A Phase II Trial of Eltrombopag for Patients with Chronic Lymphocytic Leukemia (CLL) and Thrombocytopenia

Version 3

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Short Title: Phase II Eltrombopag in CLL

1.0 OBJECTIVES

Primary objective:

a. Determine the overall response rate of eltrombopag in patients with CLL and thrombocytopenia.

Secondary objectives:

a. Determine the time-to-response and duration of response.
b. Determine time to CLL progression requiring leukemia treatment.
c. Assess tolerability and toxicities of eltrombopag in patients with CLL.
d. Assess pharmacokinetics of eltrombopag and thrombopoietin levels in patients with CLL.

2.0 BACKGROUND

Rationale:

Eltrombopag (Promacta) is a thrombopoietin (TPO)-receptor agonist that triggers a cascade that induces proliferation and differentiation of megakaryocytes from bone marrow progenitor cells[1,2]. It received FDA accelerated approval for the treatment of chronic immune thrombocytopenic purpura in November, 2008 based on the results of the pivotal phase II and III studies [3,4]. Patients with CLL frequently have thrombocytopenia, which may be the result of reduced numbers of megakaryocytes resulting from infiltration of the bone marrow by leukemia or from prior treatment; reduced function of megakaryocytes resulting from prior chemotherapy; or from Idiopathic Thombocytopenic Purpura (ITP). Among 2300 treatment-naive patients with CLL who presented to MD Anderson Cancer Center (MDACC) as new patients between 2000 and 11/2009, 102 had platelet (PLT) count ≤51-100K/μL, 21 had PLT count 21-50K/μL, and 6 had PLT count ≤20K/μL. The incidence of thrombocytopenia is higher for previously treated patients. Indeed, among 1370 previously treated patients with CLL who presented to MDACC as new patients during the same time period, 236 had PLT count ≤51-100K/μL, 120 had PLT count 21-50K/μL and 66 had PLT count ≤20K/μL. These numbers do not include patients on routine follow-up with the Leukemia Service who develop thrombocytopenia at some point during their follow-up.

Thrombocytopenia in patients with CLL is associated with morbidity and mortality from bleeding complications and significant limitation in administering chemotherapy for active, progressive CLL. Identifying an active agent to treat thrombocytopenia in patients with CLL would be a significant advance in managing these patients. Eltrombopag is an ideal candidate to evaluate as treatment for thrombocytopenia in patients with CLL, owing to the previously mentioned mechanism of action and the demonstrated activity in treating patients with chronic ITP. This trial will evaluate the activity of eltrombopag in treating thrombocytopenia in patients with CLL and PLT ≤50K/μL.

In this study, patients will be stratified into 2 groups according to physician-assessed etiology of thrombocytopenia, those due to prior treatment or disease and those due to ITP. Physicians will use available data to make this determination including, CLL

treatment history, history of thrombocytopenia, complete blood count, and bone marrow aspiration and biopsy results to evaluate for extent of CLL and presence of megakaryocytes. This determination and stratification will be declared at the time of initiation of eltrombopag.

The overall objective of this phase II study will be to determine the PLT response rate with eltrombopag in patients with CLL and thrombocytopenia (PLT $\leq$50K/μL).

3.0 BACKGROUND DRUG INFORMATION

Eltrombopag (Promacta) is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag is available in 75mg, 50mg and 25mg tablets. Also, 12.5mg tablets are available for clinical trial only. For this study, eltrombopag will be supplied by GlaxoSmithKline (GSK), Collegeville, PA, 19426.

Eltrombopag is being evaluated both in several GSK-sponsored trials and in investigator-initiated studies supported by GSK. Eltrombopag has been evaluated in healthy volunteers at a dose of up to 200 mg daily for 5 days and for treatment of thrombocytopenia related to immune thrombocytopenia, hepatitis C virus infection, myelodysplastic syndrome (MDS), and chemotherapy-induced thrombocytopenia in cancer patients. Eltrombopag is currently being evaluated in multiple trials with the following dose escalation schema: the starting dose is 75 mg/day and dose may be escalated as follows: 150 mg, 225 mg, 300 mg given daily for 10 days after completion of chemotherapy; continuous dosing is used in the MDS/AML trials. The maximum dose that is currently being considered for all eltrombopag studies is also 300 mg continuous dose. Currently 300 mg is the highest tested safe dose of eltrombopag, either in interrupted dosing (with chemotherapy) or continuous dosing. Therefore, the dose escalation schema in this protocol is consistent with GSK-sponsored trials with eltrombopag and dose-modification parameters are consistent with those recommended by GSK for all eltrombopag trials.

