ITP CONSORTIUM OF NORTH AMERICA

ICON3

A Phase 3 Study of Eltrombopag vs. Standard First-Line Management for Newly Diagnosed Immune Thrombocytopenia (ITP) in Children

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Investigational Product: Eltrombopag
IND #: 142204
Study Phase: 3

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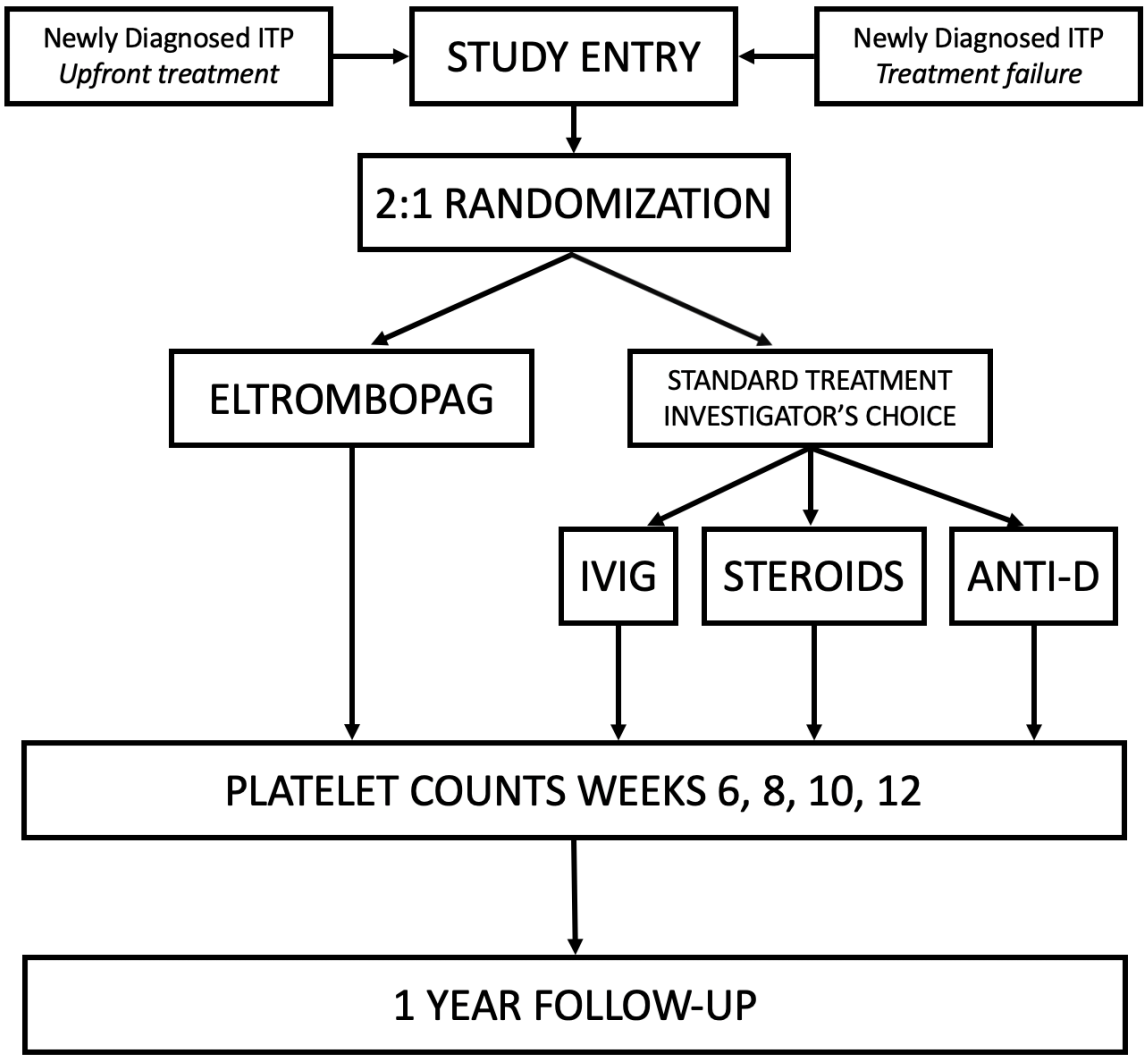
EXPERIMENTAL DESIGN SCHEMA



1 BACKGROUND

ITP is the most common autoimmune cytopenia in children, and causes an often severely reduced platelet count, variable bleeding symptoms, and health-related quality of life (HRQoL) reductions due to factors such as activity restrictions, frequent medical visits and interventions, and fatigue.[1-3] In an era when the fields of hematology and immunology are advancing rapidly with the development of drugs targeted to specific disease mechanisms, the treatment of newly diagnosed ITP remains primitive and non-specific, with no novel therapies introduced in the past 30 years.[4]

Eltrombopag is an oral, small-molecule, nonpeptide thrombopoietin-receptor agonist (TPO-RA). The drug initiates thrombopoietin-receptor signaling by interacting with the transmembrane domain of the receptor, thereby inducing proliferation and differentiation of cells in the megakaryocytic lineage. Eltrombopag is a drug that has the potential to change the landscape of newly diagnosed ITP for both children and adults. While there are myriad drugs available to choose amongst for treatment of chronic ITP, including immunosuppressants and thrombopoietin receptor agonists, the treatment of newly diagnosed ITP is generally limited to three first-line medications: corticosteroids, intravenous immunoglobulin (IVIG), and anti-D globulin. Each of these agents has either undesirable side effects, undesirable logistics of administration, or both. Additionally, each of these agents acts only transiently to raise the platelet count, and in children with continued active ITP, the platelet count will decrease days to weeks after the medication is given. As a once daily, non-immunosuppressant, oral agent, eltrombopag offers the possibility of a sustained platelet response over weeks to months with continued use. This could result in improved HRQoL and reduction in fatigue, as well as other benefits.[5]

Eltrombopag is an established therapy for pediatric patients with chronic ITP. Safety and efficacy were established in the PETIT[6] and PETIT2[7] trials, and the drug was FDA-approved for children with chronic ITP in 2015.

Off-label use for adults with newly diagnosed ITP has been described in two small single-center trials. A single-arm study of dexamethasone in combination with 4 weeks of eltrombopag used upfront in adult patients with newly diagnosed ITP produced 100% response (platelets >30 x 10^9/L) at completion of therapy, and 66.7% relapse-free survival at 1 year, better outcomes than expected for comparable patients treated with steroids alone.[8] In a second study, 76% of steroid-nonresponsive patients had a durable response to eltrombopag after 3 months of therapy.[9] Based on data from ICON2, pediatric hematologists are already using TPO-RAs in some cases of newly diagnosed ITP. Of 79 patients described in the ICON2 retrospective review who were prescribed a TPO-RA, 18% had newly diagnosed ITP.[10] TPO-RAs may be an efficacious first-line therapy for newly diagnosed ITP patients who require treatment.

While age and duration of symptoms at diagnosis are known to predict resolution of ITP[11], other biologic factors that predispose some patients to resolution of their ITP and others to a more chronic course are not known. It is also not known whether the development of chronic ITP could be prevented by intervention earlier in the patient's course. A subset of patients with chronic ITP has been reported to have resolution of their disease after treatment with TPO-RAs, which was sustained after discontinuation of the medication. One postulated mechanism is immune tolerance by increasing exposure to platelet antigens, a hypothesis supported by the decreasing titer of anti-platelet antibody in one patient who resolved.[12] Another proposed mechanism is the increase in Treg functionality due to increased TGF-β1 released by megakaryocytes.[13] Because of the implication of Tregs in the pathogenesis of ITP and the potential immunomodulatory effects of TPO-RA, early use of eltrombopag may have an impact on the number of patients who resolve versus have persistent or chronic disease. Additionally, there are likely other biological factors which influence response to TPO-RA and other therapies that are not yet understood. Identification of these biomarkers could lead to a more personalized approach to therapy, targeted to an individual patient's disease biology.

2 STUDY RATIONALE

2.1 Study Design Rationale

Eltrombopag is an attractive option for pediatric patients needing therapy for ITP because it is an oral outpatient therapy and may have fewer side effects than standard therapies. The early response rate in this setting is not known. Pilot scale studies or observational accounts cannot answer important questions about the actual efficacy of this approach. Therefore, we have designed a randomized, two-arm, Phase 3 trial to evaluate the efficacy of eltrombopag vs. standard first-line management in pediatric patients with newly diagnosed ITP. The primary endpoint (≥ 3 of 4 platelet measurements with platelets >50 $x10^9$/L at Weeks 6, 8, 10, and 12 of therapy, without rescue) is a measurable outcome clinically equivalent to the endpoint of ≥ 6 of 8 platelet measurements with platelets >50 $x10^9$/L during weeks 5-12 used in a previous pediatric study of eltrombopag in chronic ITP[7]. It is also a clinically relevant outcome in the newly diagnosed setting, as patients who are being treated because of bleeding symptoms or risk may benefit from a more sustained response during this time period, rather than repeated drops in platelet counts after transient responses to therapy.

2.2 Dose Rationale

The PETIT[6] trial started with a dose-finding phase, followed by a double-blind randomized phase in which starting doses were at the previously established doses. PETIT2[7] used starting doses based on body weight and ethnic origin. PK data demonstrate that patients age 12-17 years have similar AUC_{tau} and C_{max} values as adults for the same dose, while children age 1-11 years have higher levels.[14] With lower weight-adjusted exposure, however, younger children require higher per-kg

doses to achieve the same exposure. Pediatric dosing is now established, and there is an FDA label for use in pediatric patients > 1 year of age with chronic ITP. This study will use manufacturer label dosing for drug initiation. Dose adjustment after a platelet response is modified from the label based on abundant clinical experience with rebound thrombocytopenia when eltrombopag is held in this setting. Details for dose reduction are outlined after a sustained response after week 12 is prescribed, given reports[15] of adult patients with sustained responses after discontinuation in the setting of "persistent response despite a reduction in dose over time." As we expect the majority of newly diagnosed patients to have resolution of ITP within 1 year, we outline standardized discontinuation of drug even in the absence of thrombocytosis.

2.3 Safety Considerations

Two pediatric trials (PETIT[6] and PETIT2[7]) investigated the use of eltrombopag in pediatric patients aged 1-17 years with persistent or chronic ITP. The PETIT trial established dosing in an open-label dose-finding phase and then randomly assigned patients to receive eltrombopag vs placebo. 62% of patients receiving eltrombopag vs. 32% of patients receiving placebo (p=0.011) achieved the primary endpoint of platelet count ≥50 x10^9/L at least once in the first 6 weeks of the study without rescue. In PETIT2, 40% of patients receiving eltrombopag vs. 3% of patients receiving placebo had a sustained platelet response, with primary outcome of platelet count ≥50 x10^9/L during 6 of 8 of weeks 5-12 of the study.

Hepatobiliary events: Mild reversible elevations of alanine aminotransferase ≥3x ULN occurred in fewer than 10% of pediatric patients and were not associated with clinically significant symptoms. However, 3% of patients in the two studies were unable to continue eltrombopag.

Marrow fibrosis: There were no findings of bone marrow fibrosis in either pediatric trial.[14]

Thromboembolic events: There were no thromboembolic events in either pediatric trial.

Cataracts: In an adult randomized controlled trial (RAISE), there was no difference in cataract development between the eltrombopag group and the placebo group. In two open label studies (REPEAT and EXTEND), there was a comparable frequency of cataract incidence or progression.[16] In the pediatric trials, 2 patients in PETIT2 had a cataract event (one development of a new cataract, and one progression of a pre-existing cataract).[7] In both the adult and pediatric studies, all patients with cataract development or progression had also received corticosteroids. Current consensus among experts is that risk of cataract is not higher than baseline during eltrombopag treatment.

