational supplies are dispensed in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use. The study drug label must be clearly visible. Additional labels must not cover the Celgene label.

CC-4047 should not be handled by FCBP unless wearing gloves.

3.1.1.5. Receipt of study drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

3.1.1.6. Storage

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

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

3.1.1.7. Unused study drug supplies

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Subjects will be instructed to return empty bottles or unused capsules.

3.1.1.8 Drug dispensing requirements

Pomalidomide (POMALYST®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS™ program. Per the standard POMALYST REMS™ program requirements, all physicians who prescribe pomalidomide 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 POMALYST REMS™ program.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle. This is in accordance with the POMALYST REMS™ program.

3.2. 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. Screening procedures are outlined in Section 2, Schedule of Study Assessments and unless otherwise specified, must take place within 28 days prior to initiation of therapy.

3.3. Inclusion and Exclusion Criteria

Subjects are to be assessed for suitability for entry into the study based on the following inclusion and exclusion criteria.

3.3.1. Key Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Must be ≥ 18 years of age at the time of voluntarily signing an Institutional Review Board/Independent Ethics Committee (IRB/IEC) – approved informed consent form.
2. Must be diagnosed with myelofibrosis requiring therapy including myelofibrosis with myeloid metaplasia (MMM), de novo presentation (i.e. agnogenic myeloid metaplasia [AMMM], and developing after an antecedent history of Polycythemia vera (i.e., post-polycythemic myeloid metaplasia [PPMM]), or essential Polycythemia (i.e., post thrombocythemic myeloid metaplasia [PTMM]).
3. Screening total hemoglobin level < 10 g/dL or transfusion-dependent anemia defined as per IWG criteria (transfusion dependency defined by a history of a least 2 units of red blood cell transfusions in the last 28 days for hemoglobin < 8.5 g/dL that was not associated with overt bleeding).
4. Must have adequate organ function as demonstrated by the following ≤ 14 days prior to starting study drug:
   - ALT (SGOT) and AST(SGPT) ≤ 3 x upper limit of normal (ULN), [unless upon judgment of the treating physician, it is believed to be due to extramedullary hematopoiesis (EMH)]
   - Total bilirubin < 3 x ULN or Direct Bilirubin < 2 x ULN
   - Serum creatinine ≤ 2.5 mg/dL
   - Absolute neutrophil count ≥ 1,000/μL (≥1.0 x 10^9/L)
   - Platelet count ≥ 50,000/μL (≥50 x 10^9/L)
5. Subjects must be willing to receive transfusion of blood products.
6. ECOG performance status (PS) of 0, 1, or 2 at screening.
7. Must be willing to adhere to the study visit schedule and other protocol requirements.
8. No active malignancies with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast.
9. All study participants must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program.
10. Females of reproductive potential (FCBP[†]) must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program. Able to take

[†] A female of childbearing potential is a sexually mature woman 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).

aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).

3.3.2. Key Exclusion Criteria

1. Known positive status for HIV, hepatitis B carrier, or active hepatitis C infection.
2. The use of any growth factors, cytotoxic chemotherapeutic agents (e.g. hydroxyurea), corticosteroids, or experimental drug or therapy within 14 days of starting CC-4047 and/or lack of recovery from all toxicity from previous therapy to grade 1 or better.
3. Any serious medical condition or psychiatric illness that would prevent, (as judged by the treating physician) the subject from signing the informed consent form or any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
4. Pregnant or lactating females.
5. Prior use of CC-4047.
6. Currently enrolled on another clinical trial or receiving investigational agent

3.4. Visit schedule and assessments

Screening Assessments and all on-study scheduled visits and assessments are outlined in Appendix M: Schedule of Assessments.

For females of child bearing potential, counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood.

Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.

Counseling for all men about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen.

An unscheduled visit can occur at any time during the study. Source documentation must be maintained for these unscheduled visits. The date for the visit and any data generated

must be recorded on the appropriate source. Source documents for these unscheduled visits must also be maintained.

