Title: Eltrombopag for the Management of Thrombocytopenia Associated with Tyrosine Kinase Therapy in Patients with Chronic Myeloid Leukemia (CML) and Myelofibrosis

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Synopsis

Title of study	Eltrombopag for the Management of Thrombocytopenia Associated with Tyrosine Kinase Therapy in Patients with Chronic Myeloid Leukemia (CML) or Myelofibrosis (MF)
Investigator/study center location	University of Texas MD Anderson Cancer Center
Phase of development	Phase 2
Study objectives	**Primary:** To determine the efficacy of eltrombopag for patients with CML or MF who have developed thrombocytopenia during the course of therapy with tyrosine kinase inhibitors (TKI) as measured by recovery of platelet count **Secondary:** 1. To determine the safety of eltrombopag for patients with CML or MF who have developed thrombocytopenia during the course of therapy with TKI 2. To determine the dose intensity of TKI after start of therapy with eltrombopag 3. To determine response to TKI after start of therapy with eltrombopag
Study design	This is a non-randomized, Phase II, single arm study of individualized dosing of eltrombopag. A maximum of 29 subjects with CML and 10 subjects with MF will be evaluated. Subjects will continue receiving their TKI at the doses prescribed at the time of registration and eltrombopag therapy will be initiated. Dose escalations of TKI are allowed once improvement in platelet count (≥ 50 x 10^9/L for CML and ≥ 100 x 10^9/L for MF) is demonstrated for at least 2 consecutive weeks.
Study criteria	**Inclusion:** 1. CML patients in chronic phase receiving treatment with any FDA approved TKI; or CML patients in accelerated or blastic phase who are considered to be in this phase because of thrombocytopenia or because of clonal evolution and with no other criteria for accelerated/blastic phase or patients with myelofibrosis receiving treatment with FDA approved TKI and with peripheral blood and/or bone marrow blast ≤ 10% 2. Grade ≥ 3 thrombocytopenia (platelets <50 x 10^9/L) after the first 3 months of therapy with the TKI for patients with CML and platelets <100 x 10^9/L for patients with MF after first 3 months therapy. Thrombocytopenia must be either recurrent (i.e., second or greater episode of thrombocytopenia) or having required dose reductions of the TKI; 3. Subject is anticipated to have therapy with TKI continued for ≥3 months; 4. Adequate organ function: • Total bilirubin (except for Gilbert's Syndrome) ≤ 1.5xULN • ALT and AST < 3xULN • Creatinine ≤ 2xULN **Exclusion:** 1. CML patients in accelerated or blastic phase except for those who are considered to be in this phase because of thrombocytopenia or because of clonal evolution and with no other criteria for accelerated/blastic phase; or myelofibrosis patients who have transformed in to acute leukemia or has ≥ 10% blast in peripheral blood and/or in bone marrow. 2. Thrombocytopenia that is considered to be unrelated to treatment with TKI or accelerated phase as defined above; 3. Age < 18 years; 4. Stem cell transplantation within preceding 60 days prior to registration; 5. Patients with documented active hepatitis B or C infection;

	6. Patients with known bone marrow reticulin fibrosis (≥ grade 2) (only applicable to patients with CML); 7. Patients with palpable splenomegaly ≥ 16cm below coastal margin (only applicable to patients with CML); 8. Female subjects who are pregnant or breastfeeding. Women of childbearing potential are required to have a βHCG serum or urine pregnancy test performed within 7 days prior to first study drug dose. 9. Patients with known risk factors for thromboembolism (e.g. Factor V Leiden mutation, ATIII deficiency, Protein C and S deficiency, antiphospholipid syndrome, portal hypertension, etc.)
Expected number of patients	Maximum of 39 patients
Dosage and administration	Eltrombopag (PROMACTA) is a thrombopoietin (TPO) receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Patients will receive eltrombopag at a starting dose of 50 mg daily, except for patients of East Asian ancestry who will receive a starting dose of 25 mg daily. Treatment will be continued for as long as patients are deriving benefit from therapy with eltrombopag. Treatment cycle is defined as daily continuous dosing. Eltrombopag will be administered on an empty stomach (1 hour before or 2 hours after a meal). There should be at least 2 hours before or 4 hours after eltrombopag and other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium-fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminium, magnesium, selenium, and zinc. Eltrombopag will be commenced at 50 mg with dose escalation allowed every 2 weeks to 100 mg, 150 mg, 200 mg and 300 mg according to platelet response. For patients of East Asian ancestry, eltrombopag will be commenced at 25 mg daily with dose escalation allowed every two weeks to 50 mg. Subsequent dose escalations will follow the schema described above. Failure to achieve a platelet count ≥ 50 x 10^9 /L after 8 weeks of eltrombopag will constitute lack of response.
Monitoring and dose adjustment	Patients will be followed with regular CBC and platelet counts. Guidelines for dose adjustment for eltrombopag will be as recommended for ITP[1]. After initiating eltrombopag, the dose should be adjusted to achieve and maintain a platelet count ≥ 50 x 10^9/L as necessary to reduce the risk for bleeding. Clinical hematology and liver tests will be monitored regularly throughout therapy with eltrombopag and modified based on platelet counts. During eltrombopag therapy, CBCs, including platelet count, will be assessed weekly until a stable platelet count has been achieved. CBCs including platelet counts will be obtained monthly thereafter. The following guidelines will be used to adjust dosing of eltrombopag • **Platelet count >200 x10^9/L (at any time):** Reduce daily dose by 25 mg; reassess in 2 weeks. • **Platelet count >400 x10^9/L:** Withhold assessing platelet count twice weekly until platelet count <150 x10^9/L, resume with daily dose at a reduced dose by 25 mg. • **Platelet count >400 x10^9/L after 2 weeks at the lowest dose:** Permanently discontinue.
Laboratory	**Complete Blood Counts (CBCs**): Monitor CBCs, including platelet counts prior to