3 STUDY OBJECTIVES

3.1 Primary Objective

To determine if the proportion of patients with a platelet response is significantly greater in patients with newly diagnosed ITP treated with eltrombopag than those treated with standard first-line treatments

3.2 Secondary Objectives

3.2.1 To compare the proportion of patients with poor bleeding scores (WHO Bleeding Scale≥2 or Modified Buchanan Score≥3) at 1, 2, 3, 4, 12 weeks and 1 year in patients with newly diagnosed ITP treated with eltrombopag vs. standard first-line agents

3.2.2 To compare the cumulative number of rescue therapies (defined in section 8.4) needed during the first 12 weeks of treatment for patients with newly diagnosed ITP treated with eltrombopag vs. those treated with standard first-line agents

3.2.3 To compare platelet response during weeks 6-12 of study in patients treated with eltrombopag vs standard first line agents who required a rescue treatment during weeks 1-2 of study

3.2.4 To compare the proportion of patients who do not need ongoing treatment at 12 weeks and 6 months for patients with newly diagnosed ITP treated with eltrombopag vs. those treated with standard first-line agents

3.2.5 To compare the proportion of patients with a treatment response (4 binary endpoints (section 5.2.5)) at one year after study enrollment in patients with newly diagnosed ITP treated with eltrombopag vs. those treated with standard first-line agents

3.2.6 To compare the number of 2^{nd}-line therapies (defined in section 7.2.1) used in weeks 13-52 for patients with newly diagnosed with ITP treated with eltrombopag vs. those treated with standard first-line agents

3.2.7 To compare the absolute change in percentage of $CD4^{+}25^{+}Foxp3^{+}$ regulatory T cells (Tregs) a) from baseline to 12 weeks; and b) from baseline to 1 year, in patients with newly diagnosed ITP treated with eltrombopag vs. those treated with standard first-line agents

3.2.8 To compare change in Health Related Quality of Life (HRQoL) from a) baseline to 1 week, b) baseline to 4 weeks, c) baseline to 12 weeks, and, d) baseline to 1 year, as measured by the parent-proxy report of the Kids ITP tools (KIT) and Global Change Scale for patients with newly diagnosed ITP treated with eltrombopag vs. those treated with standard first-line agents

3.2.9 To compare fatigue at 1 week, 4 weeks, 12 weeks, and 1 year as measured by the parent-proxy report of the Hockenberry Fatigue Scale-Parent (FS-P)

for patients with newly diagnosed ITP treated with eltrombopag vs. those treated with standard first-line agents

3.2.10 To compare iron indices at 12 weeks, 6 months, and 1 year in patients with newly diagnosed ITP treated with eltrombopag vs. those treated with standard first-line agents

3.2.11 Safety Evaluations: To describe the proportion of patients with abnormal liver function tests (LFTs) in patients with newly diagnosed ITP treated with eltrombopag. To describe the proportion of patients with adverse events and serious adverse events in patients with newly diagnosed ITP treated with eltrombopag and standard first-line agents

3.3 Exploratory Objectives

3.3.1 To compare additional platelet-defined responses in patients with newly diagnosed ITP treated with eltrombopag versus those treated with standard therapy.

3.3.2 To compare additional changes in HRQoL (measured by KIT) and fatigue (measured by Hockenberry Fatigue scale) at 1 week, 4 weeks, 12 weeks, and 1 year in patients with newly diagnosed ITP treated with eltrombopag versus those treated with standard therapy.

3.3.3 To compare cost of therapy (including medications, hospitalizations, the PROMIS survey, etc.) between patients treated with eltrombopag versus those treated with standard therapy.

4 STUDY DESIGN

This is a prospective, open label, randomized, two-arm, multi-center Phase 3 trial. Patients with newly diagnosed ITP are randomized 2:1 to receive the experimental treatment, eltrombopag, or investigator's choice of 3 standard therapies. The primary objective is to determine if the proportion of patients with platelet response is significantly greater in patients treated with eltrombopag compared to those treated with standard therapies.

Randomization at study enrollment will be stratified by the two factors described below, using a block size of 3.

a) Age at enrollment
b) Whether the patient has received a first-line treatment (as defined in inclusion criteria):

- **1) Upfront treatment**: Patients *within 10 days* of ITP diagnosis who have not received previous treatment
  OR
- **2) Treatment failure**: Patients who have failed standard management (observation or treatment with one or more first-line standard agents)

Table 4A: Stratification strata and stratum-specific patient enrollment limits

Stratum	Patient Age at Enrollment	Patient Up-front Treatment Status	Maximum Number of Patients Enrolled
1	1 – <6	Requires up-front treatment	27
2	1 – <6	Failed up-front treatment	27
3	6 – <12	Requires up-front treatment	27
4	6 – <12	Failed up-front treatment	27
5	12 – <18	Requires up-front treatment	27
6	12 – <18	Failed up-front treatment	27

Patients randomized to the eltrombopag arm will be eligible to continue the treatment throughout the 1-year duration of study participation, with guidelines given for dose adjustments.

A total of up to 162 patients will be enrolled. The required sample size is 147 "informative" patients (as defined below), with 104 (estimated 98 informative) in the experimental treatment arm and 52 (estimated 49 informative) in the standard treatment arm. A conservatively high estimate of 9% of patients are anticipated to withdraw from the study prior to the 5-week platelet assessment; these patients will be classified as non-responders, and will make a non-informative contribution to the analysis response rate for the primary objective. Therefore, to obtain at least 147 informative randomized patients, we plan to enroll and randomize up to an additional 15 patients (9 and 6 for the eltrombopag and standard treatment arms, respectively) for a total of 162.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary endpoint is binary, with each patient classified as either a platelet responder or a platelet non-responder. Platelet responders are defined as patients with ≥3 of 4 platelet measurements >50 x10^9/L between Weeks 6-12. All platelet counts will be reported, and the four measurements closest in time to Weeks 6, 8, 10, and 12 will be selected for the determination of the primary endpoint. Within a sliding one-week window, only one measurement can be selected.

Patients will be classified as non-responders for any of the following reasons:

1) Failing to meet the criteria to be a responder (including having an insufficient number of values >50 $x10^9$/L due to missing data); or,
2) Requiring rescue medication at any time within the first 12 weeks of therapy; or,
3) Withdrawing from protocol therapy prior to week 6.

5.2 Secondary Endpoints

5.2.1 Poor bleeding score (binary) at 1, 2, 3, 4 weeks, 12 weeks, and 1 year after study enrollment defined as WHO Bleeding Scale≥2 or Modified Buchanan Scale≥3

5.2.2 Cumulative number of rescue therapies required during the first 12 weeks of treatment

5.2.3 Platelet response (binary), defined as ≥ 3 of 4 weeks with platelets >50 $x10^9$/L during weeks 6-12 of therapy, but patient required a rescue treatment during weeks 1-2 of study

5.2.4 No further need for treatment (binary) after 12 weeks or 6 months of study

5.2.5 Treatment response (binary endpoints) at 1 year defined as:

- **CR** is defined as platelet count >/= 150 $x10^9$/L
- **Primary Remission** at 1 year is defined as CR at 1 year with no second-line agents required and >/= 3 months after discontinuing most recent platelet active medication
- **Disease resolution** at 1 year is defined as CR at 1 year >/= 3 months after discontinuing most recent platelet active medication. May have received a second-line therapy, excluding rituximab or splenectomy.
- **Disease stability** at 1 year is defined as platelets >/=50$x10^9$/L but <150 $x10^9$/L >/= 3 months after discontinuing most recent platelet active medication.

5.2.6 Number of 2^{nd}-line therapies (defined in section 7.2.1) in weeks 13-52

5.2.7 Absolute change in percentage of $CD4^+25^+Foxp3^+$ regulatory T cells from baseline at 12 weeks and 1 year

5.2.8 Absolute change in parent proxy-reported KIT overall scores from baseline to 1 week, 4 weeks, 12 weeks, and 1 year after study enrollment (see Appendix A2)

5.2.9 Total scale intensity ratings (continuous) from the Hockenberry Fatigue Scale-Parent (FS-P) at 1 week, 4 weeks, 12 weeks, and 1 year (see Appendix A2)

5.2.10 Serum iron, TIBC, transferrin saturation, ferritin, MCV, and hemoglobin at 12 weeks, 6 months, and 1 year after study enrollment

5.2.11 Safety evaluations as defined by:

- Abnormal LFTs:
  - ALT ≥ 3x ULN in patients with normal baseline
  - ALT ≥ 3x baseline or ≥ 5x ULN (whichever is lower) in patients with abnormal baseline
  - ALT ≥ 3x ULN AND bilirubin ≥ 1.5xULN (>35% direct)

- Incidence of adverse events (see section 9.1.6)
- Incidence of serious adverse events (see section 12.2)

5.3 Exploratory Endpoints

5.3.1 Platelet-specific endpoints

- Time to response (platelets >30x10^9/L, and at least 2-fold increase in the baseline count and absence of bleeding) (IWG definition)[17]
- Treatment response (platelets >30x10^9/L, and at least 2-fold increase in the baseline count and absence of bleeding) (IWG definition) at 12 weeks
- Time to platelet count >100x10^9/L and absence of bleeding (IWG definition)
- Treatment response (platelet count >100x10^9/L and absence of bleeding) (IWG definition) at 12 weeks
- Loss of treatment response (platelet count below 30x10^9/L, or less than 2-fold increase in the baseline count or bleeding) (IWG definition) at any time during the study period after achieving response during the first 12 weeks
- Extreme thrombocytosis (platelets >1 x10^{12}/L)

5.3.2 Patient-reported outcomes endpoints

- Absolute change in child self-reported and parent impact KIT scores from baseline to 1 week, 4 weeks, 12 weeks, and 1 year after study enrollment
- Absolute change in Hockenberry fatigue (FS-C, FS-A, FS-P) scores from baseline to 1 week, 4 weeks, 12 weeks, and 1 year after study enrollment
- Global Change Scale scores at 1 week, 4 weeks, 12 weeks, and 1 year after study enrollment

5.3.3 Cost of therapy endpoints

- Number of hospitalizations

6 SUBJECT SELECTION

Subjects with a diagnosis of ITP who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.1 Inclusion Criteria

- Age: 1- <18 years
- Newly diagnosed ITP (<3 months from diagnosis (first abnormal platelet count), per international working group definition[17])
- Platelets <30 x10^9/L at screening
- Requires pharmacologic treatment from the perspective of the treating clinician. *Need to treat is at the discretion of the investigator, but there should be clinical*

equipoise about the use of eltrombopag vs standard treatment options (patients should not, in the opinion of the investigator, require concomitant therapy at time of enrollment).

- Treatment options include one of three standard therapies, (IVIg, steroids, or Anti-D). *For example, if patient has previously shown no response to IVIg or steroids and is Rh-negative, patient would not be eligible for study.*
- Patient population includes both:
  - **1) Upfront treatment**: Patient within 10 days of ITP diagnosis who has not received previous treatment **OR**
  - **2) Treatment failure**: Patients who have failed standard management (observation or treatment with one or more first-line agents)
    - *Failure of observation: no platelet recovery (>30 x10^9/L) with observation >10 days from diagnosis, with need to treat*
    - *Poor response to first-line agent (platelets remain <30 x10^9/L)*
    - *Initial response to first-line agent, but response wanes and platelets fall below 30 x10^9/L*
- Family willing and able to return for required lab studies

6.2 Exclusion Criteria

- Severe bleeding: Buchanan Overall Grade 4 or 5 bleeding (see Appendix A1), or severe bleeding requiring emergent treatment at the discretion of the provider. (e.g., intracranial hemorrhage, pulmonary hemorrhage, bleeding with ongoing need for pRBC transfusion)
- Prior treatment with TPO-RA (eltrombopag or romiplostim)
- Known secondary ITP (due to lupus, CVID, ALPS)
- Known HIV (or history of HIV positivity) or Hepatitis C (screening not required if no clinical suspicion)
- Evans Syndrome: positive direct Coombs with evidence of active hemolysis (elevated LDH or reticulocyte count not attributable to recent treatment or bleeding)
- Any Malignancy
- History of stem cell transplant or solid organ transplant
- AST or ALT >2x ULN
- Total bilirubin >1.5 × ULN
- Subjects with liver cirrhosis (as determined by the investigator)
- Creatinine >2.5 × upper limit of normal (ULN)
- Known active or uncontrolled infections not responding to appropriate therapy
- On anticoagulation or anti-platelet agents
- Known thrombophilic risk factors. Exception: Subjects for whom the potential benefits of participating in the study outweigh the potential risks of thromboembolic events, as determined by the investigator.
- Baseline ophthalmic problems that may potentiate cataract development
- Impaired cardiac function, such as:

  - Known prolonged QTc, with corrected QTc >450 msec
  - Other clinically significant cardio-vascular disease (e.g., uncontrolled hypertension, history of labile hypertension),
  - History of known structural abnormalities (e.g. cardiomyopathy).
- History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease, including any of the following:
  - Recent myocardial infarction (within last 6 months),
  - Uncontrolled congestive heart failure,
  - Unstable angina (within last 6 months),
  - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker.)
  - Long QT syndrome, family history of idiopathic sudden death, congenital long QT syndrome or additional risk factors for cardiac repolarization abnormality, as determined by the investigator.
- Known immediate or delayed hypersensitivity reaction to eltrombopag or its excipient.
- Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study. *Women of childbearing potential (have achieved menarche) must have a negative serum or urine pregnancy test and agree to use basic methods of contraception (if sexually active) or maintain abstinence for the duration of the study until 7 days after the last dose of study treatment. Basic contraception methods include:*
  - *Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception*
  - *Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment*
  - *Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject*
  - *Barrier methods of contraception: Condom or Occlusive cap. For the UK: with spermicidal foam/gel/film/cream/ vaginal suppository*
  - *Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal*

hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

- Male patients who are sexually active and do not agree to abstinence or to use a condom during intercourse while taking eltrombopag, and for 7 days after the last dose of study treatment.
- History of alcohol/drug abuse
- Presence of a medical condition that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
- Concurrent participation in an investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longer. Note: parallel enrollment in a non-therapeutic trial such as disease registry or biology study is permitted.