At treatment discontinuation, subjects will undergo off study evaluations as outlined in Appendix M: Schedule of Assessments. In addition, a safety assessment will be done approximately 28 days post the last dose of study drug.

3.5. Drug Administration

3.5.1. Treatment

Subjects who meet entry criteria will be eligible to receive 0.5mg CC-4047 and prednisone.

3.5.2. Dosing regimen

Initial dosing of CC-4047 for eligible subjects will be 0.5mg daily. Subjects will receive oral CC-4047 from day 1 through day 28, continuously, in the absence of disease progression or toxicity warranting discontinuation of therapy. Twenty-eight days is considered one cycle of therapy. Dosing will be at approximately the same time each day. CC-4047 capsules should be swallowed whole, and should not be broken, chewed or opened. CC-4047 should be taken without food, at least 2 hours before or 2 hours after a meal. If a dose of CC-4047 is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up, rather it should be taken at the next scheduled time point. Patients who take more than the prescribed dose of CC-4047 should be instructed to seek emergency medical care if needed and contact study staff immediately.

Only one cycle of study drug will be supplied to the subject each cycle. Prednisone will be given during first 3 cycles of therapy. It will be dosed orally at the dose of 30 mg/day during cycle 1, 15 mg/day during cycle 2, and 15 mg every other day during cycle 3, and then it will be discontinued.

Subjects must also receive oral low-dose aspirin (81 mg) as prophylactic anti-thrombotic treatment unless it is contraindicated or the subject has a platelet count less than 75,000/μL. If low-dose aspirin is contraindicated, the investigator should prescribe another appropriate prophylactic anti-thrombotic therapy.

Single oral CC-4047 doses of 1 and 50 mg in healthy adult males were safe and resulted in Cmax values of 11.2 and 288 ng/mL respectively. Given the short half-life in healthy adult male humans (approximately 8 to 11 hours) and once daily dosing, minimal accumulation is expected. A daily dosing schedule will be utilized for this study.

Subjects experiencing adverse events may need study treatment modifications (Table 1).

3.5.3. Special Handling Instructions

Females of childbearing potential should not handle or administer the clinical dosage forms unless they are wearing gloves.

3.5.4. Record of administration

Accurate recording of all study drug administration (including dispensing and dosing) will be made in the appropriate section of the source documents.

3.6. Dose Continuation, Modification and Interruption

All adverse events/toxicities are to be graded according to the Common Terminology Criteria for Adverse Events (CTCAE Version 3.0). Subjects who cannot tolerate dose of 0.5mg are to discontinue treatment. The dose of CC-4047 is not to be escalated.

3.6.1. CC-4047 Dose Reduction Steps

No reduction of the dose below 0.5mg a day is planned (Table 1).

3.6.2. Initiation of a New Cycle of Therapy

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1,000/μL (≥ 1 X 10^9/L);
- The platelet count is ≥ 50,000/μL (≥ 50 X 10^9/L);
- Any CC-4047-related allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1 severity;
- Any other CC-4047-related adverse event that may have occurred has resolved to ≤ grade 2 severity

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of CC-4047 will not be initiated until the toxicity has resolved as described above.

3.6.3. Instructions for dose modifications or interruption during a cycle.

Table 1: CC-4047 Dose Modification Guidelines

CTCAE CATEGORY	ADVERSE EVENTS	DOSING CHANGE
Allergy/Immunology	Allergic reaction/ hypersensitivity (including drug fever) Grade 2	Discontinue CC-4047.
	Allergic reaction/ hypersensitivity (including drug fever) Grade 3	Discontinue CC-4047.
Blood/ Bone Marrow	Neutropenia ANC < 500/μL (Grade 4) for >7 Days	Discontinue CC-4047.