monitoring	initiation, throughout, and following discontinuation of therapy with eltrombopag. Obtain CBCs, including platelet counts, weekly during the dose adjustment phase of therapy with eltrombopag and then monthly following establishment of a stable dose of eltrombopag. Obtain CBCs, including platelet counts, weekly for at least 4 weeks following discontinuation of eltrombopag. **Liver tests**: Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation. If abnormal levels are detected, repeat the tests within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels. Discontinue eltrombopag if clinically significant liver test abnormalities develop. **Renal Tests:** Monitor **c**reatinine prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. The dose adjustment for TKIs will be carried out according to institutional guidelines.
Study Endpoints/ Objectives	1. To determine the efficacy of eltrombopag for patients with CML or MF who have developed thrombocytopenia during the course of therapy with TKIs as measured by recovery of platelet count. 2. To determine the safety of eltrombopag for patients with CML or MF who have developed thrombocytopenia during the course of therapy with TKI. 3. To determine the dose intensity of TKI after start of therapy with eltrombopag. 4. To determine response to TKI after start of therapy with eltrombopag.
Additional safety wording	**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 Grade 4 liver test abnormalities. 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 controlled studies, four patients (1%) treated with eltrombopag and three patients in the placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Eighteen of the patients treated with eltrombopag in the controlled studies with hepatobiliary laboratory abnormalities were re-exposed to eltrombopag in the ITP extension study. Seven 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.

Reinitiating treatment with eltrombopag is not recommended. If the potential benefit for reinitiating treatment with eltrombopag is considered to outweigh the risk for hepatotoxicity, then cautiously reintroduce eltrombopag (consider a lower dose e.g. 25 mg) and measure serum liver tests weekly during the dose adjustment phase. If liver tests abnormalities persist, worsen or recur, then permanently discontinue eltrombopag.

Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis
Eltrombopag is a TPO receptor agonist and TPO-receptor agonists may increase the risk for the development or progression of reticulin fiber deposition within the bone marrow.

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

Prior to initiation of eltrombopag, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, examine CBCs monthly for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening clinically significant morphological abnormalities or cytopenia(s), discontinue treatment with eltrombopag and consider a bone marrow aspirate and biopsy, including staining for fibrosis.

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

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

Thrombotic/Thromboembolic Complications
Eltrombopag may increase the risk of thrombotic/thromboembolic events. In the controlled ITP clinical studies, four thrombotic/thromboembolic complications were reported within the groups that received eltrombopag and none within the placebo

	groups. Thrombotic/thromboembolic complications have also been reported in the ITP extension study. In a placebo-controlled double-blind study (ELEVATE) of 292 patients with chronic liver disease who were undergoing an elective surgical procedure, the risk of thrombotic events was increased in patients treated with 75 mg eltrombopag. Six thrombotic complications were reported within the group that received eltrombopag and two within the placebo group. All of the thrombotic complications reported within the eltrombopag group were of the portal venous system. Four of the 6 subjects receiving eltrombopag also had a tumor (2 hepatocellular carcinoma; 1 lymphoma and 1 brain tumor). Tumors are known to increase the risk for developing a thrombotic/thromboembolic event. The ELEVATE study has been terminated and remains blinded. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease. **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. Across the ITP clinical program, hematologic malignancies were reported in one eltrombopag patient and one in placebo patient. **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.
Study Variables (Clinical procedures, laboratory tests, safety assessments)	To determine the efficacy of eltrombopag for patients with CML or MF who have developed thrombocytopenia during the course of therapy with TKIs as measured by recovery of platelet count. In addition, we will measure CML disease status by cytogenetic and PCR analysis and response coded based on European Leukemia Network (ELN) guidelines[2, 3]. This is summarized in Section X. For responses in patients with MF, consensus criteria from International Working Group for Myelofibrosis Research and Treatment (IWG-MRT)[4] will be used and are summarized in section X. Safety and efficacy will also be monitored by serial evaluations of blood counts, liver enzymes as summarized in Section IX**.** Treatment discontinuations and interruptions for both eltrombopag and TKI will be recorded.
Outcome Parameters and Analytical Endpoints	The **primary endpoint** is complete (platelet) response (yes/no). A complete (platelet) response will be defined as a sustained (3 months) platelet count of ≥ 50 x 10^9/L for patients with CML and ≥ 100 x 10^9/L for patients with MF and at least a 20% increase in platelet count from baseline with no more than 3 counts in that period being < 50 x 10^9/L for patients with CML and < 100 x 10^9/L for patients with

