

Title: Randomized Double Blind Trial of the Safety and Efficacy of Eltrombopag at Escalated Doses up to 150mg in Patients with Persistent and Chronic ITP Not Responsive to 75 mg Daily of Eltrombopag

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LIST OF ABBREVIATIONS:

µL Microliter
AE Adverse event
ALT Alanine aminotransferase (SGPT)
aPTT Activated partial thromboplastin time
AST Aspartate aminotransferase (SGOT)
BUN Blood urea nitrogen
CBC Complete blood count
CIB Clinical Investigator's Brochure
CPK Creatine phosphokinase
FDA Food and Drug Administration
H Hours
IB Investigator brochure
ICF Informed consent form
IND Investigational new drug
IRB Institutional Review Board
ITP Idiopathic thrombocytopenia purpura
IUD Intrauterine device
IVIg intravenous immunoglobulin
Mg Milligram
mL Milliliter
RBC Red blood cell
REPEAT Repeated ExPosure to Eltrombopag in Adults with
idiopathic Thrombocytopenic purpura
SAE Serious adverse event
TPO Thrombopoietin
TpoR Thrombopoietin receptor
WBC White blood cell

1. INTRODUCTION

1.1. Background

In previous clinical studies of eltrombopag in ITP, there are some patients who have been reported as non-responders at the maximal approved dose of 75mg daily. The trend in both normal volunteers (Jenkins et al Blood 2007) and in patients with ITP suggests an increasing response rate with increasing doses of eltrombopag up to a dose of 75 mg . (Bussel et al. NEJM 2007) In fact, at 50 mg there was a 70% response rate and at 75 mg there was an 81% response rate in the initial ITP study.(Bussel et al. NEJM 2007) Furthermore, the occurrence of platelet counts $> 200,000/\mu\text{l}$ was substantially more frequent at 75 mg compared to 50 mg as well. In the confirmatory study, approximately 1/3 of the patients who did not respond to 50 mg did subsequently respond to 75 mg, although the response rate overall was only 59% compared to 16% in placebo.(Bussel et al. Lancet 2009). In the RAISE study, two key issues emerged. First the majority of patients ended up on 75 mg by the end of the study. Second, the odds of responding at each assessment point was barely 50% if not very occasionally below 50% during the study. (Cheng et al. Lancet 2011) Altogether these data suggest to us that a higher dose of eltrombopag may be useful in some patients

Data from the PETIT and PETIT2 studies in pediatric patients (who seem to metabolize eltrombopag differently especially at younger ages) found that in the middle and lowest age cohorts, even doses of 75 mg were sometimes insufficient to obtain a response. This was confirmed in the youngest cohort who thus far have required doses $> 2 \text{ mg/kg}$ in almost all cases (and even $> 3 \text{ mg/kg}$) in order for the children to respond. In the middle cohort this was dose limiting because a ceiling of 75 mg was reached rapidly if the child weighed more than 37.5 kg. (Bussel et al, PETIT in press Lancet Haem 2015)

Additional data accumulating from the pediatric clinical trials support this observation that younger children require an increased weight base dose to reach a platelet response. In the PETIT Study, the older pediatric patients (12-17 year olds) average dose was 1.2 mg/kg compared with 2.9 mg/kg to the youngest cohort (1-5 year olds) (Bussel et al, in press Lancet Haem 2015). The PETIT II study also reported an increased proportional dose requirement in the youngest cohort. (Grainger, in press Lancet Haem 2015). All of the available data using eltrombopag in research trials or clinical practice in > 170 children have not identified any new safety concerns and the side effect profile remains favorable, particularly given the alternatives in this age group. (Ramaswamy et al, JPeds, 2014)

Published data has shown pharmacokinetics, safety and tolerability of eltrombopag in healthy volunteers at an escalated dose range 100-200mg po daily for 5 days. (Matthys et al J Clin Pharmacol. 2011). Healthy volunteer data also showed a dose dependent platelet response, with a safety profile similar to placebo. Data recently presented at the ASH 2011 Meeting in refractory severe aplastic anemia patients showed safe dose escalation of eltrombopag to a maximum of 150mg with a 44% response rate. (Olnes et al. NEJM 2013) Additional phase I data presented in stem cell transplant patients, has shown doses of up to 300 mg daily have not caused dose limiting toxicities and are also well tolerated (Liesveld et al. Blood 2011).

Altogether these data suggest both that a higher dose in ITP may be more efficacious in increasing the platelet count. Furthermore the same data also suggests there is no overt increase in toxicity in normal volunteers, oncology patients or aplastic anemia patients treated with doses as high or higher than those proposed in this study.

1.2. Rationale

It therefore seems possible, even likely, that in ITP patients who did not respond at a dose of 75mg daily, eltrombopag could be more effective at a higher dose. Therefore, we would like to explore doses as high as 150 mg po daily in order to see if we can demonstrate efficacy in those patients unresponsive to 75 mg daily. We propose a double blind randomized controlled trial in ITP patients who have been defined as 'non-responders' at the maximum dose (75mg) of eltrombopag. The study will also assess efficacy and toxicity at higher daily doses (100mg, 125mg, 150mg) in this population. The study will be performed at a single center in North America, (Weill Cornell Medical College). There will be two parts to it. First the randomized double blind part to be described next. Subsequently an open label study similar to the EXTEND study (TRA105325;<https://www.clinicaltrials.gov/ct2/show/NCT01880047?term=Bussel+Dose+Escalation&rank=1>) in patients who responded at doses of 100 to 150mg to see if they maintain or even improve their response and to investigate the eltrombopag safety profile over up to 18 months at these higher doses.

Furthermore, the patients randomized to the placebo arm can go on open label treatment at higher doses if they did not increase their counts on placebo. Even though open label, they will serve as a confirmatory group.

2. OBJECTIVE(S)

2.1. Primary Objective

To determine the proportion of patients with chronic ITP who do not respond to 75 mg of eltrombopag daily given for at least 3 weeks but then do respond to eltrombopag given daily first for 2 weeks at doses of 100, then for 2 weeks at 125 mg and finally for 4 weeks at a dose of 150mg daily. The intial double-blind phase will stop if/when the platelet count exceeds 100,000/uL. Complete response (CR) will be defined as 2 consecutive platelet counts of greater than or equal to 50,000 AND an increase of greater than or equal to 20,000 from the study baseline within the 8 week increased dose window not as a result of rescue treatment. Partial response (PR) will be defined as 2 consecutive platelet counts of greater than or equal to 50,000 OR an increase of greater than or equal to 20,000 from the study baseline within the 8 week increased dose window not as a result of rescue treatment.

2.2. Secondary Objectives

To determine efficacy of administration of increased dosage of eltrombopag to subjects with chronic ITP who did not respond to current maximally approved daily dose of 75 mg for at least 3 weeks by measuring: number of weeks of platelet counts of response; number of patients achieving a platelet count $> 100,000$, and number of platelet counts per patient $> 100,000$. (Note if a platelet count $> 100,000$ is achieved that week and the subsequent weeks of the 8 week study will be considered to all be over 100,000 for purposes of all analyses).