6.3 Other Eligibility Criteria Considerations

- All patients and/or their parents or legal guardians must sign a written informed consent (and assent when applicable)
- Patients and/or parents who are unable to read at a grade 2 level will be excluded from the patient-reported outcome components of the study, as will non-English speaking patients and/or parents when there is no availability of translated versions in their spoken language(section 9.3). They will not be excluded from all other aspects of the study

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

7.1.1 If necessary, rescue medications are allowed as detailed in the protocol. See section 8.3.

7.1.2 **Supportive care medications**

Use of hormonal therapies and anti-fibrinolytic agents is allowed, but must be documented on appropriate case report forms (CRFs).

7.2 Prohibited Medications and Treatments

7.2.1 The use of second-line platelet-enhancing therapies in weeks 1-12 is not allowed and will result in coming off protocol therapy *(i.e. subjects will discontinue eltrombopag if on study med, but subjects will continue to be followed on study for data collection)*. In the event of severe or uncontrolled bleeding (Buchanan Bleeding Score of 4 or 5) requiring an emergency intervention listed below during weeks 1-12, the patient will come off protocol therapy. The following medications/procedures are prohibited during the first 12 weeks of the study:

- Dexamethasone

- Rituximab
- Mercaptopurine
- Azathioprine
- Dapsone
- Sirolimus
- Cyclosporine
- Mycophenolate
- Romiplostim
- Vinca alkaloids
- Cyclophosphamide
- Splenic artery embolization
- Splenectomy
- Other medications besides prednisone, IVIg, and anti-D thought to be active in the treatment of ITP

The use of these medications/procedures after week 12 for patients not currently taking eltrombopag (patients in the standard treatment arm, or patients in the eltrombopag arm who are non-responders and have been taken off investigational drug) is at the discretion of the treating physician, but must be reported on appropriate CRFs.

7.2.2 Other non-platelet-enhancing therapies (other than those described in section 7.1.2) are not allowed in weeks 1-12 and would be a protocol violation if used:

- Desmopressin acetate (DDAVP)
- Recombinant Factor VIIa
- Platelet transfusion

7.2.3 Patients taking anti-platelet agents (including aspirin, NSAIDs, or clopidogrel) or anticoagulants (including heparin, warfarin, or direct oral anticoagulants) are prohibited from enrolling, and these medications are not allowed during the study.

7.3 Concomitant medications and interactions with eltrombopag

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. Site study personnel should verify that there are no interactions with protocol therapy, as described in this section of the protocol. If an adjustment in eltrombopag dose is required due to a concomitant medication, that should be noted on the eltrombopag dosing CRF.

Any medications administered during the study given for the purpose of treating or preventing bleeding (such as hormonal therapies or antifibrinolytic agents), or that

are prohibited due to antiplatelet or antithrombotic effects (such as NSAIDs, aspirin, or anticoagulants), or that are thought to have effect in ITP must be listed on the Concomitant Medications eCRF.

HMG-CoA Reductase Inhibitors (statins)
Patients will be permitted to use HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA) inhibitors during the study, but these drugs should be used with caution and a 50% dose reduction of the HMG-CoA reductase inhibitor is recommended, with close monitoring for safety, such as liver chemistry and signs and symptoms of myolysis, and efficacy, such as cholesterol and triglycerides (refer to individual product information for monitoring recommendations).

Polyvalent Cations (Chelation)
Eltrombopag chelates with polyvalent cations such as aluminum, calcium, iron, magnesium, selenium and zinc. Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption.

Food Interaction
The administration of a single 50 mg-dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products led to reduced eltrombopag exposure. Foods low in calcium (defined as <50 mg calcium per serving) including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content. To avoid significant reduction in eltrombopag absorption, eltrombopag should be taken at least two hours before or four hours after food containing > 50 mg calcium and at least one hour before to two hours after food containing little (< 50 mg) (or preferably no) calcium.

Patients must abstain from using investigational or not marketed drugs without a well-known safety profile and from using prohibited prescription or nonprescription drugs within 7 days or 5-half-lives (whichever is longer) prior to the first dose of study treatment and until completion of follow-up procedures unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study (see Section 6.2 Exclusion Criteria).

Patients must abstain from taking herbal supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5-half-lives (whichever is longer) prior to the first dose of study treatment until completion of the 30-day follow-up period, unless the Investigator and Sponsor agree that the medication will not interfere with the study treatment.

Any other TPO-R agonists are prohibited for patients on eltrombopag (e.g. romiplostim).

Substrates of OATP1B1 or BCRP
Concomitant administration of eltrombopag and other OATP1B1 or BCRP substrates should be undertaken with caution.

Examples of OATP and BCRP substrates

OATP Substrates
aliskiren, ambrisentan, anacetrapib, atenolol, atrasentan, atorvastatin, bosentan, bromociptine, caspofungin, cerivastatin, celiprolol, danoprevir, empangliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, SN-38, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan, telmisartan, montelukast, ticlopidine.

BCRP Substrates
atorvastatin daunorubicin, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, SN-38 (irinotecan), ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, sulfasalazine

OATP1B1 and OATP1B3 substrates and inhibitors are combined into one list due to the following reasons, (1) over-lapping substrate and inhibitor specificity and (2) lack of clinical evidence implicating the sole involvement of either OATP in the observed PK interaction.

8 TREATMENT PLAN

8.1 Overview of Treatment Plan

According to the randomized treatment group assignment, patients will be treated with either eltrombopag as a single agent or physician's choice of standard therapy.

8.2 Investigational Product Dosage/Administration

8.2.1 **Standard first-line therapy**

Subjects randomized to the standard therapy arm will receive one of three treatments at the discretion of the treating physician. Patients who previously failed standard management prior to study entry must be treated with a different agent than their original failed agent. *e.g. Patient who failed steroids could receive either IVIg or anti-D if randomized to the standard treatment arm.*

Standard therapy will be administered as commercially available drug.

Investigator may choose amongst the following:

8.2.1.1 **IVIg:** IVIG 1 g/kg x1[18] (no steroids for pre-medication or adjunctive therapy)

8.2.1.2 **Steroids:** Prednisone/Prednisolone 4 mg/kg/day (Max 120 mg/day) x 4 days[19]

8.2.1.3 **Anti-D:** Anti-D globulin 75 mcg/kg x1[18] (no steroids for pre-medication or adjunctive therapy)

Table 8A Standard therapies

Treatment	*Dose*	*Route*	*Duration*
IVIg	**1 g/kg (round to closest vial size without exceeding 1g/kg)**	**IV**	**1 dose**
Prednisone/Prednisolone	**2 mg/kg/dose BID (max 120 mg/day)**	**PO**	**4 days**
Anti-D globulin	**75 mcg/kg (round to closest vial size without exceeding 75 mcg/kg)**	**IV**	**1 dose**

8.2.2 **Eltrombopag**

Patients randomized to eltrombopag will be treated for 12 weeks, with the possibility to continue therapy for up to 1 year depending on response. Instructions for titrating dose during the first 12 weeks and during weeks 13-52 are given below.

8.2.2.1 **Dose initiation**

Starting dose for eltrombopag will be based on manufacturer recommendations, and drug will be titrated to effect per guidelines, modified as below

- Children 1 to 5 years: Initial: 25 mg once daily
- Children ≥6 years and Adolescents: Initial: 50 mg once daily (25 mg once daily for patients of East-Asian ethnicity [e.g., Chinese, Japanese, Korean, Taiwanese])
- Dose should be titrated based on platelet response. Maximum dose: 75 mg once daily. Dose should be adjusted only after 2 weeks on the prior dose (unless holding for thrombocytosis)
- Adjust dose based on platelet response (Table 8B, below)

8.2.2.2 **Dosage adjustment based on platelet response weeks 1-12**

Table 8B Dose adjustment during weeks 1-12 of study

PLATELET COUNT RESULT	DOSE ADJUSTMENT OR RESPONSE

< 50 x 10^9/L following at least 2 weeks of eltrombopag	Increase daily dose by 25 mg to a maximum of 75 mg/day. For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
≥ 50 x 10^9/L to < 200 x 10^9/L	Continue current dose
≥ 200 x 10^9/L to ≤ 400 x 10^9/L at any time	Decrease the daily dose by 25 mg. **Wait 2 weeks to assess the effects** of this and any subsequent dose adjustments. For patients taking 25 mg once daily, decrease the dose to 12.5 mg once daily. For patients taking 12.5 mg once daily, discontinue eltrombopag.
> 400 x 10^9/L at any time	Hold eltrombopag; **increase the frequency of platelet monitoring to twice weekly.** Once the platelet count is < 200 x 10^9/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg. If platelets remain ≥ 200 x 10^9/L to <400 x 10^9/L after 2 weeks, decrease frequency of platelet checks to weekly.
> 400 x 10^9/L after 2 weeks of therapy at lowest dose of eltrombopag	Discontinue eltrombopag. If platelets drop to <50 x 10^9/L after discontinuing eltrombopag, restart at the last effective dose (lowest dose that achieved platelet count ≥ 50 x 10^9/L)

Please note: while platelets are checked weekly per study requirements, adjustments are made at time intervals described in the table

8.2.2.3 **Eltrombopag Stopping Criteria for Non-Responders**

Discontinue eltrombopag if platelet count <30 x10^9/L after 4 weeks at the maximum daily dose of 75 mg. *Non-responders will come off protocol therapy, but will continue on study for data collection through duration of 1 year from date of consent.*

8.2.2.4 **Weaning weeks 13-52**

For patients who have completed 12 weeks of eltrombopag and maintain a platelet count ≥ 100 x 10^9/L, eltrombopag will be weaned, by dose reducing 12.5mg q2 weeks per guidelines in table 8C below (with treating physicians exercising clinical judgement with respect to wean in the context of the patient's status, including intercurrent infections).

Patients who have been unable to be weaned off of eltrombopag by 1 year will discontinue study drug. Continuation on commercially available eltrombopag at that point is at the discretion of the investigator.

Table 8C Modified dose adjustment during weeks 13-52 of study

PLATELET COUNT RESULT	DOSE ADJUSTMENT OR RESPONSE
< 30 x 10^9/L 2 weeks after dose adjustment	Increase dose to last effective dose (to attain platelet count ≥ 30 x 10^9/L)
≥ 30 x 10^9/L to < 100 x 10^9/L	Continue current dose.
≥ 100 x 10^9/L to < 200 x 10^9/L	Decrease daily dose by 12.5 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. If platelets remain ≥ 100 x 10^9/L after 2 weeks at lowest dose, discontinue eltrombopag.
≥ 200 x 10^9/L to ≤ 400 x 10^9/L	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. For patients taking 25 mg once daily, decrease the dose to 12.5 mg once daily. For patients taking 12.5 mg once daily, discontinue eltrombopag.
> 400 x 10^9/L	Discontinue eltrombopag
< 30 x 10^9/L after weaning off eltrombopag	Restart at the last effective dose (lowest dose prior to weaning). If platelets remain < 30 x 10^9/L, increase per initial dose adjustment.

8.2.2.5 **Dose Modification for toxicities**

LFTs (AST, ALT, Tbili) will be monitored every 2 weeks during the first 12 weeks of study, then monthly for patients continuing on eltrombopag.

Repeat abnormal liver function tests within 3 to 5 days; if confirmed abnormal, monitor weekly until resolves, stabilizes, or returns to baseline.

If ALT levels ≥3 times the upper limit of normal (ULN) in patients with normal hepatic function at baseline or ≥3 times baseline (or >5 times ULN; whichever is lower) in those with preexisting transaminase elevations: Discontinue treatment.

If Tbili >1.5 times the upper limit of normal (ULN) contact the study PI to discuss management.