	MF, while continuing TKI therapy. Successful re-escalation following dose reduction of TKI will be considered as continuing TKI. In patients who required dose reduction of TKI because of thrombocytopenia, complete (platelet) response can also be defined as successful re-escalation of the dose of TKI sustained for at least 3 months without recurrence of thrombocytopenia i.e. platelet count ≤ 50 x 10^9/L for patients with CML and < 100 x 10^9/L for patients with MF. **Secondary endpoints** will include: • The frequency of adverse events; • Average dose intensity of TKI; • Failure to therapy with TKI as defined by the ELN recommmendations[2](for patients with CML). For patients with myelofibrosis, IWG-MRT criteria[4] will be used. **Exploratory endpoints:** • Platelet function (platelet aggregation studies)
Statistical Analysis Plan	**Design Considerations and Sample Size Justification** This is a phase II, open-label single-arm study of individualized dosing of eltrombopag. The primary objective is to investigate whether eltrombopag will increase platelet count, thus reducing the occurrence of thrombocytopenia in subjects with CML or MF receiving therapy with TKI. All patients will be enrolled from MDACC, with 1-2 patients per month. The objective is to demonstrate that at least 30% of subjects have a complete (platelet) response, where complete (platelet) response is achieved if a patient meets all of the following criteria: (1) reach platelet count ≥ 50 x 10^9/L for patients with CML and ≥ 100 x 10^9/L for patients with MF within 8 weeks of treatment initiation; (2) the platelet count is sustained at ≥ 50 x 10^9/L for patients with CML and ≥ 100 x 10^9/L for patients with MF for 3 months, where "sustained" means having no more than 3 platelet counts in the 3-month period being < 50 x 10^9/L for patients with CML and < 100 x 10^9/L for patients with MF; and (3) at least a 20% increase in platelet count from baseline at the end of 3 months while continuing TKI therapy. Successful re-escalation following a dose reduction of TKI will be considered as continuing TKI. In patients who required dose reduction of TKI because of thrombocytopenia, complete (platelet) response can also be defined as successful re-escalation of the dose of TKI sustained for at least 3 months without recurrence of thrombocytopenia to ≮ ≤ 50 x 10^9/L for patients with CML and < 100 x 10^9/L for patients with MF. **For the cohort of patients with CML**: Simon's optimal two-stage design [Simon, 1989] will be used to test the null hypothesis that the proportion of subjects with complete response is <=0.10 versus the alternative that it is >=0.30 (i.e., Po<=0.10 vs Pa>=0.30) at alpha=0.05 with 80% power. The design will result in an expected sample size of 15 and a probability of early termination of 0.736. After testing the drug on 10 subjects in the first stage, the trial will be terminated if 1 or fewer achieve complete (platelet) response. Otherwise, if the trial goes on to the second stage, a total of 29 subjects will be studied. If the total number of patients with complete (platelet) response is less than or equal to 5, the drug will be deemed as ineffective. The trial will suspend accrual if not at least 2 patients have achieved complete response in the first 10 patients. To be evaluable for response (improvement in platelet count and durability of improvement in platelet count) patient will need to be followed for 12-20 weeks from start of eltrombopag therapy. For safety monitoring, we will continuously monitor the occurrence of any grade 3

	or greater non-hematologic adverse events as well as leukemia failure, which is defined as failure to achieve optimal response as defined by European Leukemia Network or as progression to accelerated/blastic phase (not clonal evolution). Safety monitoring will be based on a beta-binomial distribution. The trial will be terminated early if Pr[0.15 < toxicity rate | data] > 0.90, where the prior is assumed to be beta(1, 1). Applying this stopping rule and starting from the 7th subjects, the trial will stop early if [#subjects with leukemia failure or grade 3 or greater non-hematolgic AEs]/[#subjects evaluated] >= 3/7, 4/12, 5/17, 6/22, 7/27. **For MF cohort**: As the group with MF is an exploratory group of 10 patients to study the safety and activity of eltrombopag in patients with MF treated with Ruxolitinib and thrombocytopenia, we will consider the activity promising if 3 or more patients out of 10 achieve complete (platelet) response. For safety monitoring in the cohort with MF, accrual will stop if at any time 4 out of 10 patients encounter grade 3 or more non-hematological toxicity or progression to acute leukemia. As an additional safety procedure, we will observe the first 3 MF patients on trial for at least 3 months before additional patients are accrued. **Analytic Methods** The statistical analyses as detailed below will be performed in each disease cohort (i.e., CML and MF) separately. The proportions of subjects with complete (platelet) response will be reported together with exact 95% confidence intervals. The denominator will include all subjects who received eltrombopag. The proportion of subjects with leukemia, and the proportion failing to TKI will be summarized similarly. Platelet counts over time and in relationship to exposure to eltrombopag and TKI will be summarized using descriptive statistics. Kaplan-Meier methods will be used to estimate the risk of leukemia (i.e., suboptimal response and progression to accelerated or blastic phase) over time. Descriptive statistics will be used to summarize the extent of exposure to eltrombopag, and to TKI (duration of TKI therapy and dose intensity of TKI therapy). The number (%) of subjects with adverse events, serious adverse events, and adverse events leading to discontinuation will be reported. Adverse events will be reported by type, severity and frequency. Laboratory parameters will also be summarized using descriptive statistics; laboratory toxicity will be summarized using frequency counts.

OBJECTIVES

Primary

To determine the efficacy of eltrombopag for patients with CML or MF who have developed thrombocytopenia during the course of therapy with tyrosine kinase inhibitors (TKI) as measured by recovery of platelet count

Secondary

1. To determine the safety of eltrombopag for patients with CML or MF who have developed thrombocytopenia during the course of therapy with TKI;
2. To determine the dose intensity of TKI after start of therapy with eltrombopag;
3. To determine response to TKI after start of therapy with eltrombopag.

II. RATIONALE

TKI have become standard therapy for patients with CML. Imatinib mesylate (Gleevec) was the first agent approved for this indication and induces complete cytogenetic responses in 40 to 50% of patients with CML after failure to interferon alpha [5, 6] and in 75 to 90% of those previously untreated[7, 8]. High-dose imatinib has resulted in improved outcome[9] and is currently being evaluated in a randomized study for a possible change in standard dose recommendation.

Dasatinib (Sprycel) received regulatory approval for the treatment of patients who have failed imatinib in 2006 and over 50% of patients have demonstrated a major cytogenetic response.[10] In October 2010 dasatinib received accelerated approval for treatment of patients with newly diagnosed CML in chronic phase. Nilotinib (Tasigna) was approved by the FDA in 2007, also for the treatment of patients after imatinib failure.[11] In June 2010, Nilotinib has been approved by the FDA for treatment of patients with newly diagnosed CML in chronic phase. Although these agents are overall well tolerated, some patients may develop adverse events, with myelosuppression being the most prominent. Cytopenias, particularly neutropenia and thrombocytopenia, have been consistently reported in studies of imatinib, dasatinib and nilotinib in CML[7, 8, 10-15]. For most patients, myelosuppression is grade 1 or 2 requiring no intervention. However, grade $\geq$ 3 thrombocytopenia (i.e., platelets $\leq$ 50 x10^9/L) and neutropenia (i.e., absolute neutrophil count [ANC $\leq$ 1 x 10^9/L]) have been reported in a significant proportion of patients as shown in Table 1.