CTCAE CATEGORY	ADVERSE EVENTS	DOSING CHANGE
Blood/Bone Marrow	Thrombocytopenia Platelet count < 25,000/μL (Grade 4) for >7 Days	Discontinue CC-4047.
Cardiovascular	Thrombosis/Embolism Grade 3 or 4	Hold CC-4047 and start systemic anticoagulation. Restart at the same dose level at investigator's discretion and only if approved by the Principal Investigator based on established significant benefit to the patient. The patient must sign consent form again to restart the therapy.
Dermatology/Skin	Grade 3 Rash	Discontinue CC-4047.
	Desquamating/Blistering Rash	Discontinue CC-4047.
	Rash: Erythema multiforme	Discontinue CC-4047.
Endocrine	Elevated or Reduced Thyroid Function Test results without symptoms of hyper- or hypo-thyroidism	Confirm test results. If significant, refer for appropriate therapy. Maintain dose of CC-4047 if appropriate.
	Elevated or Reduced Thyroid Function Test results with symptoms of hyper- or hypo-thyroidism	Hold study drug. Evaluate etiology and refer for appropriate therapy. Restart at the prior dose.
Neurology	Neuropathy – Cranial/motor/sensory Grade 2	Hold CC-4047. Restart once adverse event is completely resolved.
	Neuropathy – Cranial/motor/sensory Grade 3	Discontinue CC-4047.
	Neuropathy – Cranial/motor/sensory Grade 4	Discontinue CC-4047.
Other non-hematological, clinically significant toxicity	Grade 3	Discontinue CC-4047.
	Grade 4	Discontinue CC-4047.

3.6.4. Treatment compliance

At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused study drug to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit and reconcile with the subject diary.

3.7. Concomitant therapy

3.7.1. Recommended concomitant therapy

All supportive measures consistent with optimal subject care will be given throughout the study. Packed red blood cell transfusions are allowed when necessary. Growth factor use (including erythropoietin) is not allowed with the exception of the use of filgrastim (G-CSF) or pegfilgrastim, which is permitted when used to treat febrile neutropenia or those who have ≥ grade 3 neutropenia and at the investigators discretion for prolonged neutropenia. Subjects should receive full supportive care, including transfusions of blood products, antibiotics and antiemetics and prophylactic treatment for potential hypersensitivity reactions and tumor lysis syndrome when appropriate. Splenic infarcts occasionally occur and should be managed with analgesics at the discretion of the clinician and do not necessarily require withdrawal from the study.

3.7.2. Anticoagulation Consideration

CC-4047 may increase the risk of thrombotic events in subjects who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When CC-4047 is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, adriamycin) and erythropoietin the risk of thrombosis may be increased.

Subjects must receive oral low-dose aspirin (81 mg) as prophylactic anti-thrombotic treatment unless it is contraindicated or the subject has a platelet count less than 75,000/μL. If low-dose aspirin is contraindicated, the investigator should prescribe another appropriate prophylactic anti-thrombotic therapy.

3.7.3. Prohibited concomitant therapy

Concomitant use of growth factors (including erythropoietin and excluding G-CSF and pegfilgrastim), cytotoxic chemotherapeutic agents (e.g. hydroxyurea), or other experimental drug or therapy for myelofibrosis while the subject is on study is prohibited. Filgrastim (G-CSF) is permitted for use during the study when used to treat febrile neutropenia or those who have ≥ grade 3 neutropenia and at the investigators discretion for prolonged neutropenia. Chronic use (>2 weeks) of greater than physiologic doses of a corticosteroid agent (dose equivalent to >10 mg/day of prednisone) is not permitted during the study. Anagrelide is allowed to be used during the study to control elevated platelet count.

3.8. Discontinuation of Study Treatment

Subjects will receive oral CC-4047 daily from day 1 through day 28 every 28 days in the absence of disease progression or toxicity warranting discontinuation of therapy. Therapy will continue as long as there is a benefit, as judged by treating physician.

Treatment with study drug is to be discontinued when any of the following occurs:

- Lack of therapeutic effect
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy

3.9. Follow-Up

Subjects who discontinue treatment for any reason, will be followed every three months until disease progression or initiation of alternate therapy. At treatment discontinuation, subjects will undergo a safety assessment approximately 28 days post the last dose of study drug. In addition, off study evaluations per the Schedule of Assessments, Appendix M will be done.