Eltrombopag must be permanently discontinued if any of the following events occur or is identified at any time during the study:
- Cytogenetic abnormalities
  - -Monosomy 7 – discontinue eltrombopag
  - -Other abnormalities – discontinuation at physician discretion
- Thromboembolism considered related to drug occurs
- Development of MDS or AML
- Difficulties to continue the study treatment due to AE(s)

Subjects who experience a deep venous thrombosis (other than a line-related upper extremity thrombosis) or a pulmonary embolus, a transient ischemic attack or stroke, or a myocardial infarction at any time while on eltrombopag will discontinue eltrombopag.

8.2.2.6 **Dosing Guidelines**

Administer on an empty stomach, 1 hour before or 2 hours after a meal. Do not administer concurrently with antacids, foods high in calcium, or minerals (e.g., iron, calcium, aluminum, magnesium, selenium, zinc); separate by at least 4 hours.

TABLETS MUST BE SWALLOWED WHOLE.

Eltrombopag for oral suspension delivered 22% higher plasma AUC0-INF than the tablet formulation. When switching between the oral suspension and tablet, closely monitor platelet counts.

If vomiting occurs within 30 minutes of dose, dose should be re-administered.

8.3 Rescue Medications

Patients who have bleeding, have platelets drop after initial response, or who do not respond to the therapy may require rescue medications. Use and choice of rescue medications, at protocol specified dosing, is at the discretion of the investigator. Standard therapies as described will be allowed for use as rescue medications prior to week 12, and the patient may stay on protocol. *If patients have an initial response to a therapy but response wanes, they may be treated again with the same therapy, and this 2nd administration will be considered to be a rescue therapy.* If additional therapies other than the three medications listed are required prior to week 12, patient will be required to come off protocol therapy (but will continue on study).

Rescue medications may be used multiple times, but a separate form must be submitted for each episode.

IVIg: IVIG 1 g/kg x1 (no steroids for pre-medication or adjunctive therapy)
Steroids: Prednisone/Prednisolone 4 mg/kg/day (Max 120 mg/day) x 4 days
Anti-D: Anti-D globulin 75 mcg/kg x1

Data will be collected regarding the reason rescue therapies are being used and maximum platelet count after rescue therapy

After week 12, non-responders in the Eltrombopag arm or patients in the standard care arm requiring additional therapies should be treated at the discretion of the investigator. Additional medications administered after week 12 do not require patient to come off protocol but they should be documented on the case report forms (CRFs).

See section 7.1 for additional allowed and prohibited medications and supportive care.

8.4 Packaging and Labeling

Tablets: White, to almost white, round, film-coated tablets without debossing are provided for clinical use, containing eltrombopag olamine equivalent to 12.5 mg, 25 mg, 50 mg, or 75 mg of eltrombopag free acid. Tablets are packaged in HDPE bottles with plastic, induction-seal, child-resistant caps.

Powder for Oral Suspension: The powder for oral suspension (PfOS) is a reddish brown to yellow powder in heat-sealed foil laminate stickpack; a stickpack may also be referred to as a packet or sachet. Depending on dose and formulation availability PfOS contains eltrombopag olamine equivalent to 12.5 or 25 mg of eltrombopag free acid per stickpack/sachet.

The entire contents of the specified number of stickpacks/primary packages is added to the specified amount of water to produce a suspension and the appropriate patient dose is delivered as described in the study procedures manual.

8.5 Supply of Study Drug at the Sites

Novartis will ship eltrombopag directly to the investigational sites. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by ICON and Novartis and a contract has been executed). Subsequent study drug shipments will be made after site request for resupply.

8.6 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be

recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.7 Measures of Treatment Compliance

Subjects will be asked about treatment compliance at study visits, and number of missed doses will be noted on CRFs. Study drug containers will be returned to the investigational pharmacy at each visit, and pill counts will be performed to confirm reported compliance.

9 STUDY PROCEDURES AND GUIDELINES

EVALUATIONS[1] WEEK 0-12	SCREENING/DAY 0	72H	W1	W2	W3	W4	W6	W8	W10	W12	UNSCHEDULED VISITS[10]
ELIGIBILITY CHECKLIST	x										
PHYSICAL EXAM	x		x[2]			x[2]				x[2]	x
BLEEDING ASSESSMENT	x		x	x[3]	x[3]	x				x	x
TELEPHONE VISIT				x	x						
DEMOGRAPHIC FORM	x										
BASELINE FORM	x										
CONCOMITANT MEDICATIONS	x		x			x				x	x
OPHTHALMIC ASSESSMENT	x					As needed					
30 DAY FOLLOW-UP[4]						As needed					
AE/SAE FORM						As needed					
RESCUE MED FORM						As needed					
HRQOL: KIT	x		x			x				x	
HOCKENBERRY FATIGUE SCORE	x		x			x				x	
PROMIS	x									x	
GLOBAL RATE OF CHANGE			x			x				x	
PLATELET COUNT[5, 6]	x	x	x	x		x	x	x	x	x	x[6]
CBC[5]	x					x				x	x
AST, ALT, TBILI[5]	x[7]			x[8]		x[8]	x[8]	x[8]	x[8]	x	
DIR COOMBS	x[7]										
LDH, RETIC[5]	x[7]									x	
CREATININE	x[7]										
PREGNANCY TEST[5]	x[7]					x[8]				x	
FE, TIBC, %SAT FERRITIN[5]	x[7]									x	

TREGS[9]	x	x
SAMPLES FOR BANKING (OPTIONAL)	x	x

[1] 72H time point may occur +/- 24h. Week 1 – Week 4 procedures may occur +/- 72h. Week 6 – Week 12 procedures may occur +/- 1 week, as long as procedures are separated by at least 1 week.
[2] Visits may be performed via telehealth when clinically appropriate if necessary for pandemic-related safety or research restrictions
[3] Telephone administration of modified Buchanan scale
[4] Patients will be followed for safety 30 days after the last dose of study treatment
[5] Local labs (performed at outside lab not associated with ICON site) are acceptable for labs obtained between study visits
[6] All platelet counts during Week 5 – Week 12 should be reported. Additional platelet measurements between the scheduled Week 6, 8, 10, and 12 measurements should be reported as unscheduled visits.
[7] May use previously obtained values for screening assessments if done within past 7 days
[8] Patients on eltrombopag arm only (for duration of eltrombopag administration)
[9] Performed at central study lab
[10] Physical Exam, Bleeding Assessment, Concomitant Medications, Platelet count, and/or CBC to be performed at unscheduled visits when applicable

EVALUATIONS[1] 4 MOS – 1 YR	**4 MOS[2]**	**5 MOS[2]**	**6 MOS**	**7 MOS[2]**	**8 MOS[2]**	**9 MOS[2]**	**10 MOS[2]**	**11 MOS[2]**	**1 YEAR**	**UNSCHEDULED VISITS[9]**
PHYSICAL EXAM			x[3]						x[3]	x
BLEEDING ASSESSMENT									x	x
CONCOMITANT MEDICATIONS			x						x	x
OPHTHALMIC ASSESSMENT					As needed					
AE/SAE FORM					As needed					
RESCUE MED FORM					As needed					
30-DAY FOLLOW-UP[4]					As needed					

END OF STUDY FORM									x[5]	
HRQOL: KIT									x	
HOCKENBERRY FATIGUE SCORE									x	
PROMIS									x	
GLOBAL RATE OF CHANGE									x	
PLATELET COUNT[6]	x[7]	x[7]	x	x[7]	x[7]	x[7]	x[7]	x[7]	x	x
CBC[6]			x						x	x
AST, ALT, TBILI[6]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	
PREGNANCY TEST[6]		x[7]		x[7]		x[7]		x[7]		
FE, TIBC, %SAT FERRITIN[6]			x						x	
TREGS[8]									x	
SAMPLES FOR BANKING (OPTIONAL)									x	

[1] 6 month procedures may occur +/- 14 days. 1 year procedures may occur +/- 4 weeks
[2] Timepoint +/- 7 days
[3] Visits may be performed via telehealth when clinically appropriate if necessary for pandemic-related safety or research restrictions
[4] Patients will be followed for safety for 30 days after the last dose of study treatment
[5] Form should be completed earlier if patient exits study prior to 1 year
[6] Local labs (performed at outside lab not associated with ICON site) are acceptable for labs obtained between study visits
[7] Patients on eltrombopag arm only (for duration of eltrombopag administration)
[8] Performed at central study lab
[9]Physical Exam, Bleeding Assessment, Concomitant Medications, Platelet count, and/or CBC to be performed at unscheduled visits when applicable

All study assessments should be completed for patients enrolled on the study, even if subjects discontinue protocol treatment early (including patients on eltrombopag arm who discontinue eltrombopag due to non-response and patients on the standard therapy arm who receive prohibited therapies during weeks 1-12).

9.1 Clinical Assessments

9.1.1 **Concomitant Medications**

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at Study Visits Week 1, Week 4, Week 12, 6 months, and

1 year, or at unscheduled visits and at early termination when applicable, and updated throughout study participation as indicated. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 **Demographics**

Demographic information (date of birth, gender, race) will be recorded at Baseline/Screening.

9.1.3 **Medical History**

Relevant medical history, including history of current disease, other pertinent medical history, and information regarding underlying diseases will be recorded at Baseline/Screening and updated throughout study participation as indicated.

9.1.4 **Physical Examination**

A complete physical examination will be performed by either the investigator or a subinvestigator who is a physician at Baseline/Screening. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit. Exam findings consistent with bleeding will be noted on bleeding assessment CRF. Partial physical exams as able may be performed via telehealth if associated study visit is performed remotely due to pandemic-related safety or research restrictions.

9.1.5 **Bleeding Assessment**

An in-person bleeding assessment will be performed at Baseline/Screening, at Study Visits Week 1, Week 4, Week 12, and 1 year, at unscheduled visits, and at early termination when applicable. Assessments will be performed via telehealth if associated study visit is performed remotely due to pandemic-related safety or research restrictions. A telephone bleeding assessment will be performed at weeks 2 and 3. (See Appendix for details of WHO Bleeding Scale and modified Buchanan Scale).

9.2 Clinical Laboratory Measurements

9.2.1 **Hematology**

Blood will be obtained and sent to each site's clinical hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count). Interval platelet counts (between study visits) may be run at the site's clinical hematology lab or at an outside facility.

9.2.2 **Blood Chemistry Profile**

Blood will be obtained and sent to each site's clinical chemistry lab for determination of aspartate aminotransferase (AST/SGOT), alanine

aminotransferase (ALT/SGPT), iron, Total iron binding capacity (TIBC), transferrin saturation, and ferritin. Interval LFTs (between study visits) for patients on eltrombopag may be run at the site's clinical hematology lab or at an outside facility.

9.2.3 **Pregnancy Test**

A urine or serum pregnancy test will be obtained from female subjects who have achieved menarche prior to their participation in the study.

9.3 HRQoL Tools

The Kids ITP tool (KIT) will be performed at Baseline/Screening, at Study Visits Week 1, Week 4, Week 12, and 1 year. The KIT is the first disease-specific health related quality of life measure developed for ITP, specifically for use with children. It contains a child self-report version (to be completed by children ages 7 and older), a parent proxy version (to be completed by parents of children age 2 and older), and parent version (to assess parental impact of ITP - all ages). Each version consists of 26 items, and a single overall score is obtained. Scores range from 0 to 100: a higher score represents better quality of life or, as with the parental impact version, less burden. Response options are on a 5-point Likert-type scale ranging from "never" to "always", and the timeframe of interest is the "past week". KIT will be administered in English, Spanish, or Quebec French.

Assessment of global change will be performed at Week 1, Week 4, Week 12, and 1 year using the Parent Proxy-Report and Child Self-Report Change Scales.

Assessment of fatigue will be performed at Baseline/Screening, at Study Visits Week 1, Week 4, Week 12, and 1 year using the Fatigue Scale-Child (FS-C to be administered by children ages 7 to 12 years), the Fatigue Scale–Adolescent (FS-A teens ages 13 and older), and the Fatigue Scale-Parent (FS-P to be completed by parents of children of all ages). Each item has a 5-point Likert-type format; total scale intensity ratings have ben rescaled so that they range from 0 (no fatigue symptoms) to 100 (highest possible fatigue score). All of the tools have been evaluated for face, content, and construct validity and for internal consistency. The tools take five minutes to complete. Fatigue scales will be administered in English.