Table 1. Incidence of grade 3-4 neutropenia and thrombocytopenia (values in percentage) in CML chronic phase treated with TKIs.

Study	Neutropenia (%)	Thrombocytopenia (%)
Imatinib post IFN failure[8]	35	20
Imatinib frontline[7]	17	9
High-dose imatinib frontline[16]	32	25
Dasatinib after imatinib failure[10]	48	48
Nilotinib after imatinib failure[14]	28	29

Patients who develop myelosuppression have a decreased probability of achieving a major or complete cytogenetic response [17]. In one report, among 31 patients who developed grade 3 thrombocytopenia, 11 (35%) achieved a complete cytogenetic response, compared to 66 (59%) of 112 who never developed thrombocytopenia (p=0.02). Similarly, patients who developed grade 3 neutropenia had a lower rate (44%) of complete cytogenetic response compared to those who never developed neutropenia grade 3 (62%; p=0.03). This difference in prognosis was particularly noticeable for those who had myelosuppression lasting > 2 weeks[17]. In a multivariate analysis, myelosuppression was an independent adverse prognostic factor for response [17].

The reason for this decreased probability of response is not clear, but one possible explanation is that myelosuppression results in interruption of imatinib therapy and dose reductions. Thus, patients who develop myelosuppression may have prolonged periods when effective therapy is withheld. In fact, myelosuppression is the leading cause of dose reductions and treatment interruptions. The guidelines for management of myelosuppression occurring while on therapy with imatinib for CML include holding therapy when there is grade 3 neutropenia (i.e., neutrophils ≤ 1 $x10^9$/L) or thrombocytopenia (i.e., platelets ≤ 50 $x10^9$/L)[18]. Thus, it is important for patients that develop myelosuppression to have a rapid recovery and, if possible, to prevent recurrence of myelosuppression. With this intent, hematopoietic growth factors have been used to manage patients with persistent or recurrent myelosuppression. Filgrastim has been successfully used to manage neutropenia, resulting not only in the recovery of neutrophils which allows for continuation of therapy with imatinib, but it has also led to an improved response to imatinib.[19] Erythropoietin and darbepoetin have been effective in managing anemia in this setting.[20, 21] Options for the management of thrombocytopenia have been more limited. Low-dose interleukin-11 (oprelvekin) was first used to treat 3 patients with thromobocytopenia associated with imatinib therapy and demonstrated not only a good platelet response, but also allowed for uninterrupted imatinib therapy which resulted in improved response to therapy.[22] This observation was subsequently expanded to 14 patients with thrombocytopenia associated with imatinib, dasatinib or nilotinib.[23] These patients received IL-11 10 mcg/kg 3 times weekly. Eight of the 14 (57%) patients responded. Use of IL-11 allowed patients to maintain the dose intensity of their TKI with only one of the eight responders requiring any further dose reductions in the TKI therapy after initiation of IL-11. Overall 11 patients had a decrease in the number of days of TKI therapy interruption secondary to thrombocytopenia after initiation of IL-11 (6% of the total treatment time versus 34% before IL-11)[23].

The pivotal study of Ruxolitinib excluded patients with platelet count <100 x 10^9/L[24]. Among these patients, the discontinuation rate of Ruxolitinib due to low platelet counts was quite low. However thrombocytopenia was encountered in approximately 70% of patients and approximately 17% of these were grade 3/4 events. At the time of approval of Ruxolitinib, the FDA did not impose any platelet count. The package insert of Ruxolitinib advises reduction of dose by 50% for

platelet counts <100 x 10^9/L and interruption of dosing at <50 x 10^9/L[25]. In the pivotal study, MF related symptoms returned to baseline after interruption of Ruxolitinib dose for a median of one week[24], highlighting the need for continued dosing. The possibility of interruptions is expected to be much higher than reported in the pivotal study among patients whose platelet count is <100 x 10^9/L and the concomitant use of eltrombopag is expected to allow patients to stay at prescribed dose of Ruxilitinib.

Study Drug: Eltrombopag
Eltrombopag is a nonpeptide agonist of thrombopoietin (TPO) which increases platelet counts by binding to and activating the human TPO receptor. Eltrombopag has been found to be effective and well tolerated among patients with chronic idiopathic thrombocytopenic purpura (ITP) who had failed prior therapy with standard therapy. Among patients receiving a dose of 50 or 75mg daily, 70% and 80% of patients treated, respectively, improved their platelet count to greater than 50 x10^9/L after 43 days.[26-28] Responses occurred early, with 80% of patients receiving these doses having an increased platelet count by day 14. We propose to investigate whether eltrombopag may correct and/or prevent the development of recurrent thrombocytopenia (≤ 50 x 10^9/L) in patients with CML or (100 x 10^9/L) in patients with MF who are receiving therapy with TKIs.

III. PROPOSED STUDY

This will be a non-randomized, Phase II, single arm study of individualized dosing of eltrombopag. CML patients in chronic phase receiving treatment with any FDA approved TKI and experiencing Grade ≥ 3 thrombocytopenia (platelets ≤ 50 x 10^9/L) for patients with CML and patients with MF and platelets <100 x 10^9/L after the first 3 months of therapy with the TKI are eligible. Thrombocytopenia must be either recurrent (i.e., be at least the second episode of thrombocytopenia) or have necessitated dose reductions of the TKI. A maximum of 39 subjects will be evaluated.

Subjects will continue receiving their TKI at the doses prescribed at the time of enrollment into the study and eltrombopag therapy will be initiated. Dose escalations of TKI are allowed once improvement in platelet count (≥ 50 x 10^9/L for CML and ≥ 100 x 10^9/L for patients with MF) is demonstrated for at least 2 consecutive weeks.