4. SERIOUS ADVERSE EVENT REPORTING

4.1 Serious Adverse Event

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

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

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

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office. -
- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**
- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

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

4.1.1. Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 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 tracking number (PO-MMM-PI-0011) 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.

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

4.1.2. 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 IP, or within (insert time-frame which must be at least 28 days of the subject's last dose of IP), are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent 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, or approved equivalent 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, or approved equivalent 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, or approved equivalent form.

Male Subjects

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

5. BIOSTATISTICAL ANALYSIS

5.1 Overview

This is two stage, phase II trial designed to assess the effect of CC-4047 and prednisone in subjects with Primary, Post Polycythemia Vera, or Post Essential Thrombocythemia Myelofibrosis (PMF, post-PV MF, or post-ET MF). Secondary objective is to determine the safety of CC-4047 and prednisone in this population.

5.2 Datasets to be analyzed

All subjects meeting the eligibility criteria that have signed a consent form and have begun treatment will be evaluable for response.

5.3 Statistical Methodology

5.3.1. Primary Endpoint

The primary endpoint of this trial is best overall response. An evaluable subject will be classified as a treatment success for the primary endpoint if the subject's best overall response is CR, PR or CI (Clinical Improvement) as determined by International Working Group Criteria over the first 6 cycles of study treatment at 0.5mg/day dose. The largest success proportion where the proposed treatment regimen would be considered unpromising in this population is 5%, representing the probability of a response by chance. The smallest success proportion that would warrant further subsequent studies with the proposed treatment regimen in this subject population is 20%.

5.3.2. Study Design

Subjects receiving CC-4047 alone, and the new study cohort of patients receiving CC-4047 and prednisone in combination will be evaluated using the same statistical design: a two stage design with one interim analysis will be used to permit early reporting of efficacy results if there is strong evidence that the study regimen is inactive. 37 evaluable subjects will be accrued onto this study unless undue toxicity is encountered. We anticipate accruing an additional 10-20% of subjects to account for ineligibility or cancellation; i.e. we may accrue as many as 70 subjects to this study. Subjects who have been taken off study due to toxicity related to high dose pomalidomide (i.e. those who started therapy with 3mg/day) will be replaced with new patients that will start therapy with 0.5mg/day), so that the goals of the study can be accomplished.

- Decision Rule: If 3 or fewer treatment successes are observed after all 37 evaluable subjects have been followed for at least 6 cycles, we will conclude that the treatment is insufficiently active in this subject population. If 4 or more treatment successes are observed, then this will be considered adequate evidence of promising activity, and the treatment may be recommended for further testing in subsequent studies.

- Over accrual: if more than the target number of subjects are accrued, the additional subjects will not be used to evaluate the stopping rule or used in any decision making process. However, they will be included in final point estimates and confidence intervals.
- Study duration: The anticipated accrual rate for this group of subjects is approximately 3 subjects per month. It will take approximately 14 months to accrue 37 evaluable subjects. The analysis can begin as soon as the 37th evaluable subject has been observed for 6 cycles (168 days), i.e., approximately 20 months after the trial opens.

5.3.3. Analysis Plan

Primary Endpoint

The observed response rate over the first 6 cycles of therapy at 0.5mg/day will be estimated by the number of responses (confirmed CR, PR or CI) over the first 6 cycles divided by the total number of evaluable subjects. Confidence intervals for the true response rates will be calculated according to the approach of Duffy and Santner.

Secondary Endpoints

Duration of response: duration of response is defined as the date at which the subject's objective status is first noted to be a CR, PR or CI to the date progression is documented (if one has occurred) or to the date of last follow-up (for those subjects who have not progressed).

Time to response: The time to response is defined as the time from study registration to the first date at which the subject's objective status was classified as a response (CR, PR or CI). In subjects who do not achieve a response, time to response will be censored at the subject's last evaluation date. The distribution for each of these event-time variables (duration of response and time to response) will be estimated by Kaplan-Meier curves.