In ITP, the recommended starting dose of eltrombopag is 50 mg once daily except in patients who are of East Asian ancestry or who have moderate to severe hepatic impairment. For ITP patients of East Asian ancestry such as Chinese, Japanese, Taiwanese, or Korean, it is recommended to initiate eltrombopag at a reduced dose of 25 mg once daily. For all ITP patients with moderate or severe hepatic impairment, initiate eltrombopag at a reduced dose of 25 mg once daily.

Eltrombopag should be taken on an empty stomach (1 hour before or 2 hours after a meal). At least a 4-hour interval between eltrombopag and other medications (e.g., antacids) should be allotted, 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.

In patients with ITP, after initiating eltrombopag, the dose should be adjusted to achieve and maintain a platelet count ≥50 K/μL x 10K/μL as necessary to reduce the risk for bleeding.

Clinical hematology and liver tests should be monitored regularly throughout therapy with eltrombopag and modified based on platelet counts as outlined in the package insert for Promacta. Recommendations for monitoring are as follows: during eltrombopag therapy assess CBC, including platelet count and peripheral blood smears, weekly until a stable platelet count has been achieved. Obtain CBC, including platelet counts and peripheral blood smears, monthly thereafter.

Safety Considerations:
Summary
Common side effects (occurring in 3-20% of patients):

- Dermatologic: skin rash
- Gastrointestinal: nausea, vomiting
- Hematologic: bleeding including heavy menstrual bleeding, low platelets requiring transfusion
- Hepatic: abnormal liver function tests (possible liver damage)
- Musculoskeletal: pain in arms and or legs
- Neurologic: peripheral neuropathy

Potentially serious side effects (occurring in fewer than 3% of patients):

- Hematologic: bruising, epistaxis, conjunctival hemorrhage, bone marrow reticulin formation, worsening thrombocytopenia, thrombotic/thromboembolic complications (such as in the liver or other symptoms)
- Neurologic: peripheral neuropathy
- Ophthalmologic: cataracts or worsening of existing cataracts
- Other: hematological malignancies, progression of malignancies and non-Hodgkin's lymphoma

Liver toxicity
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. No patients in the placebo group experienced Grade 4 liver test abnormalities. In controlled studies, elevations of alanine aminotransferase (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, aspartate aminotransferase (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 of hepatic impairment.

Exercise caution when administering eltrombopag to patients with hepatic disease. Use a lower starting dose of eltrombopag in patients with moderate to severe hepatic disease and monitor closely

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

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

Prior to initiation of eltrombopag, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, examine peripheral blood smears and CBC 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 morphological abnormalities or cytopenia(s), discontinue treatment with eltrombopag and consider a bone marrow biopsy, including staining for fibrosis.

Worsening thrombocytopenia following discontinuation
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 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 3 severely thrombocytopenic patients within one month following the discontinuation of eltrombopag; none were reported among the placebo group.

Following discontinuation of eltrombopag, obtain weekly CBC, 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 261 patients with chronic liver disease who were undergoing an elective surgical procedure, the risk of thrombotic events was increased in patients treated with 75mg eltrombopag. Six thrombotic complications were reported within the group that received eltrombopag and one 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.

Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome and portal hypertension).

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.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion criteria:

1. Diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
2. Age ≥ 18 years
3. PLT transfusion-dependent, defined as need for transfusion to maintain PLT count ≥ 20K/μL, or the average of two (non-transfused) PLT counts taken within 2 weeks of the screening period ≤50K/μL, with no individual count >55K/μL
4. Patients with ITP must have failed at least 1 prior treatment for ITP including one of the following: corticosteroids, rituximab, splenectomy, cyclosporine
5. At least 3 weeks must have elapsed since the last chemotherapy treatment for CLL
6. ECOG performance status (PS) ≤ 2
7. Adequate liver function (total bilirubin ≤2X upper limit normal (ULN); ALT ≤2.5X ULN)
8. Adequate renal function (serum creatinine Cr ≤2.2 mg/dL)
9. For patients with ITP on corticosteroids or cyclosporine, dose of corticosteroids or cyclosporine must be stable for 2 weeks prior to enrollment and planned to be tapered in patients responding to eltrombopag
10. Able to provide informed consent

4.2 Exclusion Criteria:

1. Concurrent chemotherapy for CLL
2. Diagnosis of Richter's transformation
3. Uncontrolled autoimmune hemolytic anemia, i.e. patients with AIHA that is not controlled with treatment such as corticosteroids or cyclosporine. This would include patients who require PBRC transfusions or who do not have a stable hemoglobin (HGB) due to ongoing hemolysis.
4. Concurrent treatment for ITP (except corticosteroids and cyclosporine)
5. Diagnosis of myelodysplastic syndrome or acute myeloid leukemia
6. Active infection or significant medical illness as determined by the treating physician
7. Treatment with thrombomimetic agents in the past 3 months (rTPO, PEG-rHuMGDF, Nplate or Promacta)
8. Pregnant or breast feeding subjects and subjects not willing to use adequate contraceptive precautions

5.0 TREATMENT PLAN

Once patients have signed their informed consent form, all pretreatment evaluations have been completed and eligibility confirmed, patients will begin treatment with eltrombopag.