IV. BACKGROUND DRUG INFORMATION

Eltrombopag

Mode of Action:
Eltrombopag is a Thrombopoietin (TPO) nonpeptide agonist which increases platelet counts by binding to and activating the human TPO receptor. It activates intracellular signal transduction pathways to increase proliferation and differentiation of marrow progenitor cells. It does not induce platelet aggregation n activation.

Approved Use:

Treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) at risk for bleeding who have had insufficient response to corticosteroids, immunoglobulin, or splenectomy.

Route of Administration: Oral

Contraindications: None.

Reported Adverse Events and Potential Risks
1% to 10%:
Dermatologic: Rash (≤ 7%), bruising (2%)
Endocrine and metabolic: Menorrhagia (4%)
Gastrointestinal: Nausea (6%), vomiting (4%), dyspepsia (2%)
Hematologic: Rebound thrombocytopenia (10%), thrombocytopenia (2%)
Hepatic: Liver function tests abnormal (10%), ALT increased (2%), AST increased (2%)
Neuromuscular and skeletal: Limb pain (≤ 7%), myalgia (3%), paresthesia (3%)
Ocular: Cataract (3%), conjunctival hemorrhage (2%)

< 1%, postmarketing, and/or case reports:
Bone marrow collagen fiber deposits, bone marrow reticulin fiber deposits, cataract worsening, epistaxis, headache, hemorrhage (due to thrombocytopenia or rebound thrombocytopenia), non-Hodgkin's lymphoma, portal vein thrombosis, thrombotic/thromboembolic complications.

V. STUDY DESIGN

This will be a non-randomized, Phase II, single arm study of individualized dosing of eltrombopag. A maximum of 39 subjects will be evaluated.

Subjects will continue receiving their TKI at the doses prescribed at the time of enrollment into the study when eltrombopag therapy will be initiated. Dose escalations of TKI are permitted within the study.

Study Drug

Eltrombopag will be commenced at 50 mg (except for patients of East Asian ancestry who will receive a starting dose of 25 mg daily) with dose escalation allowed every 2 weeks to 100 mg, 150 mg, 200 mg and 300 mg according to platelet response. For patients of East Asian ancestry, dose escalation will be allowed every two weeks to 50 mg. Subsequent dose escalations will follow the schema described above. Eltrombopag will be continued for as long as patients continue to benefit clinically. Treatment cycle is defined as daily continuous dosing.

Eltrombopag will be administered on an empty stomach (1 hour before or 2 hours after a meal). There should be at least a 4-hour interval between eltrombopag and other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium-fortified juices), or supplements containing polyvalent cations such as iron,

calcium, aluminum, magnesium, selenium, and zinc that can interfere with its absorption.

Patient Registration
All patients and study-specific data will be registered through the Protocol Data Management System (PDMS)/CORe.

VI. Outside Physician Participation During Treatment

- MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.
- A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix F).
- Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
- Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
- A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
- Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
- The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
- Patients will return to MDACC every 3-4 months for evaluation.
- The patient will be contacted by telephone approximately every 4 weeks by a member of the research team.

VII. DOSE DELAY/MODIFICATIONS (Guidelines) FOR ELTROMBOPAG

Dose modifications for platelet response:
The following guidelines will be used to adjust dosing of Eltrombopag:

1. *Platelet count > 200 x10^9/L (at any time):* Reduce daily dose by 25 mg; reassess in 2 weeks.
2. *Platelet count > 400 x10^9/L:* Withhold dose; assess platelet count twice weekly; when platelet count < 150 x10^9/L, resume with the daily dose reduced by 25 mg.
3. *Platelet count > 400 x10^9/L after 2 weeks at the lowest dose:* Permanently discontinue.

Dosage adjustment for toxicity:

Hepatotoxicity:

- ALT/AST levels ≥ 3 times the upper limit of normal (ULN): Hold treatment.

- Obtain fractionation for elevated bilirubin levels grade 3.
- Repeat abnormal liver function tests within 3-5 days; if confirmed abnormal, monitor weekly until resolves, stabilizes, or returns to baseline. Discontinue treatment for ALT/AST levels ≥ 3 times the ULN and which are progressive, or persistent (≥ 4 weeks), or accompanied by increased direct bilirubin, or accompanied by clinical signs of liver injury or evidence of hepatic decompensation. Reinitiation of eltrombopag after discontinuation for these reasons will not be allowed.

Dose adjustments for other grade 3-4 toxicity:
Patients experiencing clinically significant grade 3 or greater toxicity possibly related to eltrombopag may have their treatment interrupted until toxicity resolved to grade 1 or less. Treatment can then be resumed at the immediate lower dose level. Greater dose reductions can be allowed if judged in the best interest of the patient after discussion with the principal investigator.

Dose modifications for TKIs
Appropriate dose modifications will be done according to institutional guidelines. For dasatinib and nilotinib, approved dosing will be used. Highest dose for imatinib will be 800 mg/day, for nilotinib 400 mg twice daily and for dasatinib 140 mg/day. For Ruxolitinib the highest dose will be 20 mg twice daily. Dose escalations of TKIs are allowed once improvement in platelet count (>/= 50 x 10^9/L for CML and (>/= 100 x 10^9/L for MF) is demonstrated for at least 2 consecutive weeks.

VIII. SUPPORTIVE CARE GUIDELINES

Use of growth factors (G-CSF, GM-CSF and erythropoietic growth factors) will be permitted if considered to be in the best interest of the patient. Use of prophylactic/therapeutic antiemetics, antibiotics, antivirals and antifungals are permitted as per the decision of the treating physician. The use of oprevelkin is not allowed while patients are on study.