Best overall response as determined by the International Working Group Criteria over the first 12 cycles of study treatment: will be estimated by the number of responses (confirmed CR, PR or CI) over the first 12 cycles divided by the total number of evaluable subjects. Confidence intervals for the true response rates will be calculated according to the approach of Duffy and Santner.

Cytogenetic responses and molecular response: cytogenetic responses and molecular responses will be summarized as well as evaluated graphically. Correlations among clinical responses and laboratory variables will be explored using a Wilcoxon/Kruskal-Wallis test for ordered contingency tables. Mutation status will be explored in relation to clinical outcome (response) using Fisher's exact test.

Quality of Life (QOL) assessments: For each of the QOL assessment components, changes from baseline to each of the follow-up time points will be reported. The change will be compared between two subgroups: subjects who response to the treatment and subjects who do not response. Normality testing via the Shapiro-Wilk procedure will determine whether or not parametric or nonparametric procedures will from the basis for analysis (two-sample t-test, Wilcoxon rank sum test).

Toxicity: As per NCI CTCAE Version 3.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Such adverse events will be captured by Principal Investigator and his staff in a database. The maximum grade for each type of toxicity will be recorded for each subject, including start/stop dates, and frequency tables for each group will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related" to study treatment in the event of an actual relationship developing.

5.4 Safety evaluation

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

The severity of the toxicities will be graded according to the NCI CTCAE v3.0 whenever possible.

Toxicity Stopping Rule:

This phase II clinical trial will have a stopping rule based on toxicity defined as an adverse event considered to be at least possibly related to treatment. In particular accrual to the study will be temporarily suspended if: a) 2 or more among the first 10 subjects treated on this trial experiences a Grade 4 cardiac, lung, liver or neurological toxicity that is felt to be drug related. b) 20% or more of subjects (when more than 10 subjects have been accrued) experience a Grade 4 cardiac, lung, liver or neurological toxicity that is felt to be drug related. After consideration by the study team (study chair[s], statistician, etc.) a decision will be made as to whether accrual can resumed.

5.5 Interim analyses

An interim analysis will be performed after the first 20 evaluable subjects have been observed for at least 6 cycles**.** If 1 or fewer treatment successes are observed in these 20 subjects, this treatment regimen will be considered inactive in this population and accrual will be terminated. If 2 or more treatment successes are observed in these 20 subjects, decisions about activity must await the final analysis. Enrollment into the study will continue while waiting for the 20^{th} eligible subject to complete at least 6 cycles of treatment. These additional subjects will not be used to evaluate the interim stopping rule.

5.6. Sample size and power considerations

Assuming that the number of successes is binomially distributed, this decision rule has a significance level of 0.09; i.e., there is a 9% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions and the probability of stopping after the first stage can be tabulated as a function of the true success proportion as shown in the following table:

If the true success proportion is	0.05	0.10	0.15	0.20	0.25
then the probability of declaring that the	0.09	0.44	0.75	0.91	0.97

regimen warrants further studies is					
And the probability of stopping at stage I is:	0.74	0.39	0.18	0.07	0.02

In particular, this decision rule has 91% power to detect an effective treatment given that the true response rate is at least 20% using this treatment. If the true success rate is 5%, the chance of stopping early at the first stage is 0.74 and the chance of concluding that the treatment is active is 0.09. If the true success rate is 20%, the chance of stopping early at the first stage is 0.07 and the chance of concluding that the treatment is active is 0.91 (power).

6 REGULATORY CONSIDERATIONS

6.1 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.

6.2 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 medical records, and copy filed in the regulatory binder.

6.3 Subject confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene's representatives 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.

6.4 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of eCRF 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; 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 study 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.

6.5 Premature discontinuation of study

6.5.1 Single center

The responsible local clinical Investigator, MDACC as well as Celgene have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. 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.

6.5.2 Study as a whole

Celgene and MDACC reserve the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

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.).

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