To determine efficacy of administration of increased dosage of eltrombopag to subjects with ITP who did not respond to current maximally approved daily dose of 75 mg for at least 3 weeks by measuring HRQoL and bleeding scores.

To determine the safety of administration of increased dosage of eltrombopag to subjects with ITP who did not respond to current maximally approved daily dose of 75 mg for at least 3 weeks.

To evaluate if there are subgroups of patients (despite this endpoint being underpowered) who are more likely or less likely to either respond or to experience adverse events based on:

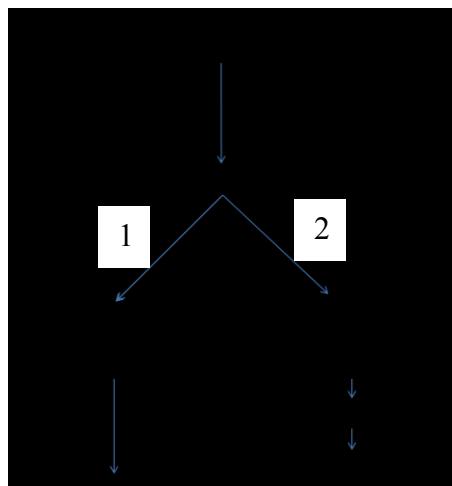
Starting platelet counts, splenectomy status, concomitant meds e.g, daily prednisone at a maximum dose of 20mg daily, duration of ITP since diagnosis, starting Hemoglobin, WBC, and Absolute Neutrophil Count (ANC), starting ALTs, bilirubins or Alk Phos levels, Platelet Reticulocyte Count.

3. INVESTIGATIONAL PLAN

3.1. Study Design

Double-blind, randomized, placebo-controlled trial in subjects with ITP who are 'non-responders' at the maximum package insert dose (75mg) of eltrombopag; non-responders are those with platelet counts $< 50,000$ despite taking 75 mg/day of eltrombopag for at least 3 weeks.

Study Design (First part): 8 Weeks



Informed consent and assent of minors will be obtained by the principal investigators or sub-investigators. Typically, informed consent/minor assent will be obtained in the outpatient clinic, although inpatients may have this discussed with them as well. Consent will be obtained after review of clinical information and satisfaction of eligibility criteria. Subjects will be randomly allocated at a two to one ratio to receive active treatment or placebo. All subjects must be ≥ 3 years old and able to swallow a tablet. in the study will receive 75 mg eltrombopag and then be randomized to receive either an additional 25 mg of eltrombopag or matching placebo tablet dispensed by the research pharmacy

Subjects and investigators will be blinded to randomization. Randomization will be stratified according to splenectomy status. Randomization will be performed at the time of informed consent with a computer generated randomization table as per the pharmacy. Subjects may enroll and begin taking 75 mg eltrombopag for at least 3 weeks. When subject's platelet count is $< 50,000$, the subject may begin day 1 of the study. Subjects and investigators will be blinded to assignment and treatment in this phase. Eltrombopag will be administered for 8 weeks or until the platelet count exceeds 100,000; at this point dosing will stop, subject will be considered a responder and the subject will eligible for entering Part 2 (the long term treatment part of the study) if desired and agreed to be appropriate by the subject giving consent, and the treating physician. The dose at which the subject achieved the primary endpoint ($> 50,000$ and increase by $> 20,000$) will be considered the dose of response. Even if a patient achieves a response, if the platelet counts remains $< 100,000$, then the dose escalation schema in the figure above will continue.

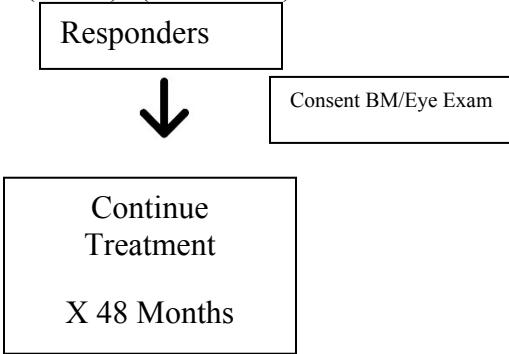
Dose escalation will continue, despite satisfaction of the primary endpoint of study ($> 50,000$ and $> 20,000$ above baseline), until the platelet count reaches 100,000. The rationale for this approach is to maximize clinically relevant responses for the subjects and standardize data for analysis. Subjects will stop study medication if the platelet count is within the normal range, thereby minimizing any safety risk associated with elevated platelet count. By continuing to dose escalate subjects until the platelet count is $> 100,000$, the maximum response and correlation of dose will be tracked allowing better understanding of sustained response and dose-dependent response, which can be applied to future consideration dosage for periods of short-term hemostasis (i.e surgical procedures). The 8 weeks of data collected in enrolled subjects on the standardized

protocol will have the balance of consistency of dosage and unequivocality of response while maintaining subject safety.

If agreed on by the P-I, subjects may obtain local counts or see their local hematologist for study visits. All study-required procedures will be faxed to the P-I for review. The appropriate dosing adjustments will be determined by the P-I.

According to the new consensus guidelines (Provan Blood, 2009), male and female subjects with > 1 year duration of ITP are diagnosed with chronic ITP. Enrollment began with adult subjects \geq 18 years of age, and was extended to include pediatric patients $>$ 12 years of age after a review of this unblinded safety information by the independent Data Safety Monitoring Officer (DSMO). Additionally, we will now allow the inclusion of pediatric patients \geq 3 year of age to enroll on the protocol. The rationale for treating patients on this study is to allow people to be successfully treated and thus increase their platelet count by using a higher dose of eltrombopag when they do not respond to 75 mg daily of eltrombopag. Since some children do not respond to 75mg, the rationale and the dosing (when and how to increase) would be the same.

Long Term Treatment Extension (Part 2): (48 months)



After 8 weeks or once dosing is stopped because the platelet count is $>100,000$, the subject will be unblinded, once the data forms are complete with the assistance of the research pharmacy.

Subjects who received and responded to eltrombopag higher dose treatment will have the option to continue therapy with periodic monitoring and ongoing dose adjustment on the open-label extension study.

Subject who had a platelet count $> 100,000$ can enter Part 2 at the dose at which the subject met primary response criteria after the platelet count decreases to $< 100,000$ /uL on serial monitoring in the immediate post-study monitoring period.

Subjects randomized to the placebo group who did not respond will have the opportunity to receive open label escalated dose eltrombopag over 8 weeks following the study protocol as if they had been randomized to active drug in the study. This group will provide the “confirmatory group” to see if the rate of response in the randomized group can be confirmed in this group.