IX. ELIGIBILITY CRITERIA

Inclusion:

1. CML patients in chronic phase receiving treatment with any FDA approved TKI; or CML patients in accelerated or blastic phase who are considered to be in this phase because of thrombocytopenia or because of clonal evolution and with no other criteria for accelerated/blastic phase; or patients with myelofibrosis receiving treatment with FDA approved TKI and with peripheral blood and/or bone marrow blast ≤ 10%

2. Grade ≥ 3 thrombocytopenia (platelets <50 x 10^9/L) after the first 3 months of therapy with the TKI for patients with CML and platelets <100 x 10^9/L for patients with MF after first 3 months therapy. Thrombocytopenia must be either recurrent

(i.e., second or greater episode of thrombocytopenia) or having required dose reductions of the TKI;

3. Subject is anticipated to have therapy with TKI continued for ≥3 months;

4. Adequate organ function:
   - Total bilirubin (except for Gilbert's Syndrome) ≤ 1.5xULN
   - ALT and AST < 3xULN
   - Creatinine ≤ 2xULN

Exclusion:

1. CML patients in accelerated or blastic phase except for those who are considered to be in this phase because of thrombocytopenia or because of clonal evolution and with no other criteria for accelerated/blastic phase; or MF patients who have transformed in to acute leukemia or has ≥ 10% blast in peripheral blood and/or in bone marrow.

2. Thrombocytopenia that is considered to be unrelated to treatment with TKI or accelerated phase as defined above;

3. Age < 18 years;

4. Stem cell transplantation within preceding 60 days prior to registration;

5. Patients with documented active hepatitis B or C infection;

6. Patients with known bone marrow reticulin fibrosis (≥ grade 2) (only applicable to patients with CML);

7. Patients with palpable splenomegaly ≥ 16cm below coastal margin (only applicable to patients with CML);

8. Female subjects who are pregnant or breastfeeding. Women of childbearing potential are required to have a βHCG serum or urine pregnancy test performed within 7 days prior to first study drug dose.

9. Patients with known risk factors for thromboembolism (e.g. Factor V Leiden mutation, ATIII deficiency, Protein C and S deficiency, antiphospholipid syndrome, portal hypertension, etc.)

X. EVALUATIONS

Pretreatment evaluation (within 7 days of start of study drug except where noted)

- History and physical exam.
- CBC, platelet count, differential, peripheral blood smear.
- Serum chemistry to include bilirubin, AST, ALT, BUN, creatinine.

- Hepatitis panel (within 6 weeks).
- Bone marrow aspirate and biopsy (including reticulin stain) and cytogenetics (within 6 weeks).
- Record all concomitant medications and baseline adverse events.
- Q-PCR for BCR-ABL for assessment of response to TKIs (peripheral blood or bone marrow) (within 6 weeks).
- Pregnancy test (if applicable). βHCG serum or urine pregnancy test for women of childbearing potential. 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 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months). Women of child-bearing potential and men must agree to use contraception prior to study entry and for the duration of study participation.

Evaluation During Study

- Physical examination every 3-4 months. After the first year physical examinations can be every 12 months (+/- 2 months).
- CBCs, including platelet count, weekly at beginning or at any time dose adjustments are made for eltrombopag or TKI until a stable platelet count has been achieved. Obtain CBCs including platelet counts, monthly thereafter; every 12 months (+/-2 months) after the first year.
- Monitor serum liver tests (ALT, AST, and bilirubin) every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation. If abnormal levels are detected, repeat the tests within 3 to 5 days. If the abnormalities are confirmed, monitor liver tests weekly until the abnormality (ies) resolve, stabilize, or return to baseline levels.
- Bone marrow aspiration and/or biopsy including cytogenetics studies every 3-4 months in the first year; not required after the first year
- Q-PCR studies for BCR-ABL as indicated for assessment of response to TKIs (peripheral blood and/or bone marrow), every 3-4 months in the first year; every 12 months (+/- 2 months) after the first year.
- Record all concomitant medications and adverse events every 3-4 months; every 12 months (+/- 2 months) after the first year.

CBCs and serum chemistry tests can be performed by the patient's local physician following baseline exams. Results will be faxed to the appropriate research nurse at MD Anderson Cancer Center. All other testing will be performed at MD Anderson Cancer Center.

End of Treatment Evaluation (30 days [± 5 days] after the last dose of study drug)

- Physical examination
- CBC, platelet count, differential
- Serum chemistry to include bilirubin, AST, ALT, BUN, creatinine.
- Record adverse events.

XI. CRITERIA FOR RESPONSE

Criteria of Response to Eltrombopag

1. A complete (platelet) response will be defined as a sustained (3 months) platelet count of ≥ 50 x 10^9/L and at least a 20% increase in platelet count from baseline with no more than 3 counts in that period being ≤ 50 x 10^9/L , while continuing imatinib or other TKI therapy. Successful re-escalation following dose reduction of TKI will be considered as continuing TKI.
2. In patients who required dose reduction of imatinib or other TKI because of thrombocytopenia, complete (platelet) response can also be defined as successful re-escalation of the dose of imatinib or other TKI sustained for at least 3 months without recurrence of thrombocytopenia to ≤ 50 x 10^9/L.

Criteria of Response to TKIs in CML (adapted from ELN guidelines[2, 3])

- **Complete Hematologic Remission** (CHR):
  - Normalization for at least 4 weeks of the bone marrow (less than 5% blasts) and peripheral blood with WBC within normal institutional limits with no peripheral blasts, promyelocytes or myelocytes, and basophils <5%.
  - This is in addition to disappearance of all signs and symptoms of the disease

- **Partial Hematologic Response** (PHR):
  - CHR except for persistence of immature cells (myelocytes, metamyelocytes), or splenomegaly < 50% of pretreatment, or thrombocytosis > 450x10^9/L but < 50% of pretreatment.