The National Institute of Health funded and developed the web based patient-reported outcomes measurement information system (PROMIS®). PROMIS® contains a number of pediatric self-report short items that each assess domains of physical and emotional function in general and over a seven-day time interval [20-23]. Patients (age 7-18 years) will complete PROMIS® global health pediatric measures (Appendix A2c). These measures have been tested and reliability of each is ≥0.85 over 2 to 4 standard deviations [23-27]. Each of the measures consists of ten questions. Three questions ask the participant to respond based on the past 7 days. Responses utilize a 5-point Likert scale ranging from "excellent" to "poor" or "never" to "always" [21,24]. The PROMIS®

measures will be scored in accordance with their scoring manuals [24-27].PROMIS will be administered in English and Spanish.

Patients may be excluded from participation in Patient Reported Outcome Measures (PROMIS, KIT, Change Scale, and Hockenberry Fatigue Scale) if a translated tool is not available.

HRQoL surveys may be completed remotely and emailed, mailed, or faxed to study site if associated study visit is performed remotely due to pandemic-related safety or research restrictions.

9.4 Research Laboratory Measurements

(see the study Manual Of Operations for samples and processing details)

9.4.1 **Regulatory T cells**

Whole blood in EDTA will be sent to Texas Children's Hospital/Baylor College of Medicine for quantification of $CD4^{+}25^{+}Foxp3^{+}$ regulatory T-cells.

This is a non-CLIA approved test, and results will not be made available to individual investigators or patients.

- 12 ml (two 6 ml EDTA tubes) will be collected unless there are volume restrictions for smaller children.
- For smaller children a minimum of 6 ml will be collected. To avoid clotting in cases like this smaller tubes may be used (e.g. three 2ml EDTA tubes).

Blood for the *Research Laboratory Measurements* will be collected at the following time points:

i. Day 0 (Baseline), prior to receiving study drug
ii. Week 12
iii. End of study (1 year)
iv. In the event of sample processing failure or inadequate yield, the site will be asked to collect a new sample at the time of a blood draw during a later study visit.

9.5 Optional Research Studies

If consent is obtained for optional studies, baseline and serial blood samples will be sent to Texas Children's Hospital/Baylor College of Medicine for banking and for future correlative biology studies.

- DNA: 6 ml whole blood collected in EDTA tube
- RNA: 2.5 ml whole blood collected in PaxGene RNA tube. (At Texas Children's Hospital site only, 6mL EDTA tube will be collected as well.)

Blood for the *Optional Research Studies* will be collected at the following time points:

i. Day 0 (Baseline), prior to receiving study drug: DNA & RNA
ii. Week 12: RNA
iii. End of study (1 year): RNA
iv. In the event of sample processing failure or inadequate yield, the site will be asked to collect a new sample at the time of a blood draw during a later study visit.

10. SAFETY

10.1 Liver Function Monitoring

AST/ALT/Tbili will be monitored every 2 weeks during the first 12 weeks of study, then monthly for patients continuing on eltrombopag. See section 8.2.2.5 for dose modifications

10.2 Ophthalmic Assessments

Assessment of cataract risk will be completed by investigator at baseline. Patients at elevated risk (due to history of radiation, prolonged steroid use, or diabetes) should be referred to an ophthalmologist for baseline exam. For patients at standard risk, investigator should perform ophthalmologic exam, and if there are any findings of concern for cataracts, patient should be referred to ophthalmologist for baseline exam. For patients continuing on eltrombopag >12 weeks, consider referral to ophthalmologist for monitoring, especially if receiving other medications (such as steroids) contributing to cataract risk.

10.3 Pregnancy Testing

Women of child-bearing potential (achieved menarche) must have a negative serum or urine pregnancy test to be eligible. Pregnancy test must be checked every 2 months for patients continuing on eltrombopag.

10.4 Follow-Up

Patients will be followed for adverse events for 30 days after the last dose of study treatment. Follow up information may be obtained via phone call or email.

11. ADVERSE EVENTS REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.

An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

Information regarding occurrence of adverse events will be captured throughout the study. The collection period for all AEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed, or thirty days after the subject takes the last dose of study drug, whichever is later.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.
Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or other support), or require changes in study medication(s).

Adverse events that begin or worsen after first dose of study drug should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and an assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

If an adverse event occurs more than once in a course of therapy, only the most severe grade of the event is reported. If an adverse event progresses through several grades during one course of therapy, only the most severe grade is reported. An adverse event that persists from one course (cycle) to another is only reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course (cycle), is reported each course (cycle) it recurs.

For reporting purposes, the duration of the AE should be the duration of the highest (most severe) grade of the toxicity. The resolution date of the AE is defined as the date at which the AE returns to baseline (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date is recorded as "ongoing". Dates used in adverse event reporting for laboratory test abnormalities should be the date the sample was collected (not the date the sample was processed or the date the results were reported). Toxicities reported from off site laboratories

are graded using normal values of the laboratory processing the specimen. Source documents from off site laboratories, such as copies of laboratory test results, are filed in patient medical record and/or research chart, as applicable.

The completed CRF summarizing the non-serious AE should be reviewed and signed off by the PI or their designee.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 should be used to assess and grade any AE or SAE, including laboratory abnormalities judged to be clinically significant. Events grade 3 or higher should be collected and documented and reported as indicated. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 11A below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 11A. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 11B.

Table 11B. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.

Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Events (SAE) and unanticipated problems involving risk to subjects or others (UPIRSOs)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization[++]
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

[++] Note that hospitalizations for the following reasons should not be reported as serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

Any serious or immediately life-threatening adverse experience, including those resulting in death, occurring while the subject is receiving study drug, or within 30 days of the subject's last dose of protocol therapy, regardless of the treating

physician's opinion regarding drug relationship, will be reported by telephone and/or e-mail (within 24 hours of the event) to the Study PI and appropriate parties.

Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per IRB Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed, or thirty days after the subject takes the last dose of study drug, whichever is later.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

SAEs (as well as reports of drug exposure during pregnancy and reports of study drug misuse or abuse) will be forwarded to Novartis within one business day of Study PI becoming aware.

The principal investigator has the obligation to report all serious adverse events to the FDA (if applicable), IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E)
All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form), if applicable
To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) within 24 hours.
Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.
Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.
If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be reported by the investigator to the Novartis Oncology Drug Safety and Epidemiology Department (DS&E) by fax (fax: 877-778-9739). Pregnancy follow-up should include an assessment of the possible relationship to the [investigational/study treatment] any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.
Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

All SAEs, regardless of causality, will be reported to:

- Site Principal Investigator
- Site IRB of Record (per institutional policy)
- Coordinating Center within 24 hours of a member of the research team becoming aware of the event.

SAEs should be recorded on the appropriate SAE Form. The SAE Form, along with any relevant information or documentation, must be submitted to the Site Principal Investigator for review and signature then reported via email to the Coordinating Center per contact information in Manual of Operations.

Protocol Defined Important Medical Findings Requiring Real Time Reporting

- Grade 5 hemorrhage
- Thromboembolic event
- Death

- Malignancy

UPIRSOs

An UPIRSO is defined as an event that meets all three of the following criteria:
Unexpected (in terms of the nature, severity or frequency) given

- The research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
- The characteristics of the subject population being studied.
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or acknowledged.

"Related to the research procedures": An event is "related to the research procedures" if in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures or if it is more likely than not that the event affects the rights and welfare of current participants.

All UPIRSOs will be reported to:

- Site Principal Investigator (immediately upon member of research team becoming aware)
- Site IRB of Record (in accordance with site's institutional policy)
- Coordinating Center as soon as possible, but no more than 24 hours from the time a member of the research team is aware of the event.

UPIRSOs should be recorded on the appropriate SAE Form. The SAE Form, along with any relevant information or documentation, must be submitted to the Site Principal Investigator for review and signature then reported via email to the Coordinating Center (Boston Children's Hospital) and Baylor College of Medicine as per manual of operations. IRB approval/acknowledgment should also be provided to the coordinating center upon site's receipt.

11.3 Medical Monitoring

Medical Monitoring is provided by the study PI Dr. Amanda Grimes and Co-Investigator Dr. Kristin Shimano. For any medical concerns or questions regarding eligibility or safety please contact ICONstudy-dl@childrens.harvard.edu.
SAEs need to be reported within 24 hours of the local PI becoming aware of the event.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Treatment

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the study PI feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from protocol therapy at any time, for any reason, specified or unspecified, and without prejudice.

The following is a list of possible reasons for ***study treatment discontinuation***:

a) Subject withdrawal of consent (or assent) – see section 12.2
b) Subject is not compliant with study procedures
c) Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
d) Administration of rescue medication or ITP-directed therapy prior to Week 12 other than those permitted by the study protocol (see section 7.2.1), including for emergent intervention in the event of severe or uncontrolled bleeding.
e) Lost to follow-up – see section 12.2
f) Positive pregnancy test (females)
g) Change in diagnosis: patient no longer has diagnosis of primary ITP – see section 12.2
h) Death – see section 12.2
i) Completion of protocol therapy

If a subject is discontinued from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible. **Unless they are withdrawn from the study (see section 12.2) subjects should complete all remaining scheduled visits and procedures.**

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.2 Withdrawal of Subjects from the Study

All data collected up until the time of subject withdrawal will remain part of the study. Subjects will be followed for 30 days after the last dose of study drug.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Week 12) should have an early

discontinuation visit. Subjects who withdraw after Week 12 but prior to 1 year should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

Reasons for withdrawal from the study are:

a) Subject withdrawal of consent for data submission
b) Lost to follow-up
c) Death
d) Subject no longer has diagnosis of primary ITP

Otherwise, all subjects should be followed for collection of data to assess the protocol objectives.

12.3 Replacement of Subjects

A subject who withdraws from the study after enrollment and randomization will not be replaced.

13 PROTOCOL VARIANCES AND DEVIATIONS

Protocol deviations are defined as unintended variances from the approved protocol. The term deviation is often used in contrast to a violation, which is usually seen as more serious than a deviation.

Participating sites should report deviations to the coordinating center and BCM PI/designee as soon as possible and to their institution's IRBs per that site's institutional guidelines.

Participating sites in addition to their local requirement will be required to complete the variance form (see Manual of Operations) for all protocol deviations, and send to Baylor College of Medicine and Boston Children’s Hospital Coordinating Center as soon as identified and not later than 5 days of occurrence.

As needed, the BCM PI or designee will report these protocol variances to the BCM IRB per local policies and to other regulatory agencies as applicable.

All serious adverse events and any unanticipated problems involving risk to subjects or others (UPIRSOs) that meet reporting criteria as defined by the BCM IRB as IRB of record will be submitted to the BCM IRB per their policy. Expected adverse events will not be reported. Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

A protocol variance or deviation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject

safety and primary endpoint criteria. Protocol deviations for this study include, but are not limited to, the following:
Failure to meet inclusion/exclusion criteria
Use of a prohibited concomitant medication
Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. ICON will determine if a protocol violation will result in withdrawal of a subject.
When an event occurs, it will be discussed with the investigator and a Protocol Deviation/Variance Form detailing the event will be generated. Baylor College of Medicine will determine if the event qualifies as UPIRSO that meet reporting criteria as defined by the BCM IRB.

14 DATA SAFETY MONITORING

The Boston Children's Hospital will establish a Data Safety Monitoring Committee (DSMC) to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according to a DSMC Charter to be established for this protocol. There will be 2 interim review(s) conducted by the DSMC for the purpose of monitoring study conduct and assessing patient safety. Further details regarding the timing and content of the interim reviews is included in the statistical section below.

15 STEERING COMMITTEE

A Study Steering Committee (SSC) will be appointed.
The SSC will ensure transparent management of the study according to the protocol by recommending and approving study modifications as the need arises. The SSC will review protocol amendments as appropriate. Together with the clinical trial team, the SSC will also develop recommendations for publications of study results. The SSC will consist of investigators participating in the trial and representatives from the Clinical Trial Team.
Other members may be added after consultation with SSC members.

16 STATISTICAL METHODS AND CONSIDERATIONS

Overview

This is a prospective, open label, randomized, two-arm, multi-center Phase 3 trial. Enrolled patients with newly diagnosed ITP are randomized at enrollment 2:1 to the experimental treatment arm (eltrombopag) and standard treatment arm (investigator's choice of 3 standard therapies); randomization will be stratified by patient's age at enrollment and up-front treatment status, with block size of 3. Each stratum will be limited to a maximum of 27 patients. Hence, the age distribution of the final accrued cohort may not be representative of the patient population. This is appropriate in the context of this study to ensure sufficient number of patients to study treatment effects in each age group. The primary objective is to determine

whether the proportion of patients with platelet response is greater in the experimental treatment arm compared to the standard therapy arm using a one-sided Cochran-Mantel-Haenszel (CMH) test at alpha=0.025 (see section 16.b).