Consent will be obtained for additional monitoring with bone marrow aspirate and biopsy at 1 year (at year 2, year 3, year 4) and additional ophthalmologic examinations for cataracts at 6 months and 18 months.

It is considered standard of care to monitor all patients as possible who have been on eltrombopag treatment for 1 year because of the higher doses of eltrombopag administered in this protocol. All subjects will have bone marrow aspiration/biopsies for their clinical care, no bone marrows will be performed for research purposes only.

Optional PK sampling will be done 4 weeks after the subject has been on active study drug (or at another time point if this is not convenient). There will be 3 samples drawn: the 1st sample will be drawn prior to taking the study drug for that day, the 2nd PK sample will be drawn 2-4 hours after the dose was taken and the 3rd sample will be drawn 5-8 hours after the dose was taken. These PK tests are being done to measure how much eltrombopag is in the blood at various time points following administration of eltrombopag and can be compared to published data.

The trial will have an 80% statistical power at the 5% level of significance (two sided) to detect a difference in the proportion of subjects receiving increased dose of eltrombopag with a primary response (2 consecutive platelet counts of > 50,000 and an increase of > 20,000 from the study baseline with in the 8 week increased dose window not as a result of rescue treatment) to subjects without a primary response in the placebo group assuming 50% of subjects randomized to active drug will have a response and 5% of subjects randomized to placebo would have a response. The same statistical test will be run for subjects who achieve partial response. An interim analysis was performed after 18 subjects to test for futility and efficacy.

Dose modification during the long term extension portion of the trial will be made on the basis of individual platelet response to a maximal dose of 150mg. All subjects can be monitored at 4 weeks intervals and then can go to every 8 weeks for the remainder of the study at the discretion of the investigator (investigator may require subjects to come in for additional monitoring if deemed necessary).

If the platelet count is > 150,000 ul and < 400,000 ul the daily dose will be adjusted and if > 400,000 ul the medication will be held and monitor will be as per the prescribing information for eltrombopag in the package insert. However, if the P-I determines that adjusting the subject's dose will negatively affect the subject, he or

she may decide not to escalate or reduce the subject's dose. Circumstances in which this may occur include, but are not limited to: investigator is tapering other medications or the subject has a viral infection. Viral infections have been known to both increase and decrease platelet count in patients with ITP. It is suggested that the increased presence of inflammatory molecules during a viral infection increases platelet production, causing platelet count to increase. Alternatively, platelet count may decrease by virtue of activating the reticuloendothelial system causing greater phagocytosis of antibody-coated platelets and/or platelet production.

Laboratory/Assessment Testing

Please see Appendix 1 for Schedule of Events.

Screening

CBC with Differential
Reticulocyte Count
Peripheral Smear
CMP (Sodium, Potassium, Bicarbonate, Chloride, BUN, Creatinine, Glucose, Calcium, Total Protein, Albumin, including AST/ALT, Fractionated Bilirubin Level)
Urine Pregnancy Test (when appropriate)

At Enrollment: (Part 1)

CBC with Differential
Reticulocyte Count
Peripheral Smear
CMP (Sodium, Potassium, Bicarbonate, Chloride, BUN, Creatinine, Glucose, Calcium, Total Protein, Albumin, including AST/ALT, Fractionated Bilirubin Level)
Platelet Reticulocyte Count
Eye Examination for caratacts
History, Physical with Vital Signs and Bleeding Score
HRQOL

Every 2 Weeks until week 8:

Reticulocyte count, Platelet Reticulocyte count
Peripheral Smear (if indicated)
CMP
History, Physical with Vital Signs and Bleeding Score

Long Term Treatment Extension: (Part 2)

Performed at each study visit:

CBC with Differential platelet count, Reticulocyte count, Platelet Reticulocyte count
Peripheral Smear (if indicated)
History, Physical with Vital Signs

After the end of treatment during the dose escalation phase, all subjects can be monitored at 4 weeks intervals and then can go to every 8 weeks for the remainder of the study at the discretion of the investigator (investigator may require subjects to come in for additional monitoring if deemed necessary).

After 6 months on therapy:

Eye Examination

After 12 months on therapy:

Bone Marrow Aspirate and Biopsy
HRQOL

After 18 months on therapy:

Eye Examination

After 24 months on therapy

Bone Marrow Aspirate and Biopsy

*Please Note: A bone marrow aspiration/biopsy will only be performed at 24 months if the subject's reticulin fibrosis grade is a 2 or 3 during the 12 month procedure.
HRQOL

After 36 Months on therapy

Bone Marrow Aspirate and Biopsy

*Please Note: A bone marrow aspiration/biopsy will only be performed at 36 months if the subject's reticulin fibrosis grade is a 2 or 3 during the 24 month procedure.

HRQOL

After 48 Months on therapy

Bone Marrow Aspirate and Biopsy

*Please Note: A bone marrow aspiration/biopsy will only be performed at 48 months if the subject's reticulin fibrosis grade is a 2 or 3 during the 36 month procedure.

HRQOL

Post Study Period after completion of dosing

Weekly

CBC with Differential platelet count, Reticulocyte count, Platelet Reticulocyte count
Peripheral Smear (if indicated)

History, Physical with Vital Signs and Bleeding Score
HRQOL (Week 1 – End of 8 Week Blinded study/ End of Extension Study)

Every 2 Weeks until week 4:
CMP
History, Physical with Vital Signs and Bleeding Score

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects:

60 subjects will be enrolled.

4.2. Inclusion Criteria:

Subject or their parent/ guardian has signed and dated a written informed consent

Males and Females aged 3 year or older, who can swallow a tablet, and are diagnosed with chronic ITP according to the new consensus guidelines (Provan, Blood, 2009) are eligible.

No indication of a disease which may cause thrombocytopenia other than ITP---- no specific testing required

Subjects with thrombocytopenia $\leq 50,000 /uL$ after at least 21 days of daily dosage with eltrombopag 75mg

Stable dosage of concomitant treatments for ITP
 ≥ 2 weeks or longer (corticosteroids);

At least 2 weeks from rescue therapy for ITP (WinRho, IVIG, corticosteroids, platelet transfusion) or 1 week if therapy has clearly been ineffective

At least 4 weeks from rituximab treatment

Pregnant or Lactating Women are excluded

Women of child-bearing age with a negative pregnancy test within 7 days of enrollment and who agree to use acceptable methods of birth control will be eligible for this study

Female subjects or female partners of male subjects must either be of non-child bearing potential (hysterectomy, bilateral oophorectomy , bilateral tubal ligation or post menopausal for more than one year) OR, if of child bearing potential, using one of the following highly effective methods of contraception.
-complete abstinence from intercourse

- Intrauterine device (IUD)
- Two forms of barrier contraception. diaphragm plus spermicide, or for males condoms plus spermicide.
- Male partner is sterile and is the only partner of the female.
- Systemic contraceptives

4.3. Exclusion Criteria:

Previous history of eltrombopag-related LFT elevation that required sustained interruption of treatment