- **Complete Hematologic Remission:**
  Will further be classified according to suppression of the Philadelphia chromosome (Ph) by cytogenetics (FISH if cytogenetic analysis not informative, e.g., insufficient metaphases)
  - No cytogenetic response: Ph positive 100% of pretreatment value
  - Minor cytogenetic response: Ph positive 36-90% of pretreatment value
  - Partial cytogenetic response: Ph positive 1-35% of pretreatment value
  - Complete cytogenetic response: Ph positive 0%

  *Major cytogenetic response = complete + partial (Ph positive < 35%)

- **Molecular response**
  - Major (MMR): BCR-ABL/ABL ratio < 0.1% in the International Scale
  - Complete: Undetectable BCR-ABL, confirmed by nested PCR
  - **Optimal, suboptimal responses and failure to TKI** will be based on European Leukemia Network recommendations.

Criteria for response in Myelofibrosis[4]

Criteria for response for MF:
Best overall response will be categorized according to the International Working Group (IWG) Criteria:

Complete remission (CR): Requires all of the following in the absence of both transfusion and growth factor support:

- Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.
- Peripheral blood count remission defined as hemoglobin > 11 g/dL, platelet count ≥ 100 x 10^9/L, and absolute neutrophil count ≥ 1.0 x 10^9/L.
- Normal leukocyte differential including disappearance of nucleated red blood cells and immature myeloid cells in the peripheral smear, in the absence of splenectomy. *
- Bone marrow histological remission defined as the presence of age-adjusted normocellularity, < 5% myeloblasts, and an osteomyelofibrosis grade of ≤ 1. **

Partial remission (PR): Requires all of the above criteria for CR except the requirement for bone marrow histological remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.

Clinical improvement (CI): Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment *(CI response is validated only if it lasts for ≥ 8 weeks).*

- A ≥ 2 g/dL increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of < 10 g/dL).
- Either a ≥ 50% reduction in palpable splenomegaly of a spleen that is ≥ 10 cm at baseline or a spleen that is palpable at > 5 cm at baseline becomes not palpable.
- A ≥ 100% increase in platelet count and an absolute platelet count of ≥ 50,000 x 10^9/L. (applicable only for patients with baseline platelet count of < 50 x 10^9/L).
- A ≥ 100% increase in ANC and an ANC of ≥ 0.5 x 10^9/L (applicable only for patients with baseline absolute neutrophil count of < 1 x 10^9/L).

Progressive disease: Requires one of the following:

- Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at > 5 cm below the left costal margin or a ≥ 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a ≥ 50% increase in palpable distance for baseline splenomegaly of > 10 cm.
- Leukemic transformation confirmed by a bone marrow blast count of ≥ 20%.
- An increase in peripheral blood blast percentage of ≥ 20% that lasts for ≥ 8 weeks.

Stable disease: None of the above.

Relapse: Loss CR, PR, and CI. In other words, a patient with CR or PR is considered to have undergone relapse when he or she no longer fulfills the criteria for CI.

**Because of subjectivity in peripheral blood smear interpretation; CR does not require absence of morphological abnormalities of red cells, platelets, and neutrophils.*

*** In patients with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20-bone marrow- or peripheral blood-derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged.*

XII. CRITERIA FOR REMOVAL

- Patients who develop accelerated/blastic disease features (except when clonal evolution is the only criterion for accelerated phase).
- Hematologic resistance while on optimal therapy.
- Unacceptable severe (grade 3-4) toxicity possibly related to eltrombopag despite dose optimization.
- Patient request.
- Development of ≥ 2 reticulin fibrosis in marrow (only applicable to CML patients).
- Pattern of non-compliance.

XIII. REPORTING REQUIREMENTS

Reporting requirements will be as per institutional guidelines.

Adverse events (AE) related to study conditions

The serious adverse event (SAE) reporting period will begin with the signing of the informed consent.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate.

Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols

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 the informed consent is signed, 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.

The principal investigator has the obligation to report all serious adverse events to the IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

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.

Investigator Communication with Supporting Companies:

Prompt Reporting of Serious Adverse Events and Other Events to Novartis

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported by the investigator and documented in PDMS/CORe and to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) within 24 hours.**

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period *(or 5 half-lives, if half-life is established,* whichever is longer) should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be reported by the investigator to the Novartis Oncology Drug Safety and Epidemiology Department (DS&E) by fax **(fax: 877-778-9739)**. Pregnancy follow-up should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

XIV. ADVERSE DRUG REACTION REPORTING

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting according to the MDACC guidelines (Appendix C). A copy of the CTCAE 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 CTCAE Version 4.0. Only clinically significant drug-related toxicities will be recorded. Known grade 1 or 2 toxicities of the drugs will not be recorded or reported. Grade 3, 4 and 5 toxicities, whether related or not, will be recorded. Lower grade toxicities not known to be related to drug may be recorded if considered clinically significant by the investigator. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

XV. DRUG ACCOUNTABILITY

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) and adhere to Good Clinical Practice guidelines

Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Clinical supplies will not be administered to any

individual who is not enrolled in the study.

XVI. STATISTICAL CONSIDERATIONS

Design considerations and Sample Size Justification

This is a phase II, open-label single-arm study of individualized dosing of eltrombopag in patients with CML or MF. The primary objective is to investigate whether eltrombopag will increase platelet count, thus reducing the occurrence of thrombocytopenia in subjects with CML and MF receiving therapy with TKI. The objective is to demonstrate that at least 30% of subjects have a complete (platelet) response, where complete (platelet) response is achieved if a patient meets all of the following criteria:

(1) reach platelet count ≥ 50 x 10^9/L within 8 weeks of treatment initiation for patients with CML and ≥ 100 x 10^9/L for patients with MF;
(2) the platelet count is sustained at ≥ 50 x 10^9/L for CML and ≥ 100 x 10^9/L for patients with MF for 3 months, where "sustained" means having no more than 3 platelet counts in the 3-month period being < 50 x 10^9/L in CML and < 100 x 10^9/L for patients with MF; and
(3) at least a 20% increase in platelet count from baseline at the end of 3 months while continuing TKI therapy.