5.1 Patients will take eltrombopag 75 mg PO daily as the starting dose.

5.2 Dose adjustments may occur every 2 weeks:

- Dose reduction may occur for toxicity or PLT count over 400K/μL.
- Dose may be increased according to the following guidelines after the first 2 weeks on eltrombopag.

5.3 Dose levels:

-2 = 25 mg PO daily
-1 = 50 mg PO daily
0 = 75 mg PO daily
+1 = 150 mg PO daily
+2 = 225 mg PO daily
+3 = 300 mg PO daily

5.4 Dose modification schema:

PLT count x 10K/μL	Dose
< 100	Increase by 1 dose level
101 - 200	No change
201- 400	decrease by 1 dose level
> 400 at any time	hold drug and resume when PLT reaches < 400K/μL at next lower dose level. Additional dose adjustment will be necessary for platelets remaining > 400.

5.5 Eltrombopag treatment will continue until loss of PLT response (i.e. a return to PLT count as at enrollment into the study) or until treatment (chemotherapy) for CLL is necessary.

6.0 PRETREATMENT EVALUATION

6.1 Pretreatment evaluation will consist of history, physical examination, CBC with differential and PLT count, blood chemistries (SMA 12), serum β2 microglobulin, pregnancy test for women of childbearing potential, bone marrow aspirate and biopsy with qualitative and semi-quantitative evaluation of megakaryocytes. Fractionated bilirubin should be obtained for individuals with total bilirubin greater than the upper limit of normal.

6.2 CLL prognostic factors will be characterized including chromosome abnormalities by FISH, CD38 expression, ZAP-70 expression, and *IGHV* gene mutation status. FISH and CD38 must be repeated if not done within 4 months; ZAP-70 and *IGHV* mutation status do not need to be repeated if previously done. If there is

inadequate amount of CLL present to obtain prognostic factor results for patients with ITP, then these will not be obtained.

6.3 Assessment of bruising and bleeding using the World Health Organization (WHO) Bleeding Scale (Appendix C) will be performed prior to treatment. The investigator or designee should ask questions such as “have you experienced any bruising or bleeding within the last 7 days?” The bruising or bleeding grade (0-4), using the WHO Bleeding Scale, will be collected and recorded.

7.0 EVALUATION DURING STUDY

7.1 Monitoring of patients while on treatment will consist of weekly physical exam, including vital signs, interval history, CBC with differential and PLT count, and blood chemistries (SMA12), including liver function tests (±3 days) for the first month, then every two weeks (±3 days) for the second and third months on treatment, then monthly (±1 week) thereafter. Additional evaluations may be ordered as clinically indicated by the healthcare provider. The patients’ referring physician may perform monitoring labs and clinic visits; results will be obtained and monitored by the MDACC treating physician.

7.2 Assessment of bruising and bleeding using the World Health Organization (WHO) Bleeding Scale (Appendix A) will be performed at each visit. Any sign or symptom of thrombocytopenia observed during the Bleeding Assessments that fulfils the definition of an AE or SAE, as described, should be documented. The investigator or designee should ask questions such as “have you experienced any bruising or bleeding within the last 7 days or since your last visit?” The bruising or bleeding grade (0-4), using the WHO Bleeding Scale, will be collected and recorded.

7.3 A physician will see patients at least monthly (±1 week). A mid-level provider will evaluate patients and review counts weekly or biweekly (±3 days) when not seen by the physician, for the first 3 months.

7.4 Review of response and toxicity will be done with weekly counts (±3 days) for the first month, then every other week for months 2 and 3 on treatment, then monthly thereafter; formal response evaluation will occur monthly and will include review of PLT transfusion history and blood counts.

7.5 Patients will have a bone marrow evaluation upon achieving a complete response or after 3 months on eltrombopag (whichever comes first), then subsequently as clinically indicated. Bone marrow samples will be evaluated for changes in megakaryocyte number and characteristics. This visit, including bone marrow evaluation, history and physical examination, and laboratory evaluation must occur at MDACC. Overall response will be the best response achieved according to Section 8.1 over the first 3 months of treatment.