Previous history of immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to eltrombopag

Known HIV Infection

History of Arterial or Venous Thrombosis within the past year or requiring ongoing therapy

Known Active Hepatitis C infection

Elevated AST/ALT or Creatinine > 1.5 times upper limit of normal in 4 weeks prior to enrollment*

Abnormalities in WBC, ANC and Hemoglobin > 1.5 times upper or lower limit of normal*

* Subjects can be rescreened to be included

4.4. Withdrawal Criteria:

Subject may withdraw consent at any time

Adverse event that would in the investigators judgement, make continued participation in the study an unacceptable risk

Development or diagnosis of new thrombotic event

Development of new onset clinically significant ocular changes related to cataracts on serial ophthalmologic examination

Development of MF3 fibrosis on bone marrow examinations

Development of Drug Induced Liver Injury necessitating sustained interruption of study drug

Please see Liver Chemistry Stopping and Follow up Criteria (see 6.3.1)

5. STUDY TREATMENTS

5.1. Treatment Assignment

Subjects will be randomly allocated in a two to one ratio to receive treatment or placebo. Subjects and investigators will be blinded to randomization. Randomization will be stratified according to splenectomy status. Randomization will be performed at the time of informed consent with a computer generated randomization table

5.2. Product Accountability

Product will be dispensed from Investigational Pharmacy to investigators and study coordinators for distribution to subjects.

5.3. Treatment Compliance

Subjects will bring in used medication vials at each study visit for review and medication compliance will be assessed.

5.4. Concomitant Medications and Non-Drug Therapies

5.4.1. Permitted Medications and Non-Drug Therapies

Subjects will be allowed to continue with concomitant non-ITP medications, but will be excluded from analysis as described (for the subsequent 2 weeks) if rescue therapy for treatment of ITP is needed during the duration of the study.

A subject whose platelet count is > 50,000/ μ l can receive aspirin or Plavix or warfarin at the discretion of the investigator.

5.5. Treatment after the End of the Study

As described for cross-over of placebo patient after unblinding and long term extension phase of study.

5.6. Treatment of Investigational Product Overdose

Treatment of any suspected or confirmed overdose with eltrombopag should be symptomatic with supportive care as dictated by good clinical practice. There is no known antidote for eltrombopag, although antacids can be considered to limit the absorption of eltrombopag.

5.7. Treatment Plan

| Bodily Fluid | Amount | Frequency | Total |
|--------------|--------|-----------|-------|
|--------------|--------|-----------|-------|

| | | | |
|------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Blood | 10-80cc As needed amounts will be adjusted for pediatric subjects | Bi-weekly for 8 weeks, in 4 week intervals, then every 8 weeks (visits at the discretion of the investigator) | > 400 cc |
| Bone Marrow Aspiration | 10 cc | 1 time (after 12 +2 months of study medication during Part 2 of the study) unless bone marrow fibrosis grade is a 2 or 3 (then annually) | 10 cc per bone marrow aspiration |
| Urine | 5- 10 cc | 1 time | 5-10 cc |

STUDY ASSESSMENTS AND PROCEDURES

Table 1 See Appendix 1

6.1. Critical Baseline Assessments

Screening to ensure subject eligibility criteria will occur within 30 days prior to administration of study medication. Screening assessments will include CBC, CMP (Sodium, Potassium, Bicarbonate, Chloride, BUN, Creatinine, Glucose, Calcium, Total Protein, Albumin, including AST/ALT, Fractionated Bilirubin Level), D-Dimer and urine pregnancy test (for women of childbearing potential).

6.2. If subject meet all other criteria for enrollment, a baseline ophthalmologic examination will be performed within 2 weeks of administration of study medication.

6.3. Primary Response Criteria:

Complete Response (CR) will be defined as a 2 consecutive platelet counts $\geq 50,000 / \mu\text{L}$ AND $> 20,000$ more than the baseline platelet count at enrollment within the 8 week increased dose window not as a result of rescue treatment. Partial Response (PR) will be defined as a 2 consecutive platelet counts $\geq 50,000 / \mu\text{L}$ OR $> 20,000$ more than the baseline platelet count at enrollment within the 8 week increased dose window not as a result of rescue treatment.

For uniformity of dosing and data analysis and for better understanding of increased dose effects, patients randomized to the treatment arm will automatically take:

- 100 mg for 2 weeks
- 125 mg for 2 weeks
- 150 mg for 4 weeks

However, if the platelet count increases to $\geq 100,000 / \mu\text{L}$, study drug will be interrupted and will not be resumed until platelet count is below 100,000 / μL and the patient desires to enroll on the Part 2 long term treatment extension study. The patient will finish with the Part 1 of the study at this point but can enter Part 2 the long term treatment extension study at dose at which the patient met primary response criteria, after the platelet count decreases to $< 100,000 / \mu\text{L}$ on serial immediate post-study monitoring period.

Rescue treatment will be defined as new treatment for chronic ITP eg IV anti-D or IVIG, an increased dose of steroids, or platelet transfusion. Use of rescue treatments will be allowed, but patients will be regarded as non-responders for the duration of rescue treatment and until 2 weeks beyond.

Secondary Response Criteria:

-Platelet Count $\geq 50,000$ and $> 20,000$ above baseline for at least 3 of the last 4 of 8 weeks independent of rescue therapy

- Platelet Count \geq 50,000 /uL and $>$ 20,000 above baseline for any 4 of 8 weeks independent of rescue therapy
- At least One Platelet count \geq 100,000
- Number of weeks with Platelet Counts \geq 50,000 /uL and $>$ 20 from baseline in 8 Weeks reduction of bleeding score from baseline to the last count of the study improvement of HRQoL
- Number of weeks with Platelet Counts $>$ 100,000 in 8 Weeks

Secondary Efficacy Endpoints:

- Dose required achieving first platelet count \geq 50,000 /uL and $>$ 20 from baseline
- Average Platelet Count at each dose level
- Bleeding scores using WHO score
- Use of Rescue Treatments

6.4. Safety

Increased Liver Chemistries

Eltrombopag administration may cause hepatotoxicity. In the ITP controlled clinical studies, one patient experienced Grade 4 (NCI Common Terminology Criteria for Adverse Events [NCI CTCAE] toxicity scale) elevations in serum liver test values during therapy with Eltrombopag, worsening of underlying cardiopulmonary disease, and death. One patient in the placebo group experienced a Grade 4 liver test abnormality. In controlled studies, elevations of ALT and indirect bilirubin were observed more frequently on the eltrombopag arm than placebo. Overall, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 11% and 7% of the eltrombopag and placebo groups, respectively. In the three controlled studies, four patients (1%) treated with eltrombopag and three patients in the placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seven of the patients treated with eltrombopag in the controlled studies with hepatobiliary laboratory abnormalities were re-exposed to eltrombopag in the ITP extension study. Six of these patients again experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of eltrombopag in one patient. In the ITP extension study, one additional patient had eltrombopag discontinued due to liver test abnormalities (all \square Grade 3). Liver chemistry stopping criteria and follow up requirements have been designed to assure subject safety and evaluate liver event etiology in alignment with the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009, www.fda.gov).

Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis

Eltrombopag may increase the risk for the development or progression of reticulin fiber deposition within the bone marrow.

In the ITP extension study, 151 patients have had bone marrow biopsies evaluated for increased reticulin and collagen fiber deposition. Bone marrow biopsies taken after 1 year of therapy showed predominantly myelofibrosis (MF) Grade 1 or less in 140/151 (93%) of patients (Saleh et al 2013, Blood). There were 11/151 (7%) of patients with MF Grade 2. Four patients had collagen deposition reported. One patient with a pre-existing MF Grade 1 developed a MF Grade 2 and subsequently discontinued treatment with eltrombopag. Clinical studies have not yet excluded a risk of bone marrow fibrosis with clinical consequences. .

If new or worsening blood morphological abnormalities or cytopenias occur, a bone marrow biopsy should be considered, including staining for fibrosis..

Thrombotic/thromboembolic complications

Thrombotic/thromboembolic complications may result from increases in platelet counts with eltrombopag and those reported in controlled clinical studies in patients with chronic ITP included both venous and arterial events and were observed at low and normal platelet counts.

Use caution when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for thrombotic/thromboembolic complications, do not use eltrombopag in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve and maintain a platelet count of $\geq 50 \times 10^9/L$ as necessary to decrease the risk for bleeding

In a placebo-controlled double-blind study (ELEVATE) of 292 patients with chronic liver disease who were undergoing an elective surgical procedure, the risk of portal venous thrombosis was increased in patients treated with 75 mg eltrombopag once daily for 2 weeks in preparation for their invasive procedure. Seven thrombotic complications (six patients) were reported within the group that received eltrombopag and three thrombotic complications were reported in the placebo group (two patients). All of the thrombotic complications reported within the eltrombopag group were of the portal venous system. Five of the six patients in the group that received eltrombopag experienced a thrombotic complication within 30 days of completing treatment with eltrombopag and at a platelet count above $200 \times 10^9/L$. Malignancy is known to increase the risk for developing a thrombotic event and four of the 6 patients either had a diagnosis or suspicion of malignancy (2 hepatocellular carcinoma; 1 possible lymphoma and 1 brain tumor).

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

The ELEVATE study was terminated in November 2009 and a Dear Health Care Professional Letter (DHCPL) was sent to all physicians enrolled in Promacta Cares in May 2010.

Hematologic Malignancies

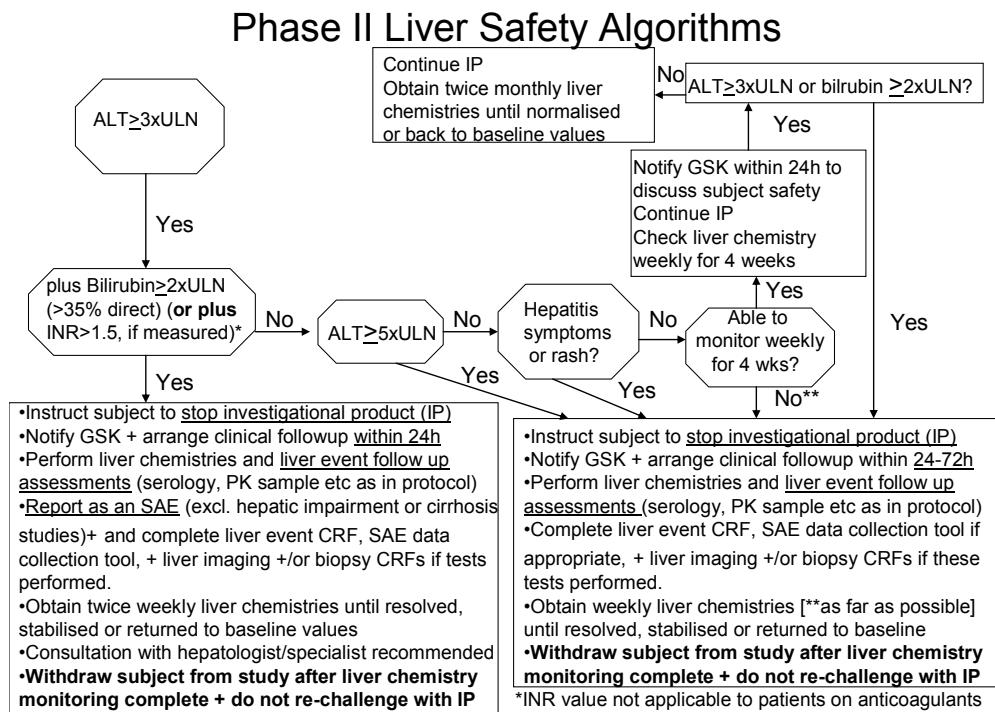
Stimulation of the TPO receptor on the surface of hematopoietic cells by eltrombopag may increase the risk for hematologic malignancies. In the controlled clinical studies, patients were treated with eltrombopag for a maximum of 6 months. During this period no hematologic malignancies were reported in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

Cataracts

Cataracts were observed in toxicology studies of eltrombopag in rodents (see Non-clinical Information). To date, there is however, no evidence that eltrombopag increases the incidence nor progression of cataracts in patients who have received eltrombopag. In the three placebo-controlled ITP studies, 7% of patients in both the placebo and eltrombopag treatment groups had a report of cataract. A significant proportion of patients in the ITP clinical studies were also exposed to chronic corticosteroid administration.

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

6.4.1. Liver chemistry stopping and follow-up criteria



Liver chemistry stopping criteria and follow up requirements have been designed to assure subject safety and evaluate liver event etiology in alignment with the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009, www.fda.gov).

Liver chemistry stopping criteria 1-5 are defined as follows:

1. ALT \geq 3x ULN and bilirubin \geq 2x ULN (>35% direct bilirubin) (or ALT \geq 3x ULN and INR $>$ 1.5, if INR measured)

NOTE: If serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT \geq 3x ULN and bilirubin \geq 2x ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

1. ALT \geq 5x ULN
2. ALT \geq 3x ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
3. ALT \geq 3x ULN persists for \geq 4 weeks

4. ALT \geq 3x ULN and cannot be monitored weekly for 4 weeks

When any of the liver chemistry stopping criteria 1 - 5 is met, do the following:

- Immediately discontinue study treatment
- Report the event to Novartis within 24 hours of learning its occurrence
 - All events of ALT \geq 3x ULN and bilirubin \geq 2x ULN ($>35\%$ direct bilirubin) (or ALT \geq 3x ULN and INR > 1.5 , if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
 - NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT \geq 3x ULN and bilirubin \geq 2x ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Do not rechallenge with investigational product.