Intent-to-Treat and Evaluability

For the primary objective, all randomized patients will be included in an intent-to-treat (ITT) analysis. Evaluability for the secondary and exploratory objectives: In the experimental treatment arm, patients will be considered evaluable if they receive at least one dose of eltrombopag. In the standard treatment arm, patients will be considered evaluable if they receive at least one dose of one of the standard of care treatments.

Statistical Analysis

a. Baseline Demographic and Clinical Characteristics

Patient demographic and clinical characteristics at study enrollment will be summarized using descriptive statistics, including frequencies and proportions for categorical measures, and means, medians, ranges, and standard errors for continuous measures.

b. Analysis of Primary Endpoint

To address the primary objective, we will first test for normality of the distribution of the proportion of platelet responders. If the assumption of normality is upheld, a one-sided Cochran-Mantel-Haenszel (CMH) test, at alpha=0.025, will be used to compare the proportion of platelet responders between the two arms. If the normality assumption is violated, then a one-sided Fisher's exact test will be used. The monitoring boundaries and levels of significance for the interim and final analyses of the primary endpoint are detailed in Table 16A. If a monitoring boundary is crossed in an interim analysis, an independent Data Safety Monitoring Board (DSMB) will make a non-binding recommendation regarding trial conduct or potential closure. In the final analysis, we will reject the null hypothesis if the upper (efficacy) boundary z-value of 1.99302 is crossed; in that case, it will be reasonable to conclude that the rate of platelet response is significantly greater in patients treated with eltrombopag than standard first-line treatments. Otherwise, we will conclude that there is insufficient evidence to support superiority of eltrombopag over standard first-line treatments. All randomized patients will be analyzed in the ITT analysis.

Selection of platelet measurements for the determination of platelet response.

All platelet counts will be reported, and the four measurements closest in time to Weeks 6, 8, 10, and 12 will be selected for the determination of the primary endpoint. Within a sliding one-week window, only one measurement can be selected. Patients who have <3 platelet measurements due to missing data will be classified as non-responders.

c. Analysis of Secondary Endpoints

Analyses of all secondary endpoints will be performed in the subset of evaluable patients. To determine the effects of missing data, sensitivity analyses will be performed using two approaches: a) assuming missing at random; and, b) assuming missing not at random. For each secondary endpoint, the assumption of normality will be tested. If violated for binary endpoints, a Fisher's exact test will be used. If violated for continuous endpoints, a Wilcoxon rank-sum test will be used.

To address secondary objective 3.2.1, the Cochran-Mantel-Haenszel test will be used to compare the proportion of patients with poor WHO Bleeding Score and poor Modified Buchanan Score between the two arms.

To address secondary objective 3.2.2, an ANCOVA model will be used to compare the number of rescue therapies between the two arms.

To address secondary objective 3.2.3, the observed proportion and 95% confidence interval of platelet responders will be calculated in the subset of patients who required a rescue treatment during weeks 1-2 of the study.

To address secondary objective 3.2.4, the Cochran-Mantel-Haenszel test will be used to compare the proportion of patients who do not need ongoing treatment at 12 weeks and 6 months between the two arms.

To address secondary objective 3.2.5, the Cochran-Mantel-Haenszel test will be used to compare the proportion of patients with a treatment response at one year between the two arms.

To address secondary objective 3.2.6, an ANCOVA model will be used to compare the number of 2nd-line therapies between the two arms

To address secondary objective 3.2.7, an ANCOVA model will be used to compare the absolute change from baseline in percentage of regulatory T cells at 12 weeks and 1 year between the two arms

To address secondary objective 3.2.8, KIT scores will be calculated as per the methods described in Klaassen et al.[28] Spaghetti plots will be used to visualize the KIT scores over time per patient by treatment arm. An ANCOVA model will be used to compare the absolute change from baseline in KIT overall score at 1 week, 4 weeks, 12 weeks, and 1 year between the two arms. An ANCOVA model will be used to compare the Change Scale score at 1 week, 4 weeks, 12 weeks, and 1 year between the two arms.

To address secondary objective 3.2.9, fatigue scores will be calculated as per the methods described in Hockenberry et al.[29] All measures will be rescaled from 0 (no fatigue) to 100 (high fatigue) for consistency in scoring. Spaghetti plots will be used to visualize the fatigue scores over time per patient by treatment arm. The PROMIS tired question: "My child (I) got tired easily never to almost always" will be used as an anchor with severe fatigue defined as "often" or " almost always" with moderate fatigue being "sometimes". An ANCOVA model will be used to compare the absolute change from baseline in fatigue at 1 week, 4 weeks, 12 weeks, and 1 year between the two arms.

To address secondary objective 3.2.10, an ANCOVA model will be used to compare iron indices at 12 weeks, 6 months, and 1 year between the two arms

To address secondary objective 3.2.11, the frequency and proportion (with 95% confidence interval) of patients with abnormal LFTs will be calculated. Adverse event rates will be coded by body system and MedDra classification term. Adverse events and serious adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug. If a patient experiences the same toxicity multiple times, a patient will be counted only once for a given toxicity at the maximum grade.

d. Analysis of Exploratory Objectives

Exploratory objectives are hypothesis-generating only. Any exploratory findings need to be confirmed in an independent study.

To address the platelet exploratory objectives 3.3.1, a Cochran-Mantel-Haenszel test will be used to compare the proportion of patients between treatment arms with: (1) specific platelet-defined treatment response at 12 weeks, (2) extreme thrombocytosis, and (3) loss of treatment response (in the subgroup of patients who achieved treatment response during the first 12 weeks. Cumulative incidence curves by treatment arm will be created to describe: (1) time to response and (2) time to platelet and bleeding response. Gray's test will be used to compare the cumulative incidence between treatment arms.

To address the patient-reported outcomes exploratory objectives 3.3.2, KIT scores and fatigue scores will be calculated as described. Spaghetti plots will be used to visualize the scores over time per patient by treatment arm. An ANCOVA model will be used to compare the absolute change from baseline at 1 week, 4 weeks, 12 weeks, and 1 year between the two arms.

To analyze the non-survey endpoints of exploratory objective 3.3.3, a Cochran-Mantel-Haenszel test (for categorical outcomes) or an ANCOVA model (for

continuous outcomes, like the cost of therapy) will be used to compare the the two arms.

To address the survey-related aspects of exploratory objectives 3.3.3, the PROMIS® measures will be scored as according to the described approach [22]. Mixed-effects model and the generalized estimating equations (GEE) allow for covariate adjustment and can model both within group effects (time) and between group effects [30]. The results will be summarized with adjusted means with associated 95% confidence intervals at each time point for each treatment group. For the primary analysis, these models will include the main effect of time (T0-T2). PHIS is a confidential database that allows use among the 47 member hospitals including a number of prominent pediatric hematology centers that participate in ICON. Descriptive analysis will be performed using PHIS data after patients have been identified using PHIS diagnosis codes to identify patients with ITP. Descriptive statistics will be performed to analyze financial burden measures. As instruments have not been validated, item level comparisons will be made between standard therapy and eltrombopag.

During the trial, on an ongoing basis the study team will monitor the response rate to each of the surveys. A patient will be counted as having responded to a given survey if both the baseline survey and at least one post-baseline survey are submitted. If the observed response rate for a given survey falls below 33%, the study team may consider halting the collection of that survey from subsequent patients, as it is an inappropriate use of resources, and unfair to patients, to continue to require survey submission if the survey data will be too sparse to address the study objective.

e. Interim Analysis

Interim analysis for efficacy and futility

To monitor for early evidence of efficacy or lack of efficacy (futility), we will perform group sequential analyses for a total of three "looks" at the data. Power calculations were performed using PASS 14 (NCSS, LLC. Kaysville, Utah, USA). We will conduct two interim analyses using a two-sided Cochran-Mantel-Haenszel test to compare the proportion of platelet responders between the two treatment arms, after 33% and after 67% of randomized patients are accrued. If the trial has not been terminated due to efficacy or futility, the third and final analysis will be conducted after accrual of all randomized patients at the end of the trial. We used the O'Brien-Fleming spending function to determine the monitoring boundaries for these three group sequential tests (Table 16A, Figure 1). For interim analysis 1, significant evidence that the experimental drug is more efficacious than the standard of care will have been provided if we observe a z-test statistic ≥ 3.71. Significant evidence that the experimental drug is less efficacious than the standard therapy will have been provided if $z \leq -3.71$. For

interim analysis 2, significant evidence that the experimental drug is efficacious or not will have been provided if $z \geq 2.51$ or ≤ -2.51, respectively. For the final analysis, significant evidence of the efficacy of the experimental drug will have been provided if $z \geq 1.99302$. The members of the study committee will remain masked to the results of the interim analyses. Because the results of this trial will set a new standard of care for this patient population, an independent Data Safety Monitoring Board (DSMB) will make a non-binding recommendation if/when it is appropriate to close the trial early on the basis of the statistical evidence.

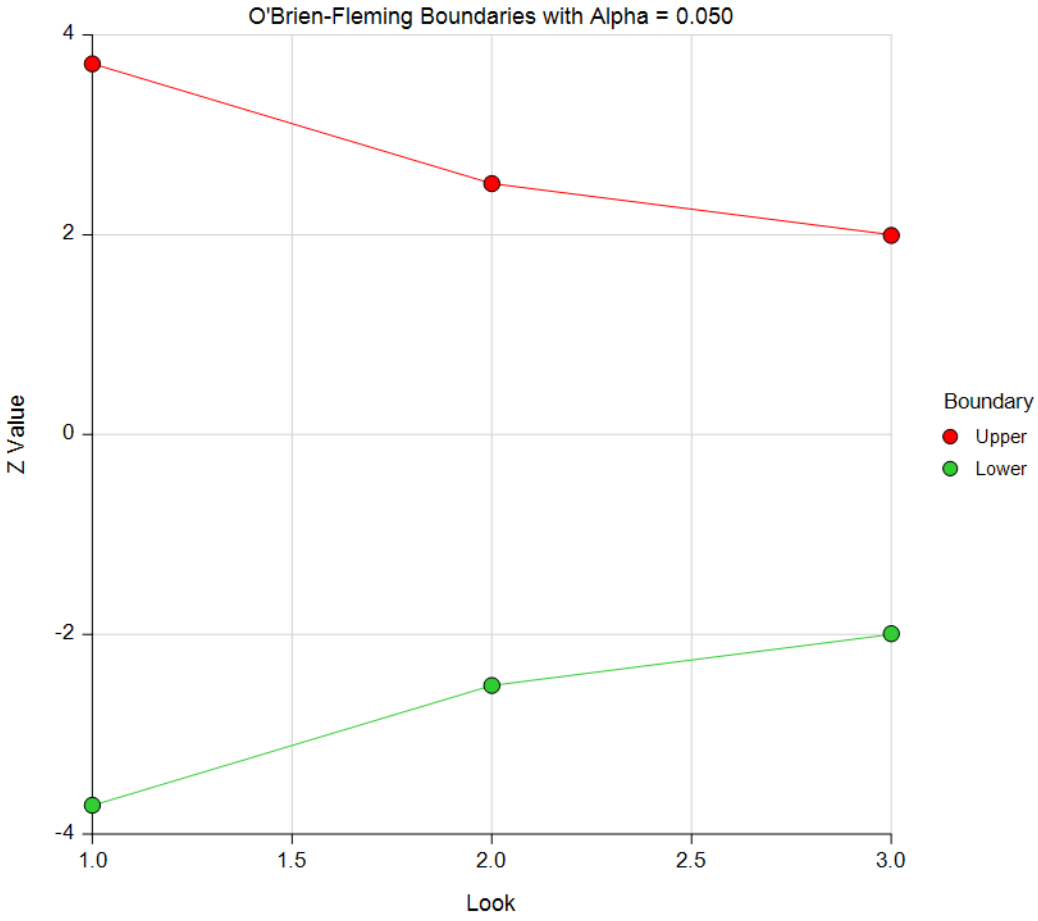
Table 16A: Interim analysis monitoring boundaries and operating characteristics

Look	Proportion accrued	Lower Bndry	Upper Bndry	Nominal Alpha	Alpha Spent	Total Alpha	Power Spent	Total Power
1	0.33	-3.7103	3.7103	0.0002	0.0002	0.0002	0.02009	0.0201
2	0.67	-2.51142	2.51142	0.012	0.0119	0.0121	0.41425	0.4343
3	1	-1.99302	1.99302	0.0463	0.0379	0.05	0.38006	0.8144

Definitions:

- Nominal alpha: the significance level to be used for a single, standalone test at each interim test.
- Alpha spent: the amount of alpha spent by this interim test.
- Total alpha: the total amount of alpha that is used up to and including the current test.
- Power spent: the probability that the significance is found and the trial is stopped, given the alternative hypothesis (also called “exit probabilities”).
- Total power: these are the cumulative power values.