Table 1. Schedule of Events

Test and Evaluations	Screening Visit Day ≤ -14	M1 D1	M1 D8	M1 D15	M1 D22	M2& 3 D1	M2& 3 D15	M ≥4 D1	End of Tx
Informed consent	X								
Medical history	X								
Interval history & WHO Bleeding Assessment	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[2,8]	
PE including vital signs	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[2,8]	
Pregnancy test	X								
Eltrombopag		X	→	→	→	→	→	→	
CBC with diff, PLT	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[2,8]	X[1,3]
SMA 12[6]	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[2,8]	
CLL prognostic factors	X								
Bone Marrow aspirate and core biopsy	X							X[2,5,8]	
PK & PD, optional samples		X[1]	X[1]	X[1]	X[1]	X[1]	X[1,7]	X[2,8]	
Formal PLT response assessment		X[1]				X[1,4]		X[2,8]	

D=day; M=month; PE=physical examination; VS=vital signs; CBC=complete blood count; PK=pharmacokinetic; PD=pharmacodynamic; Tx=treatment;

[1] indicates ± 3 days

[2] indicates ± 1 week

[3] indicates to be done weekly after discontinuation of eltrombopag for at least 4 weeks

[4] begins M2

[5] BM to be done after 3 months on eltrombopag or at complete response, which ever is first.

[6] If bilirubin is elevated at any time, 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 for the development of liver test abnormalities

[7] indicates additional sampling done pre-dose, 2, 4 and 6 hour at M2D15 only

[8] indicates visits and evaluations that must occur at MDACC starting on Month 4 and continuing every 3 months thereafter while on treatment

7.6 Concurrent chemotherapy, including investigational treatment for CLL or Richter's transformation is not permitted. Growth factor support including G-CSF, GM-CSF and erythropoietin and prophylactic antibiotics are permitted.

8.0 TOXICITY EVALUATION AND RESPONSE CRITERIA

8.1 Formal PLT response criteria reflect clinically meaningful improvement in PLT counts and are based on International Working Group (IWG) response criteria for myelodysplasia[5]. Formal PLT response criteria as follows:

- Complete Response (CR): Increase in PLT count to ≥100K/μL for at least 4 weeks

- Major Response (MR): Increase in PLT count from <20K/μL to ≥20K/μL and by at least 100% for at least 8 weeks; or for patients starting with >20K/μL platelets, absolute increase in

PLT count of ≥30K/μL for at least 4 weeks: or PLT transfusion independence (no PLT transfusion) for at least 4 weeks).

- Minor Response (MNR): Increase of PLT counts by ≥50% and by an absolute count of ≥10K/μL (non-transfused) for at least 4 weeks.

- Sustained Response (SR): Includes CR, MR, and MNR. Platelets response of at least MR lasting for ≥8 weeks on therapy.

- Treatment failure: Failure to respond by the above criteria after at least 2 weeks treatment at the highest tolerated dose level or 300 mg/day, which ever is higher.

8.2 The primary efficacy endpoint is overall response (OR), which is defined as the composite of complete response (CR) and major response (MR). Individual response criteria (CR, MR, MNR, SR) will be summarized as secondary endpoints.

8.3 Secondary Endpoints:

1. Time-to-response (start of eltrombopag to response) and duration of response (initial response to loss of PLT response).
2. Time to CLL progression requiring chemotherapy (start of eltrombopag to chemotherapy for CLL).
3. Assess tolerability and toxicities of eltrombopag.
4. Pharmacokinetics (PK) of eltrombopag and thrombopoietin levels in patients with CLL.

9.0 REMOVAL FROM STUDY

9.1 Progressive CLL Disease

Progressive CLL disease (PD) will be characterized by at least one of the following:

a. ≥ 50% increase in the sum of the products of at least two nodes on two consecutive examinations two weeks apart (at least one node must be ≥ 2 cm).

b. ≥ 50% increase in the size of liver and/or spleen as determined by measurement below the respective costal margin.

c. ≥ 50% increase in absolute number of circulating lymphocytes and at least 10L/μl.

