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A Phase 3 Randomized Trial of Eltrombopag vs. Standard First-Line Pharmacologic Management for Newly Diagnosed Immune Thrombocytopenia (ITP) in Children: Methods and Rationale

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Title: A Phase 3 Randomized Trial of Eltrombopag vs. Standard First-Line Pharmacologic Management for Newly Diagnosed Immune Thrombocytopenia (ITP) in Children: Methods and Rationale

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ABSTRACT

Introduction: Immune thrombocytopenia (ITP) is an acquired disorder of low platelets and risk of bleeding. Although many children can be observed until spontaneous remission, others require treatment due to bleeding or impact on health-related quality of life. Standard first line therapies for those who need intervention include corticosteroids, intravenous immunoglobulin, and anti-D globulin, though response to these agents may be only transient. Eltrombopag is an oral thrombopoietin receptor agonist approved for children with chronic ITP who have had an insufficient response to corticosteroids, IVIg, or splenectomy. This protocol paper describes an ongoing open-label, randomized trial comparing eltrombopag to standard first-line management in children with newly diagnosed ITP.

Methods and Analysis: Randomized treatment assignment is 2:1 for eltrombopag versus standard first-line management and is stratified by age and by prior treatment. The primary endpoint of the study is platelet response, defined as ≥6 of 8 weeks with platelets >50 $x10^9$/L during weeks 5-12 of therapy. Secondary outcomes include number of rescue therapies needed during the first 12 weeks, proportion of patients who do not need ongoing treatment at 12 weeks and 6 months, proportion of patients with a treatment response at one year, and number of second-line therapies used in weeks 13-52, as well as changes in regulatory T cells, iron studies, bleeding, health-related quality of life, and fatigue. A planned sample size of up to 162 randomized pediatric patients will be enrolled over 2 years at 20 sites.

Ethics and Dissemination: The study has been approved by the centralized Baylor University Institutional Review Board. The results are expected to be published in 2023.

Trial Registration Number: NCT03939637

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a multicenter randomized controlled trial that will provide valuable information about the efficacy of eltrombopag for newly diagnosed children with ITP.
- The primary endpoint is a well-defined definition of platelet response that has been used in other ITP trials, while the secondary endpoints include important assessments of patient-related outcomes, including bleeding scores, fatigue, and health-related quality of life, all of which may be more significant to patients than a platelet count alone.
- Correlative biology studies will allow exploration of biologic differences between patients with ITP who are responders and non-responders, as well as biologic mechanisms related to outcomes of specific interventions and the natural history of the disease in children receiving treatment.
- A limitation of this study is that patients who are managed with a close observation approach are not included or compared to those who require treatment.
- An additional limitation of this study is the lack of a uniform definition of “requiring treatment,” which is left to the discretion of individual investigators; however, this allows for a “real-world” approach and ultimately the potential for broader applicability of trial results to clinical practice.

Introduction

Immune thrombocytopenia (ITP) is the most common autoimmune cytopenia in children, causing an often severely reduced platelet count, variable bleeding symptoms, and reduction in health-related quality of life (HRQoL) related to activity restrictions, frequent medical visits and interventions, anxiety from risk of bleeding, and fatigue.[1-3] In an era when the fields of hematology and immunology are advancing rapidly with the development of drugs targeted to underlying disease mechanisms, the available treatments for newly diagnosed ITP remain non-specific, with no novel or targeted therapies introduced in the past 30 years.[4]

Many children with ITP can be closely observed without treatment until they experience spontaneous remission.[5] Others require pharmacologic treatment for moderate bleeding or HRQoL limitations. While many therapies exist for treatment of chronic ITP, the treatment of newly diagnosed ITP is generally limited to close observation and three first-line medications: corticosteroids, intravenous immunoglobulin (IVIg), and anti-D globulin. Each of these agents has either undesirable side effects, challenging logistics of administration, or both (Table 1). Furthermore, they act only transiently to raise the platelet count, and in children with ongoing ITP, the platelet count will decrease days to weeks after the medication is given.