Successful re-escalation following a dose reduction of TKI will be considered as continuing TKI. In patients who required dose reduction of TKI because of thrombocytopenia, complete (platelet) response can also be defined as successful re-escalation of the dose of TKI sustained for at least 3 months without recurrence of thrombocytopenia to ≤ 50 x 10^9/L for patients with CML and <100 x 10^9/L for patients with MF. All patients will be enrolled from MDACC, with 1-2 patients per month.

For the cohort of CML patients:

Simon's optimal two-stage design [Simon, 1989] will be used to test the null hypothesis that the proportion of subjects with complete response is <=0.10 versus the alternative that it is >=0.30 (i.e., Po<=0.10 vs Pa>=0.30) at alpha=0.05 with 80% power. The design will result in an expected sample size of 15 and a probability of early termination of 0.736. After testing the drug on 10 subjects in the first stage, the trial will be terminated if 1 or fewer achieve complete (platelet) response. Otherwise, if the trial goes on to the second stage, a total of 29 subjects will be studied. If the total number of patients with complete (platelet) response is less than or equal to 5, the drug will be deemed as ineffective. The trial will suspend accrual if not at least 2 patients have achieved complete response in the first 10 patients. To be evaluable for response (improvement in platelet count and durability of improvement in platelet count) patient will need to be followed for 12-20 weeks from start of eltrombopag therapy.

For safety monitoring, we will continuously monitor the occurrence of any grade 3 or greater non-hematologic adverse events as well as leukemia failure, which is defined as failure to achieve optimal response as defined by European Leukemia

Network or as progression to accelerated/blastic phase (not clonal evolution). Safety monitoring will be based on a beta-binomial distribution. The trial will be terminated early if Pr[0.15 < toxicity rate | data] > 0.90, where the prior is assumed to be beta(1, 1). Applying this stopping rule and starting from the 7th subjects, the trial will stop early if [#subjects with leukemia failure or grade 3 or greater non-hematolgic AEs]/[#subjects evaluated] >= 3/7, 4/12, 5/17, 6/22, 7/27.

The operating characteristics are summarized in the following table:

True toxicity rate	True complete (platelet) response rate	Prob(stop the trial early)
0.05	0.30	0.166
	0.20	0.388
	0.10	0.741
	0.05	0.916
0.15	0.30	0.433
	0.20	0.584
	0.10	0.824
	0.05	0.943
0.30	0.30	0.916
	0.20	0.938
	0.10	0.974
	0.05	0.991

For the cohort of MF patients:

As the group with MF is an exploratory group of 10 patients to study the safety and activity of eltrombopag in patients with MF and thrombocytopenia, we will consider the activity promising if 3 or more patients out of 10 achieve complete response.

For safety monitoring in the cohort with MF, accrual will stop if at any time 4 out of 10 patients encounter grade 3 or more non-hematological toxicity or progression to acute leukemia. As an additional safety procedure, we will observe the first 3 patients on trial for at least 3 months before additional patients are accrued.

Analytic Methods

The statistical analyses as detailed below will be performed in each disease cohort (i.e., CML and MF) separately.

The proportions of subjects with complete (platelet) response will be reported together with exact 95% confidence intervals. The denominator will include all subjects who received eltrombopag. The proportion of subjects with leukemia, and the proportion failing to TKI will be summarized similarly

Platelet counts over time and in relationship to exposure to eltrombopag and TKI will be summarized using descriptive statistics.

Kaplan-Meier methods will be used to estimate the risk of leukemia (i.e., suboptimal response and progression to accelerated or blastic phase) over time.

Descriptive statistics will be used to summarize the extent of exposure to eltrombopag, and to TKI.

The number (%) of subjects with adverse events, serious adverse events, and adverse events leading to discontinuation will be reported. Adverse events will be reported by type, severity and frequency. Laboratory parameters will also be summarized using descriptive statistics; laboratory toxicity will be summarized using frequency counts.

XVII. STUDY SCHEDULE*:

	Screening/ Baseline	**During adjustment phase of eltrombopag or TKI dose**	**Every 3-4 months in first year**	**Yearly after first year**	**End of Treatment[8]**
History and physical examination	Within 7 days		X	X	X
CBC, platelet count, differential and peripheral blood smear[1]	Within 7 days	Weekly (**Monthly** on stable dose)		X	X
Serum Chemistry[2]	Within 7 days	Every 2 weeks[3] (**Monthly** on stable dose)			X
Hepatitis panel	Within 6 weeks				
Bone marrow aspirate and biopsy[4]	Within 6 weeks		X		
Cytogenetics	Within 6 weeks		X		
BCR-ABL QPCR[6]	Within 6 weeks		X	X	

(CML only)					
Concomitant Medications	Within 7 days		X	X	
Adverse Events	Within 7 days		X	X	X
β-hCG or urine pregnancy test[7]	Within 7 days				

[1]Peripheral blood smear at baseline only
[2]Includes bilirubin, AST, ALT, BUN, creatinine
[3]If bilirubin is elevated, perform fractionation. If abnormal levels are detected, repeat the tests within 3 to 5 days. If the abnormalities are confirmed, monitor liver tests weekly (± 3 days) until the abnormality(ies) resolve, stabilize or return to baseline level.
[4]Includes reticulin staining.
[5]Aspiration **and/or** biopsy.
[6]Peripheral blood or bone marrow
[7]Women of childbearing potential only: Serum β-hCG or urine pregnancy test. [8]30 days (± 5 days) after the last dose of study drug.
*Weekly schedule is ±3 days; bi-weekly is ±5 days; monthly is ±7 days; every 3 months is ± 1 month; every 12 months is ±2 months.

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