9.2 Patient request.

9.3 Active HBV infection or hepatitis.

9.4 Eltrombopag failure as defined in Section 5.5 for initial responders and Section 8.1 for non-responders.

10.0 STATISTICAL CONSIDERATIONS

This is a phase II, open label study. The primary efficacy endpoint is overall response rate (OR), which is defined as the composite of complete response (CR) and major response (MR). CR is defined as an increase in PLT count to ≥100K/μL for at least 4 weeks. MR is defined as an increase in PLT count from <20K/μL to ≥20K/μL and by at least 100% for at least 8 weeks; or for patients starting with >20K/μL platelets, absolute increase in PLT count of ≥30K/μL for at least 4 weeks: or PLT transfusion independence (no PLT transfusion) for at least 4 weeks). Overall response will be the best response achieved according to Section 8.1 over the first 3 months of treatment.

The objective is to demonstrate a 30% Overall Response Rate (ORR) for the cohort of patients with CLL and ITP and 30% ORR for the cohort of patients with disease-related thrombocytopenia. There will be a total of 36 patients enrolled in this study and with an average enrollment of 1-2 monthly, total enrollment is anticipated to take 15-20 months. Simon's two-stage optimal design will be used in this study for the 2 different cohorts, separately.

In each of these cohorts, a total sample size of 18 is chosen to differentiate between a desirable ORR of 30% and a poor response rate of 10% at the significance level of 0.10 with 80% power. Specifically, 7 patients will be enrolled in the first stage. If there are no responders, the trial will be terminated due to lack of efficacy; otherwise an additional 11 patients will be treated resulting in a total of 18 patients. If there are 3 or fewer responses among 18 patients, the treatment will be concluded ineffective. The probability of early termination due to futility is 0.48.

Safety monitoring will be based on a beta-binomial distribution. The probability of toxicity will be monitored based on a beta-binomial model, assuming a priori that p = Prob(toxicity) ~ beta(1, 1). The trial will be terminated if Prob(p > .15 | data) > .9. This rule will stop the trial if [# patients with toxicity]/[# patients evaluated] $\geq$ 3/7, 4/12, 5/17, 6/22, 7/27, 8/32. Toxicity events, for purposes of safety monitoring, will be defined as eltrombopag-related, grade ≥ 4 toxicity by CTCAE V 4.0, that persist longer than 1 week despite holding drug and/or dose reduction. The operating characteristics for toxicity are summarized in Table 2.

Table 2. Operating characteristics based on 10000 simulation study

true Prob(tox)	Pr(stop)	Median # Pts (25%, 75%)
0.05	0.02	36 (36, 36)
0.10	0.13	36 (36, 36)
0.15	0.36	36 (15, 36)
0.20	0.63	20 (9, 36)
0.30	0.94	9 (7, 15)

Efficacy will be analyzed separately for each cohort. The proportions of subjects with overall response (CR+MR) will reported together with exact confidence intervals. All other response categories (minor, response, sustained response, failure) will be summarized using frequency counts and percentage. The denominator will include all subjects who received eltrombopag.

Continuous data including eltrombopag and thrombopoietin levels will be summarized using descriptive statistics (n, mean, sd, median, range). Graphical, histograms, or box-plots will be used where appropriate. Descriptive statistical analysis will be used to explore the data, including histograms or box-plots, proportions, means, standard deviations. The Fisher's exact test or Chi-square test will be used for the univariable analysis on categorical variables (response variable with Yes versus No, for example). The t-test or Wilcoxon test will be used for continuous variables. The Kaplan-Meier methods will be used to estimate overall and event-free survival over 36 months.

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

Sample size determination:
Simon's optimal two-stage design will be used to test the null hypothesis that the proportion of subjects with overall response is <=0.10 versus the alternative that it is >=0.30 (i.e., Po<=0.10 vs. Pa>=0.30) at alpha=0.10 with 80% power. It has an expected sample size of 13 and a probability of early termination of 0.478. After testing the drug on 7 subjects in the first stage, the trial will be terminated if 0 respond. If the trial goes on to the second stage, a total of 18 patients will be studied. If the total number responding is less than or equal to 3, the null hypothesis is not rejected.

11.0 PHARMACODYNAMIC AND PHARMACOKINETIC ENDPOINTS

Biomarkers:

We will evaluate eltrombopag and thrombopoietin levels for patients on this trial. Bone marrow will be evaluated for changes in megakaryocyte number and characteristics.

PD samples will be shipped to:

Attn: Ruth LaPushin
MD Anderson Cancer Center
1515 Holcombe Blvd., T6-3849
Houston, TX 77030
Phone: 713-792-3690

PK samples will be shipped to:

GlaxoSmithKline
Department of Drug Metabolism and PharmacoKinetics
Mail Stop UW2710, Swedeland Road
King of Prussia, PA 19406
Attn: Josh Albert/Michael Adamek
Phone: 610-270-6549

12.0 REFERENCES

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