Eltrombopag is an oral, small-molecule, nonpeptide thrombopoietin receptor agonist (TPO-RA). It initiates thrombopoietin receptor signaling by interacting with the transmembrane domain of the receptor, inducing proliferation and differentiation of cells in the megakaryocytic lineage. Eltrombopag is currently approved for children ages ≥1 year with chronic ITP who have had an insufficient response to corticosteroids, IVIg, or splenectomy. Safety and efficacy were established in the PETIT[6] and PETIT2[7] trials. Forty percent of patients who received eltrombopag vs 3% of patients randomized to placebo in the PETIT2 trial achieved the primary outcome, ≥ 6 of 8 non-consecutive weeks with platelets >50 $x10^9$/L during weeks 5-12 of therapy (odds ratio 18.0, 95% CI, 2.3-140.9; p=0.0004).[7] The drug was approved by the US FDA in 2015[8] and the European Medicines Agency in 2016 for children with chronic ITP. The majority of the literature to date evaluating the use of eltrombopag in the pediatric population has been in the setting of chronic ITP (Table 2), although multicenter retrospective studies document that pediatric hematologists are using TPO-RAs off-label in some cases of newly diagnosed ITP.[9,10] Eltrombopag has been studied prospectively for adults with newly diagnosed ITP 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.[11] In a second study, 76% of steroid-nonresponsive patients had a durable response to eltrombopag after 3 months of therapy.[12] TPO-RAs may, therefore, be a safe and efficacious first-line therapy for newly diagnosed ITP patients who require treatment.

The issue of long-term expense of a drug that costs thousands of dollars monthly and requires ongoing use has been both a practical and conceptual hurdle for use of TPO-RAs in children since their launch, but that thinking has evolved to consider that early in the course of illness

the majority of cases of pediatric ITP will eventually resolve. While standard therapies like steroids, or when appropriate, observation only, are much less expensive than TPO-RAs, a few courses of IVIg may rival the cost of a short course of eltrombopag, as well as require IVs and inpatient stays with associated complications that yield additional expense.

Eltrombopag has the potential to change the landscape of newly diagnosed ITP for children. The earliest randomized trial in children with newly diagnosed ITP took place in 1984 comparing prednisone to observation.[13] Since that time only a handful of additional randomized trials have been conducted in this population, with the majority comparing IVIg to Anti-D immunoglobulin.[14-21] The most recent randomized trial, conducted in 2018, was unable to show any long-term benefit to IVIg compared to observation.[22] No trial to date has investigated a novel agent for this patient population in a randomized manner. As an oral outpatient therapy which can be continued until ITP has remitted, eltrombopag has clear benefits over the transiently effective current first-line options. In addition, eltrombopag may have fewer side effects than standard therapies. However, the early response rate in the newly diagnosed setting is not known. We therefore describe here our design of an ongoing randomized trial investigating the up-front use of eltrombopag in pediatric patients with ITP: PINES (*P*ediatric *I*TP *N*ewly diagnosed patients *E*ltrombopag vs *S*tandard therapy) Study, NCT03939637. The trial was FDA-approved in January 2019, and the first site opened to enrollment in May 2019. With this publication we aim to provide researchers and funding agencies with early-stage information about this novel clinical trial which contributes to the gap in randomized trials for patients with pediatric newly diagnosed ITP. Ultimately, we hope that this will allow for transparency and collaboration with other research consortiums, as well as dissemination of knowledge about the study to patients not treated at PINES sites, which may encourage them to explore engagement in research protocols with their physicians.