In addition, for subjects meeting liver stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (refer to Section 0), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For subjects meeting any of the criteria 2 – 5:

- Make every reasonable attempt to have subjects return to clinic within 24-72 hrs for repeat liver chemistries and liver event follow up assessments (refer to Section 0)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;

subjects meeting criterion 5 should be monitored as frequently as possible

Liver Event Follow Up Assessments

For subjects meeting any of the liver chemistry stopping criteria 1 – 5, make every attempt to carry out the liver event follow up assessments described below:

- Viral hepatitis serology including:
 - Hepatitis A IgM antibody
 - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
 - Hepatitis C RNA
 - Cytomegalovirus IgM antibody
 - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
 - Hepatitis E IgM antibody
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin \geq 2x ULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or

hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE form.

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form.
- Record alcohol use on the liver event alcohol intake form.

The following assessments are required for subjects with ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN ($>35\%$ direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Liver Chemistry Monitoring Criteria

For subjects with ALT ≥ 3 x ULN but <5 x ULN and bilirubin <2 x ULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify Novartis within 24 hours of learning of the abnormality to discuss subject safety
- Can continue study treatment
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline values
- If at any time the subject meets any of the liver chemistry stopping criteria 1 – 5, proceed as described above
- If, after 4 weeks of monitoring, ALT <3 x ULN and bilirubin <2 x ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

6.4.2. Adverse Events

6.4.2.1. Definition of an AE

An **Adverse Event (AE)** is any unfavorable or unintended effect on a research participant whether or not the event is deemed study-related. AEs include new or increased symptoms, diagnoses, lab results or changes to a pre-existing condition. AEs are monitored throughout the duration of a study and for a specified period after the completion of study procedures (e.g. 30 days after the last treatment).

6.4.2.2. Definition of a SAE

A **Serious Adverse Event (SAE)** includes death, life threatening events, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the health or well-being of the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.4.3. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

6.4.4. Pregnancy

No Pregnant or Lactating Women will be eligible for this study,

Women with a negative pregnancy test within 7 days of enrollment and agree to use acceptable methods of birth control will be eligible for this study

6.4.5. Time Period and Frequency of Detecting AEs and SAEs

Investigators in writing must notify the NYPH-WCMC IRB as per Human Research Protection Policy in an immediate report within 7 working days of the occurrence of all serious or unexpected Adverse Events (AEs) in NYPH-WCMC research subjects, whether or not the events are considered study-related and within 24 hours of protocol deviations to eliminate hazards or breech of confidentiality

6.4.6. Prompt Reporting of Serious Adverse Events and Other Events to Novartis

Reporting to Novartis:

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

All serious adverse events must be reported by facsimile within 24 hours to Novartis: usdrugsafety.operations@novartis.com .

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to Novartis within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of eltrombopag and considered by the investigator to be related or possibly related to eltrombopag must be reported to Novartis if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

6.4.6.1. Regulatory reporting requirements for SAEs

The PI and/or data coordinator will be reporting unexpected serious adverse events promptly to the IRB, FDA and to Novartis within appropriate regulatory timeframe.

We will be reporting:

- WCMC IRB as per WCMC AE Reporting Policy
- FDA as per Safety Reporting Requirements for IND and BA/BE (21CFR312.32)
- Novartis will be informed of all SAE within 24 hours
- WCMC Data Safety Monitoring Board

6.4.6.2 Data Safety Monitoring Plan:

We will be utilizing the Weill Cornell Medical College Data Safety Monitoring Board (DSMB) to review the IRB-approved protocol, informed consent forms and safety reports. The DSMB will review data semi-annually to evaluate the safety, efficacy, and compliance with all local IRB, FDA and ICH regulations/requirements for this study. Adverse events and unanticipated problems will be submitted to the DSMB semi-annually. A Grade 4 or above adverse event will result in an immediate submission of a periodic report to the DSMB. All serious adverse events will be immediately submitted to Novartis and to the FDA under the IND.

The Principal Investigator will submit all written DSMB recommendations at the time of the continuing review. Individual recommendations will be submitted upon receipt of review comments.

Safety Evaluation

This protocol is investigator initiated. The Principal Investigator is responsible for the study and will monitor the safety of the patients on the protocol.

The following safety will be reviewed by the Principal Investigator:

- Physical Exam
- Vital Signs
- Laboratory results (blood count, liver function tests, reticulocyte count)
- SAE and AE events
- Bone marrow aspirations/biopsies (if relevant)

Early Stopping Rules

Individual Stopping Rules

- Adverse event that would in the investigators judgment, make continued participation in the study an unacceptable risk
- Development or diagnosis of new thrombotic event

- Development of new-onset, clinically-significant, ocular changes related to cataracts on serial ophthalmology examinations
- Development of MF3 fibrosis on bone marrow examinations
- Development of Drug Induced Liver Injury

Liver chemistry stopping criteria and follow up requirements have been implemented to assure subject safety and evaluate liver event etiology in alignment with the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation.

Liver chemistry stopping criteria 1-5 are defined as follows:

1. ALT $>3x$ ULN and bilirubin $>2x$ ULN ($>35\%$ direct bilirubin) (or ALT $>3x$ ULN and INR > 1.5 , if INR measured and prolongation not related to another medication known to prolong INR)

NOTE: If serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT $>3x$ ULN and bilirubin $> 2x$ ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT $\geq 5x$ ULN

3. ALT $\geq 3x$ ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

4. ALT $\geq 3x$ ULN persists for ≥ 4 weeks

5. ALT $\geq 3x$ ULN and cannot be monitored weekly for 4 weeks

When any of the liver chemistry stopping criteria 1 - 5 is met, do the following:

- Immediately discontinue study treatment
- Report the event to Novartis and DSMB within 24 hours of learning its occurrence
- All events of ALT $> 3x$ ULN and bilirubin $>2x$ ULN ($>35\%$ direct bilirubin) (or ALT $>3x$ ULN and INR > 1.5 , if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
- NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT $>3x$ ULN and bilirubin $>2x$ ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below

- Do not rechallenge with investigational product.

In addition, for subjects meeting liver stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (refer to Section 0), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For subjects meeting any of the criteria 2 – 5:

- Make every reasonable attempt to have subjects return to clinic within 24-72 hrs for repeat liver chemistries and liver event follow up assessments
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; subjects meeting criterion 5 should be monitored as frequently as possible

Liver Event Follow Up Assessments

For subjects meeting any of the liver chemistry stopping criteria 1 – 5, make every attempt to carry out the liver event follow up assessments described below:

- Viral hepatitis serology including:
 - Hepatitis A IgM antibody
 - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
 - Hepatitis C RNA
 - Cytomegalovirus by PCR
 - Epstein-Barr virus by PCR
- Hepatitis E IgM antibody
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin $>2x$ ULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form.
- Record alcohol use on the liver event alcohol intake form.