Figure 1. O’Brien-Fleming interim monitoring efficacy (red) and futility (green) boundaries for the rate of sustained of platelet response, comparing the eltrombopag arm to the standard of care arm using a two-sided Cochran-Mantel-Haenszel test



Interim analyses for safety
AEs and SAEs will also be reviewed at interim analysis 1 and 2. If any toxic deaths, or 2 intracranial hemorrhages, or 2 unprovoked thromboses are found at the first interim analysis, study will be temporarily halted to accrual for further evaluation.

f. Sample Size and Study Duration

Power Calculations for the Primary Objective

147 "informative" (as defined below) patients, randomized 2:1 to the experimental treatment arm and standard treatment arm, will be required to provide 81.4% power to detect an absolute difference of 25% in the proportion of patients who are platelet responders, assuming the response rate is 75% in the experimental treatment arm and 50% in the standard treatment arm, using a one-sided Cochran-Mantel-Haenszel (CMH) test and a type I error rate of 0.025. In order to provide at least 147 informative patients, up to 162 patients will be enrolled and randomized.

The first time point at which the primary endpoint, platelet response, will be assessed is 5 weeks after enrollment. A small number of patients, approximately

9%, are anticipated to withdraw from the study (i.e., withdraw from protocol therapy AND data submission) prior to the 5-week platelet assessment. It is reasonable to assume that the study withdrawal rate will be similar across the treatment arms. These patients are non-informative for the primary objective to assess the efficacy of eltrombopag; such patients dilute the treatment effect and as a result the power is diminished. These "non-informative" patients will be classified as non-responders and included in the ITT analysis. We will assume that 9% of randomized patients, a conservatively high estimate, will be non-informative. To account for the diluting effect the non-informative patients have on the comparison of response rates, we plan to enroll and randomize up to an additional 15 patients (~9%).

Total sample size and study duration

In summary, a total of up to 162 (estimated: 147 informative + 15 non-informative) patients will be enrolled and randomized 2:1 to the experimental treatment arm (N=108) and standard treatment arm (N=54). All randomized patients will be included in the ITT analysis of the primary objective.

We anticipate enrolling 45 patients per year (3.7 patients per month). The total accrual duration is expected to be about 3 years, plus 1 year follow-up on the last patient, for a total study duration of 4 years.

17 DATA COLLECTION, RETENTION, AND MONITORING

a. Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

b. Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural

documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices for the handling and analysis of data for clinical trials.

c. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries.

Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

d. Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form (if applicable) and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

e. Monitoring

1. **Monitoring of Coordinating Center at BCH**

On site monitoring visit to the Coordinating Center at Boston Children's Hospital

Frequency: At site initiation, following the first patient completion of study and then every 6 months or as needed

Purpose: Ensure that required documents for study conduct, including but not limited to the required IRB documents, are properly maintained

2. **Monitoring of Clinical Sites**

Remote monitoring visit with all clinical sites with the exception of Boston Children's Hospital clinical site

Frequency: Every 6 months or as needed
Purpose: Review patient records, data entered into database, and pharmacy documents for accuracy and completeness. Ensure all regulatory documentation is being maintained

f. Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

18 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

a. Protocol Amendments

Any amendment to the protocol will be written by ICON. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

b. Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by a central IRB, and reliance agreements with participating sites will be utilized. For any sites that do not have or choose not to use reliance agreements with the central IRB, the IRB/IEC of that participating center will be utilized. Serious adverse experiences regardless of causality will be reported to the central IRB/IEC and single site IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to ICON prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

c. Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations. The Investigator or study staff will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the

signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

d. Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

e. Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
1. Personally conduct or supervise the study (or investigation).
2. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
3. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
5. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
6. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
7. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
8. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
9. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

19. APPENDICES

A1. Bleeding Assessment Tools

- **a. WHO Bleeding Scale**
- **b. Buchanan Bleeding Scale**

A2. HRQoL Tools

- **a. KIT**
- **b. Hockenberry Fatigue Scale**
- **c. PROMIS® v1.0 Global Health**
- **d. Change Scale**

A1. Bleeding Assessment Tools

WHO Bleeding Scale[30]

Grade	Definition
0	No bleeding
1	Petechiae
2	Mild blood loss
3	Gross blood loss
4	Debilitating blood loss

WHO, World Health Organization

Buchanan Bleeding Score[31]

Overall bleeding severity	
0 - None	Definitely no new hemorrhage of any kid
1 - Minor	Few petechiae (≤100 total) and/or ≤5 small bruises (≤3 cm diameter); no mucosal bleeding
2 - Mild	Many petechiae (>100 total) and/or >5 large bruises (>3 cm diameter); no mucosal bleeding
3 - Moderate	Overt mucosal bleeding (epistaxis, gum bleeding, oropharyngeal blood blisters, menorrhagia, gastrointestinal bleeding, etc.) that does not require immediate medical attention or intervention
4 - Severe	Mucosal bleeding or suspected internal hemorrhage (in the brain, lung, muscle, joint, etc.) that requires immediate medical attention or intervention
5 – Life-threatening or fatal	Documented intracranial hemorrhage or life-threatening or fatal hemorrhage in any site
Grades of epistaxis	
0 - None	
1 - Minor	Spotting on sheet or pillow and/or blood noted in nares, no active bleeding or need to apply pressure
2 - Mild	Active bleeding on 1 or more occasions with need to apply pressure for <15 min
3 - Moderate	Active bleeding on 1 or more occasions with need to apply pressure for at least 15 min
4 - Severe	Repeated, continuous and/or profuse bleeding
Grades of oral bleeding	
0 - None	None
1 - Minor	Petechiae on palate or buccal mucosa
2 - Mild	One or more buccal blood blisters (hemorrhagic bullae or infiltrates) with or without petechiae, no active bleeding

3 - Moderate	Intermittent active bleeding from gums, lips, buccal mucosa, or posterior oropharynx
4 - Severe	Continuous bleeding from gums, lips, buccal mucosa, or posterior oropharynx
Grades of skin bleeding	
0 - None	No new cutaneous bleeding
1 - Minor	Possibly a few new petechiae (≤100 total)
2 - Mild	Definitely a few new petechiae (≤100 total) and/or ≤5 small bruises (<3 cm diameter)
3 - Moderate	Numerous new petechiae (>100 total) and/or >5 large bruises (>3 cm diameter)
4 - Severe	Extensive (hundreds of) petechiae and >5 large bruises (>3 cm diameter)

A2. HRQoL Tools

ID #: _____

Date: _____

KIDS' ITP TOOLS

(North American English)

Parent Report of Child's Quality of Life

INSTRUCTIONS

For this questionnaire, we are asking: **How much of a problem has this been for your child over the past week?** Mark the answers that you think your child would select. We know that ITP has had an impact on your child since diagnosis, but for this study, we need you to **focus on what your child would have answered about the past week.** Record the answer by putting a checkmark (✓) in the box of the most correct choice. **Answer in general, don't worry if an answer is not because of ITP.**

It is important that you answer all questions about this past week.

What do the answers mean?

Answers		Meaning
Never	=	none of the time
Seldom	=	almost none of the time
Sometimes	=	once in a while
Often	=	almost all of the time
Always	=	all of the time

Note: You may provide other comments about your child's ITP at the end of the questionnaire.

Please answer as your child would.

In general, over the past week …	Never	Seldom	Sometimes	Often	Always
1. My child felt sick…	❑	❑	❑	❑	❑
2. My child had a headache…	❑	❑	❑	❑	❑
3. My child felt tired…	❑	❑	❑	❑	❑
4. My child felt upset (sad or angry)…	❑	❑	❑	❑	❑
5. My child felt cranky…	❑	❑	❑	❑	❑
6. My child felt anxious (worried, nervous or afraid)…	❑	❑	❑	❑	❑
7. My child was more hungry than usual…	❑	❑	❑	❑	❑

In general, over the past week …	Never	Seldom	Sometimes	Often	Always
8. My child was bothered that she/he could not do things with friends…	❑	❑	❑	❑	❑
9. My child was bothered because he/she could not do the activities he/she likes…	❑	❑	❑	❑	❑
10. My child was more frustrated with me than usual…	❑	❑	❑	❑	❑
11. My child was bothered by how much I watched her/him…	❑	❑	❑	❑	❑
12. My child was bothered because she/he did not know enough about ITP…	❑	❑	❑	❑	❑
13. My child was bothered that he/she didn't know how long the ITP would last…	❑	❑	❑	❑	❑
14. My child was bothered that she/he could not do anything to get better…	❑	❑	❑	❑	❑

Over the past week …	Never	Seldom	Sometimes	Often	Always
15. My child worried about his/her platelet count…	❑	❑	❑	❑	❑
16. My child worried about the ITP getting worse…	❑	❑	❑	❑	❑
17. My child worried about having a more serious disease…	❑	❑	❑	❑	❑

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Please Note: The next set of questions have an **additional** answer.

Over the past week …	Never	Seldom	Sometimes	Often	Always
18. My child was bothered by her/his bruises…	*Never* ☐	*Seldom* ☐	*Sometimes* ☐	*Often* ☐	*Always* ☐
or ☐ **My child did not have any bruises in the past week.**					
19. My child was bothered by changes in how he/she looked…	*Never* ☐	*Seldom* ☐	*Sometimes* ☐	*Often* ☐	*Always* ☐
or ☐ **My child did not have any changes in how he/she looked in the past week.**					
20. Having blood taken bothered my child…	*Never* ☐	*Seldom* ☐	*Sometimes* ☐	*Often* ☐	*Always* ☐
or ☐ **My child did not have blood taken in the past week.**					
21. Staying overnight in the hospital bothered my child…	*Never* ☐	*Seldom* ☐	*Sometimes* ☐	*Often* ☐	*Always* ☐
or ☐ **My child did not stay overnight in hospital in the past week.**					
22. Going to clinic bothered my child…	*Never* ☐	*Seldom* ☐	*Sometimes* ☐	*Often* ☐	*Always* ☐
or ☐ **My child did not go to clinic in the past week.**					
23. Having a treatment through an IV bothered my child…	*Never* ☐	*Seldom* ☐	*Sometimes* ☐	*Often* ☐	*Always* ☐
or ☐ **My child did not have IV treatment in the past week.**					
24. Taking medicine by mouth bothered my child…	*Never* ☐	*Seldom* ☐	*Sometimes* ☐	*Often* ☐	*Always* ☐
or ☐ **My child did not take medicine by mouth in the past week.**					
25. My child was bothered by missing school…	*Never* ☐	*Seldom* ☐	*Sometimes* ☐	*Often* ☐	*Always* ☐
or ☐ **My child did not miss any school in the past week.**					
26. My child worried that she/he might need to have a bone marrow test…	*Never* ☐	*Seldom* ☐	*Sometimes* ☐	*Often* ☐	*Always* ☐
27. Has your child ever had a bone marrow test?	☐ yes	☐ no			

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Was there anything else that bothered your child?

Thank you!

If you have any questions about these forms, please talk to the person who gave them to you. If you have any questions about your child's ITP, please talk to your child's doctor or nurse.

ID #: _____

Date: _____

KIDS' ITP TOOLS

(North American English)

Child Self-Report of Quality of Life

INSTRUCTIONS

On the next three pages, there are questions that ask you **about this past week.** We know that ITP has mattered to you from when you were diagnosed, but **for this study, we really need you to focus on what you thought about and did over the past week.** You may have done things at home, at the hospital, at school and with your friends. Record your answer by putting a checkmark (✓) in the box of the most correct choice.

It is important that you answer all questions about this past week.

What do the answers mean?

Answers		Meaning
Never	=	none of the time
Seldom	=	almost none of the time
Sometimes	=	once in a while
Often	=	almost all of the time
Always	=	all of the time

Note: You may provide other comments about your ITP at the end of the questionnaire.