The following assessments are required for subjects with $ALT >3x$ ULN and bilirubin $>2x$ ULN ($>35\%$ direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Liver Chemistry Monitoring Criteria

For subjects with $ALT >3x$ ULN but $<5x$ ULN and bilirubin $<2x$ ULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions

should be taken:

- Notify Novartis and DSMB within 24 hours of learning of the abnormality to discuss subject safety
- Can continue study treatment
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline values
- If at any time the subject meets any of the liver chemistry stopping criteria 1 – 5, proceed as described above
- If, after 4 weeks of monitoring, ALT <3x ULN and bilirubin <2x ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

Protocol Stopping Rules

Novartis and the Principle Investigator may terminate the study at any time. Early termination may occur due to emergent risk information or the decision by Novartis to discontinue the development of Eltrombopag.

Dose Escalation Rules

In Part 1 of the study, subjects will be randomly allocated at a two to one ratio to receive active treatment or placebo. All subjects in the study will receive 75 mg eltrombopag and then be randomized to receive either an additional 25 mg of eltrombopag or matching placebo tablet dispensed by the research pharmacy.

Eltrombopag will be administered bi-weekly for 8 weeks. If platelet count does not exceed 100,000, the additional eltrombopag or matching placebo tablet will be increased by 25 mg until the patient receives 75 mg eltrombopag and 75 mg eltrombopag or matching placebo (100mg x 2 weeks, 125 mg x 2 weeks, 150 x 4 weeks). If the patient's platelet count exceeds 100,000 during part 1 dosing will stop, subject will be considered a responder, and the subject will eligible for entering Part 2 (the long term treatment part of the study).

Dose modification during the long term extension portion of the trial will be made on the basis of individual platelet response to as high a dose as 150mg. If the platelet count is > 150,000 ul and < 400,00 ul the daily dose will be adjusted and if > 400,000 ul the medication will be held and monitor will be as per the prescribing information for eltrombopag in the package insert. However, if the P-I determines that adjusting or stopping the subject's dose will negatively affect the subject, he or she may decide not to escalate, reduce, or stop the subject's dose. Circumstances in which this may occur include, but are not limited to: investigator is tapering other medications or the subject has a viral infection. Viral infections have been known to both increase and decrease platelet count in patients with ITP. It is suggested that the increased presence of inflammatory molecules during a viral infection increases platelet production, causing platelet count to increase. Alternatively, platelet count may decrease by virtue of activating the reticuloendothelial system causing greater phagocytosis of antibody-coated platelets and/or platelet production.

Data Collection and Monitoring

Data will be collected and entered into a Microsoft excel eCRF by the clinical research coordinator. Data will be entered into the eCRF after each study visit. The Principal investigator will verify the data quarterly to ensure that the data collected and entered is accurate.

Interim Analysis:

An interim analysis was performed after 18 patients were enrolled in the study. The data suggested that non-splenectomized patients tended to have higher average platelet counts compared to splenectomized patients for the first 8 weeks in the open-label extension phase. When subjects were on active drug, the results revealed that males tended to have a higher complete response rate compared to females. Of note, three subjects were removed due to SAEs, however only one patient was removed because of a study drug related event (elevated LFTs). Further analysis will be performed to evaluate the long term efficacy and safety of Eltrombopag at doses higher than 75 mg after 36 and then 60 patients have completed 8 weeks of active medication.

6.4.7. Other Safety Outcomes

7. DATA MANAGEMENT

Data will be kept in locked filing cabinets in a locked room away from the clinical area. All data that is computer generated will password protected. The FDA, New York Presbyterian Hospital, the IRB, and the Office for Human Research Protection (OHRP) may have access to the study records without the patient's permission and will maintain confidentiality of the information.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

Subject who did not respond at a dose of 75mg daily, eltrombopag will respond with increasing platelet count to $> 50,000$ and $> 20,000$ above baseline at a higher daily dose of 100, 125 and 150mg.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

The trial will have a 80% statistical power at the 5% level of significance (two sided) to detect a difference in the proportion of patient receiving increased dose of eltrombopag with a primary response (Platelet Count $\geq 50,000$ per cubic millimetre and $> 20,000$ above baseline) to patients without a primary response in the placebo group. assuming 50% of patients randomized to active drug will have a response and 5% of patients

randomized to placebo would have a response. An interim analysis will be performed after 18 subjects to test for futility and efficacy and also to re-estimate sample size. If neither futility nor efficacy are met the trial would continue to enroll. Based on the observed treatment effect at the interim analysis the sample size would be allowed to expand to up to 60 subjects

8.2.2. Sample Size Sensitivity / Re-estimation

If the estimates of study size are incorrect, a preliminary look will take place after 18 patients to see if the study size needs to be increased.

8.3. Data Analysis Considerations

8.3.1. Key Elements of Analysis Plan

The analysis would primarily be descriptive except for the primary endpoint. In order to make the study feasible, the current plan for 36 patients does not allow for much flexibility. It does allow for a confirmatory study from the patients on placebo who can then follow the 8 weeks of dose escalation treatment as an open label study (note they will have been on 75 mg of eltrombopag for at least 11 weeks at that time). All secondary analyses will be underpowered but will be descriptive.

Analysis of efficacy will be based on the intention to treat population of all subjects who underwent randomization.

8.3.1.1. Interim analysis

Results of Interim analysis:

In the interim analysis of 18 subjects, the data suggests that non-splenectomized patients tended to have greater average platelet counts compared to splenectomized patients for the first 8 weeks in the open-label extension phase. When subjects were on active drug, the results revealed that males tended to have a higher complete response rate compared to females.

Of note, three subjects were removed due to SAEs, however only one patient was removed because of a study drug related event (elevated LFTs). Further analysis will be performed after 36 patients and 60 patients are enrolled to evaluate the long term efficacy and safety of eltrombopag at doses higher than 75 mg.

Primary Response Criteria:

Complete Response (CR) will be defined as a 2 consecutive platelet counts $\geq 50,000 / \mu\text{L}$ AND $> 20,000$ more than the baseline platelet count at enrollment within the 8 week increased dose window not as a result of rescue treatment. Partial Response (PR) will be defined as a 2 consecutive platelet counts $\geq 50,000 / \mu\text{L}$ OR $> 20,000$ more than the baseline platelet count at enrollment within the 8 week increased dose window not as a result of rescue treatment. Odds of response will be analyzed using logistical regression for binary response variables.

Secondary Response Criteria:

- Platelet Count \geq 50,000 and $>$ 20,000 above baseline for at least 3 of the last 4 of 8 weeks independent of rescue therapy
- Platelet Count \geq 50,000 /uL and $>$ 20,000 above baseline for any 4 of 8 weeks independent of rescue therapy
- At least One Platelet count \geq 100,000
- Number of weeks with Platelet Counts \geq 50,000 /uL and $>$ 20 from baseline in 8 Weeks reduction of bleeding score from baseline to the last count of the study improvement of HRQoL
- Number of weeks with Platelet Counts $>$ 100,000 in 8 Weeks

Secondary Efficacy Endpoints:

- Dose required achieving first platelet count \geq 50,000 /uL ?and $>$ 20 from baseline
- Average Platelet Count at each dose level
- Bleeding scores using Page score and WHO score
- Use of Rescue Treatment

8.3.1.2. Safety Analyses

For safety analysis the population for analysis will include all randomized subjects who received at least one dose of study medication. Subjects will be evaluated according to the treatment they received.

Malignancy

Malignancy will be descriptive

Bone Marrow Reticulin Fibrosis

Bone Marrow Fibrosis monitoring will involve performing bone marrow aspirate and biopsy on any consenting patient who elects to remains enrolled in long term extension after 12 months of therapy. All marrows will be read by Drs Julia Geyer and Attilio Orazi at Weill-Cornell Medical Center.

Re-occurrence of thrombocytopenia

Re-occurrence of thrombocytopenia will be defined as platelet count $<$ 10,000 uL or 10,000 ul decrease from baseline platelet count at enrollment in the 4 weeks following discontinuation of the study medication

Thrombosis

Thrombosis will be descriptive

Drug Induced Liver Injury

Elevations in ALT > 3 time upper limit of normal or bilirubin level > 2 times the upper limit of normal will be monitored and assessed for continuation or stopping of study drug as per Phase II Liver Safety Algorithm (see Appendix)

Incidence of new and progression of previously identified cataracts

Cataract assessment will involve a baseline eye exam in all enrolled patients with subsequent evaluations at 6 months and 18 months in the patients that continue to receive therapy in the long term extension study. If possible re scheduling, all exams will be performed by Dr Chris Starr.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

9.2. Quality Control (Study Monitoring)

CRF monitoring will be performed by one of the coordinators not involved in the study.

The WCMC data safety monitoring board will be used to review the IRB-approved protocol, informed consents, and safety reports on a quarterly basis.

Quality Assurance

To ensure compliance with good clinical practice and regulatory requirements, regulatory agencies may conduct a regulatory inspection at any time during or after the study completion. In the event of an audit, the investigator will agree to grant the inspectors direct access to all relevant documents and allocate time/staff time to discuss findings and relevant issues.

9.3. Records Retention

Primary data be retained until there is no reasonable possibility that they will be required to defend against an allegation of scientific misconduct and as per FDA regulations of

studies conducted under IND until two years after marketing approval or withdrawal of IND.

10. APPENDICES

10.1. Appendix 1

Attached Table 1: Study Assessments and Procedures

| Part 1 | Screen < 28 days | Day 1 | Week 2 | Week 4 | Week 6 | Week 8 |
|-------------------------------------------|------------------|-------|--------|--------|--------|--------|
| Written Informed Consent | X | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | |
| Demographics | X | | | | | |
| Register | X | | | | | |
| Eye Exam | X | | | | | |
| Pregnancy Test * | X | | | | | |
| Randomization | X | | | | | |
| History and Physical (Vital Signs) | | X | X | X | X | X |
| Bleeding Score | | X | X | X | X | X |
| HRQOL | | X | | | | |
| CBC | X | X | X | X | X | X |
| Reticulocyte | X | X | X | X | X | X |
| Platelet Reticulocyte | X | X | X | X | X | X |
| Peripheral Smear* | X | X | X | X | X | X |
| CMP | X | X | X | X | X | X |

| Part 2 | 6 Month | 12 Month | 18 Month | 24 Month | 30 Month | 36 Month | 42 Month | 48 Month |
|--------------------------------|---------|----------|----------|----------|----------|----------|----------|----------|
| Eye Exam | X | | X | | | | | |
| Bone Marrow Examination | | X | | X** | | X** | | X** |
| HRQOL | | X | | X | | X | | X |
| CBC | | | | | | | | |
| Reticulocyte | | | | | | | | |
| Platelet Reticulocyte | | | | | | | | |
| Peripheral Smear * | | | | | | | | |
| CMP | | | | | | | | |

*If clinically indicated

** Bone marrow aspirations/biopsies will be performed annually depending on the reticulin fibrosis grade of the bone marrow performed at year 1. A bone marrow

aspiration/biopsy will be repeated the next year if the subject's reticulin fibrosis grade is a 2 or 3.

| Post Study Period | Week 1 | Week 2 | Week 3 | Week 4 |
|------------------------------|---------------|---------------|---------------|---------------|
| CBC | X | X | X | X |
| Reticulocyte | X | X | X | X |
| HRQ0L | X | | | |
| Platelet Reticulocyte | X | X | X | X |
| Peripheral Smear * | X | X | X | X |
| CMP | X | | X | |

10.2 Appendix 2

PHARMACOKINETIC SAMPLING

PK Sample Collection

After a minimum of 4 weeks on active study drug, 2mL blood samples for PK analysis will be collected in K2 EDTA-containing tubes. One sample will be collected at each of the following times: within 1 hour prior to eltrombopag dosing (pre-dose sample), and at 2- 4 hours and 5-8 hours after eltrombopag dosing.

Record the date, time, and amount (in mg) of the dose administered prior to the pre-dose sample (this dose should have been taken on a day prior to PK sample collection), and record the dosing frequency (for example: once daily).

Record the date, time, and amount (in mg) of the dose administered after the pre-dose PK sample (this dose should be administered within a few minutes after collecting the pre-dose PK sample).

Collect each whole blood PK sample as close as possible to the planned time relative to dosing.

Record the actual date and time that each sample was collected.

If a cannula is used, the cannula will be inserted into an arm vein within sufficient time prior to dosing, will be kept patent with normal saline and will be removed after the last blood sample is collected or earlier if the subject requests. In order to avoid artificial dilution of the PK sample by the saline, 0.5-1mL of whole blood will be collected and discarded before each PK sample is collected.

PK Sample Processing and Storage

Each PK samples will be gently mixed by inversion 8 to 10 times (do not shake). Place the samples on ice immediately after collection. Within 1 hour of sample collection, the samples will be centrifuged in a refrigerated (2°C to 8°C) centrifuge at 1500 RPM for 10 minutes. The resulting plasma will be transferred into a properly-labeled polypropylene tube. Immediately, place the plasma samples upright in a -20°C freezer and retain the samples in the freezer until they are shipped for analysis.

PK Sample Shipment

Samples should be shipped in batches, no less than every 3 months.

Samples should be shipped **only on Monday, Tuesday, or Wednesday**. Samples must be shipped on dry ice via overnight courier to:

Maria EdwardsPPD
2244 Dabney Road
Richmond VA, 23230, USA
Tel: (804) 254.8430, Fax: (804) 254.1104
[Email: Maria.Edwards@ppdi.com](mailto:Maria.Edwards@ppdi.com)