In general, over the past week …	Never	Seldom	Sometimes	Often	Always
1. I felt sick…	❑	❑	❑	❑	❑
2. I had a headache…	❑	❑	❑	❑	❑
3. I felt tired…	❑	❑	❑	❑	❑
4. I felt upset (sad or angry)…	❑	❑	❑	❑	❑
5. I felt cranky…	❑	❑	❑	❑	❑
6. I felt anxious (worried, nervous or afraid)…	❑	❑	❑	❑	❑
7. I was more hungry than usual…	❑	❑	❑	❑	❑

In general, over the past week …	Never	Seldom	Sometimes	Often	Always
8. I was bothered that I could not do things with my friends…	❑	❑	❑	❑	❑
9. I was bothered because I could not do the activities I like…	❑	❑	❑	❑	❑
10. I was more frustrated with my parents than usual…	❑	❑	❑	❑	❑
11. I was bothered by how much my parents watched me…	❑	❑	❑	❑	❑
12. I was bothered because I did not know enough about ITP…	❑	❑	❑	❑	❑
13. I was bothered that I didn't know how long my ITP would last…	❑	❑	❑	❑	❑
14. I was bothered that I could not do anything to get better…	❑	❑	❑	❑	❑

Over the past week …	Never	Seldom	Sometimes	Often	Always
15. I worried about my platelet count…	❑	❑	❑	❑	❑
16. I worried about my ITP getting worse…	❑	❑	❑	❑	❑
17. I worried about having a more serious disease…	❑	❑	❑	❑	❑

Please Note: The next set of questions have an **additional** answer.

Over the past week …	Never	Seldom	Sometimes	Often	Always
18. I was bothered by my bruises…	Never ☐	Seldom ☐	Sometimes ☐	Often ☐	Always ☐
or ☐ I did not have any bruises in the past week.					
19. I was bothered by changes in how I looked…	Never ☐	Seldom ☐	Sometimes ☐	Often ☐	Always ☐
or ☐ I did not have any changes in how I looked in the past week.					
20. Having blood taken bothered me…	Never ☐	Seldom ☐	Sometimes ☐	Often ☐	Always ☐
or ☐ I did not have blood taken in the past week.					
21. Staying overnight in the hospital bothered me…	Never ☐	Seldom ☐	Sometimes ☐	Often ☐	Always ☐
or ☐ I did not stay overnight in hospital in the past week.					
22. Going to clinic bothered me…	Never ☐	Seldom ☐	Sometimes ☐	Often ☐	Always ☐
or ☐ I did not go to clinic in the past week.					
23. Having my treatment through an IV bothered me…	Never ☐	Seldom ☐	Sometimes ☐	Often ☐	Always ☐
or ☐ I did not have IV treatment in the past week.					
24. Taking medicine by mouth bothered me…	Never ☐	Seldom ☐	Sometimes ☐	Often ☐	Always ☐
or ☐ I did not take medicine by mouth in the past week.					
25. I was bothered by missing school…	Never ☐	Seldom ☐	Sometimes ☐	Often ☐	Always ☐
or ☐ I did not miss school in the past week.					
26. I worried that I might need to have a bone marrow test…	Never ☐	Seldom ☐	Sometimes ☐	Often ☐	Always ☐
27. Have you ever had a bone marrow test?	☐ yes	☐ no			

Was there anything else that bothered you?

Thank you!

If you have any questions about these forms, please talk to the person who gave them to you. If you have any questions about your ITP, please talk to your doctor or nurse.

ID #: _____

Date: _____

KIDS' ITP TOOLS

(North American English)

Parent Impact Report

INSTRUCTIONS

For this questionnaire, we are asking that you **answer about yourself**. Although we realize that your child's ITP has had an impact since diagnosis, this study needs to capture your experiences over a short period of time. Therefore, we are asking you to **focus only on the past week.** Record the answer by putting a checkmark (✓) in the box of the most correct choice. **Answer in general, don't worry if an answer is not because of ITP.**

It is important that you answer all questions.

What do the answers mean?

Answers		Meaning
Never	=	none of the time
Seldom	=	almost none of the time
Sometimes	=	once in a while
Often	=	almost all of the time
Always	=	all of the time

Note: You may provide other comments about your child's ITP at the end of the questionnaire.

Please answer about yourself.

In general, over the past week …	Never	Seldom	Sometimes	Often	Always
1. Did you wish that you understood more about ITP?	❑	❑	❑	❑	❑
2. Did leaving your child with someone else bother you?	❑	❑	❑	❑	❑
3. Did your child's ITP change your usual activities or family plans?	❑	❑	❑	❑	❑
4. Did you worry that your child had a more serious disease?	❑	❑	❑	❑	❑
5. Did you feel that you had to be constantly watching out for your child?	❑	❑	❑	❑	❑
6. Did you find it challenging to protect your child from injury?	❑	❑	❑	❑	❑

In general, over the past week …	Never	Seldom	Sometimes	Often	Always
7. Did you need to know your child's platelet count?	❑	❑	❑	❑	❑
8. Was it stressful when you did not know your child's platelet count?	❑	❑	❑	❑	❑
9. Did you feel your child was more likely to be seriously hurt than another child?	❑	❑	❑	❑	❑
10. Did you worry about what ITP could mean for your child's future?	❑	❑	❑	❑	❑
11. Did not knowing about what will happen in the future with your child's ITP bother you?	❑	❑	❑	❑	❑
12. Were you bothered that your child looked well but had a health problem?	❑	❑	❑	❑	❑
13. Did you worry that your child might have a bleed into her/his head?	❑	❑	❑	❑	❑

Over the past week …	Never	Seldom	Sometimes	Often	Always
14. Did you worry that your child might not get better?	❑	❑	❑	❑	❑
15. Did you worry about your child's ITP getting worse?	❑	❑	❑	❑	❑
16. Did it bother you that other parents who do not have a child with ITP were unable to understand what you were going through?	❑	❑	❑	❑	❑

Please Note: The next set of questions have an **additional** answer.

Over the past week …	Never	Seldom	Sometimes	Often	Always
17. Were you worried about the possible side effects of your child's treatment?	☐	☐	☐	☐	☐
or ☐ **My child has NEVER had any treatment for ITP.**					
18. Did you worry about your child getting a serious infection from the treatment of ITP?	☐	☐	☐	☐	☐
or ☐ **My child has NEVER had any treatment for ITP.**					
19. Did it bother you that your child could not do her/his usual activities?	☐	☐	☐	☐	☐
or ☐ **My child was able to do her/his usual activities in the past week.**					
20. Did it bother you that **you** had to limit your child's activities?	☐	☐	☐	☐	☐
or ☐ **It was not necessary to limit my child's activities in the past week.**					
21. Did your child's bruising worry you?	☐	☐	☐	☐	☐
or ☐ **My child did not have any bruises in the past week.**					
22. Did you find changes in your child's emotions stressful?	☐	☐	☐	☐	☐
or ☐ **My child's emotions did not change in the past week.**					
23. Did you find changes in your child's behaviour stressful?	☐	☐	☐	☐	☐
or ☐ **My child's behaviour did not change in the past week.**					
24. Were you worried when you knew that your child's platelet count was less than 20,000 (20×10^9)?	☐	☐	☐	☐	☐
or ☐ **My child's platelet count was not <20,000 (20×10^9) / I did not know my child's platelet count in the past week.**					
25. Were you upset when your child needed an intravenous infusion (IV)?	☐	☐	☐	☐	☐
or ☐ **My child did not need an IV in the past week.**					
26. Were you worried that your child might need to have a bone marrow test?	☐	☐	☐	☐	☐
27. Has your child ever had a bone marrow test?	☐ yes	☐ no			

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Was there anything else that bothered you?

Thank you!

If you have any questions about these forms, please talk to the person who gave them to you. If you have any questions about your child's ITP, please talk to your child's doctor or nurse.

Hockenberry Fatigue Scale

Child

How have you been feeling during the past week?	Please circle one answer for each item.				
	Not at all	A Little	About Half the Time	Quite a Bit	All the Time
1. I have been tired.	0	1	2	3	4
2. I needed a nap.	0	1	2	3	4
3. I've been too tired to play.	0	1	2	3	4
4. I have been sad.	0	1	2	3	4
5. I have been mad.	0	1	2	3	4
6. I had to stop and rest when walking.	0	1	2	3	4
7. I've been too tired to do my usual activities.	0	1	2	3	4
8. I've been too tired to run.	0	1	2	3	4
9. It has been hard to keep my eyes open.	0	1	2	3	4
10. I have trouble thinking.	0	1	2	3	4

Adolescent

How have you been feeling during the past 7 days?	Please circle one answer for each item.				
	Not at all	A Little	About Half the Time	Quite A Bit	All the Time
1. My body has felt tired.	0	1	2	3	4
2. My mind has felt worn out.	0	1	2	3	4
3. I move more slowly.	0	1	2	3	4
4. I want to rest more.	0	1	2	3	4
5. I sleep more often.	0	1	2	3	4
6. It's harder to keep up with school work.	0	1	2	3	4
7. I don't feel like doing much.	0	1	2	3	4
8. My body hasn't kept up with others.	0	1	2	3	4
9. I have felt angry.	0	1	2	3	4
10. I have not felt like talking.	0	1	2	3	4
11. I need help to do my usual activities.	0	1	2	3	4
12. I don't feel like being with others.	0	1	2	3	4
13. I have to work harder to do my usual activities.	0	1	2	3	4

Parent

Please indicate how the questions reflect your child's behaviors during the past week.		Please circle one answer for each item				
		Not at all	Almost Never	Sometimes	Almost Always	Always
1.	My child has been tired in the morning.	0	1	2	3	4
2.	My child has had a hard time getting out of bed.	0	1	2	3	4
3.	My child has been too tired to eat.	0	1	2	3	4
4.	My child has not slept through the night.	0	1	2	3	4
5.	My child has been tired in the afternoon.	0	1	2	3	4
6.	My child has needed a nap.	0	1	2	3	4
7.	My child has not had the energy to participate in daily activities.	0	1	2	3	4
8.	My child has been well-rested after each night's sleep.	0	1	2	3	4
9.	My child is able to play as much as he/she would like to.	0	1	2	3	4
10.	My child has wanted only to lie down and rest.	0	1	2	3	4
11.	My child has had to stop and rest when walking.	0	1	2	3	4
12.	My child has been more quiet.	0	1	2	3	4
13.	My child has been interactive with family and friends.	0	1	2	3	4
14.	My child has been more irritable.	0	1	2	3	4
15.	My child has been in a good mood.	0	1	2	3	4
16.	My child has been uncooperative.	0	1	2	3	4
17.	My child has had dark circles under the eyes.	0	1	2	3	4

Pediatric Global Health 7+2

Please respond to each question or statement by marking one box per row.

		Excellent	Very Good	Good	Fair	Poor
Global01R1	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02R1	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03R1	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04R1	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Never	**Rarely**	**Sometimes**	**Often**	**Always**
PedGlobal2R1	How often do you feel really sad?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Always	**Often**	**Sometimes**	**Rarely**	**Never**
PedGlobal5R1	How often do you have fun with friends?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PedGlobal6R1	How often do your parents listen to your ideas?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…					
		Never	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
2876R1r	I got tired easily	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3703R1r	I had trouble sleeping when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Parent Proxy Global Health 7+2

Please respond to each question or statement by marking one box per row.

		Excellent	Very Good	Good	Fair	Poor
Global01_PXR1	In general, would you say your child's health is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02_PXR1	In general, would you say your child's quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03_PXR1	In general, how would you rate your child's physical health?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04_PXR1	In general, how would you rate your child's mental health, including mood and ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Never	**Rarely**	**Sometimes**	**Often**	**Always**
PedGlobal2_PXR1	How often does your child feel really sad?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Always	**Often**	**Sometimes**	**Rarely**	**Never**
PedGlobal5_PXR1	How often does your child have fun with friends?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PedGlobal6_PXR1	How often does your child feel that you listen to his or her ideas?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
PHWeltgue3r	My child got tired easily.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PEpaindr	My child had trouble sleeping when he/she had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

CHANGE SCALE – PARENT PROXY-REPORT

Instructions: Please answer the questions below about your child.
Since the start of the study, how has <u>your child's</u> overall quality of life related to ITP changed?

- ☐ Much worse
- ☐ Worse
- ☐ A little worse
- ☐ No change
- ☐ A little better
- ☐ Better
- ☐ Much better

CHANGE SCALE – CHILD SELF-REPORT

Instructions: Please answer the questions below.
Since the start of the study, how has your overall quality of life related to ITP changed?

- ☐ Much worse
- ☐ Worse
- ☐ A little worse
- ☐ No change
- ☐ A little better
- ☐ Better
- ☐ Much better

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