Methods and Analysis

Study Objectives and Hypothesis

The primary objective of the trial is 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 pharmacologic treatment. The primary endpoint, platelet response, is defined as ≥ 6 of 8 non-consecutive weeks with platelets >50 $x10^9$/L during weeks 5-12 of therapy. We hypothesize that children with newly diagnosed ITP treated with eltrombopag will have an increased likelihood of a sustained platelet response as compared with those treated with standard therapy. The endpoints and statistical analysis plans of the primary and secondary objectives are listed in Table 3. In addition, exploratory objectives will include comparisons by treatment arm of other platelet-related endpoints, patient-related outcomes, and cost of therapy. By obtaining data on patient-related outcomes such as health-related quality of life we will be able to assess the potential impact of differences in drug delivery such as dietary restrictions, need for daily medication administration, and potential impact of infusion therapy.

Overview of Study Design and Oversight

The PINES Study is a national, multicenter, randomized, open-label, standard therapy-controlled trial. The study was designed to align with usual care for children with newly diagnosed ITP (Figure 1). The screening period occurs from the time of diagnosis up until 3 months from the first low platelet count. Randomization and initiation of treatment occurs at the baseline visit, and follow up visits occur at week 1, and 1, 3, 6, and 12 months from enrollment. Weekly platelet counts are obtained from baseline through week 12. Patients will be followed for a total of 1 year from enrollment. Planned study visits and assessments are outlined in Table 4. The study is being conducted at 20 national sites through the Pediatric ITP Consortium of North America (ICON). Participating sites are listed on clinicaltrials.gov.

The trial is designed and led by a Steering Committee that includes academic investigators from ICON and statisticians from Dana-Farber/Boston Children's Cancer and Blood Disorders Center, the coordinating center for ICON. The Steering Committee will ensure transparent management of the study, recommend and approve study modifications, and develop recommendations for publications of study results. The trial is operated under an IND held by Baylor College of Medicine, cross-filed with Novartis. Novartis is providing funding for this investigator-initiated trial and supplies the drug used on the eltrombopag arm. An independent Data Monitoring Committee monitors patient safety and outcomes at intervals during the study and makes recommendations to the Steering Committee regarding ongoing trial conduct. The protocol was reviewed and approved by regulatory authorities, a central institutional review board at Baylor College of Medicine, and institutional review boards at individual institutions. The study is registered at clinicaltrials.gov (NCT03939637). This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines[23] (see SPIRIT checklist in supplemental files).

Study Population, Randomization, and Stratification

The study population includes children ages 1 to <18 years with newly diagnosed ITP (<3 months from first abnormal platelet count). At time of study screening, patients must have a platelet count <30 x10^9/L and require pharmacologic treatment from the perspective of the treating clinician. A platelet count of <30 x10^9/L was selected in order to provide a real-world approach to treatment in which patients often receive treatment based not on a platelet count threshold but rather for bleeding history or secondary to disease impact on HRQoL, both of which may occur at a higher platelet count. Recognizing that there will be variation in physician practice with regards to treatment as well as heterogeneity in the reasons for treatment (bleeding, platelet count, HRQoL, etc.) we have elected to apply randomized trial design to help balance this variability between the two treatment groups. Patients who have previously received a TPO-RA are excluded. As we do not want to impede appropriate critical care management, patients with severe bleeding, defined as overall Grade 4 or 5 bleeding,[24] or bleeding requiring emergent treatment will be excluded. Additional exclusion criteria are outlined in Supplementary Table 1. All patients and/or their parents or legal guardians must sign a written informed consent and assent when applicable.

Patients who meet all of the inclusion and none of the exclusion criteria will be enrolled and randomly assigned to receive eltrombopag or standard therapy in a 2:1 ratio. Central

randomization at study enrollment will occur via the online InForm system, with randomization allocation delivered only to the enrolling site study staff. Randomization will utilize blocking and will be stratified by the age of the patient (1-<6, 6-<12, and 12-<18 years) and by prior treatment status. "Upfront treatment" refers to patients within 10 days of ITP diagnosis who have not received previous pharmacologic treatment. This allows for a reasonable window from time of diagnosis to enrollment as well as for proper time to confirm the diagnosis and rule out other transient causes of thrombocytopenia. The "treatment failure" stratum is for patients who have received standard initial management (observation >10 days, IVIg, Anti-D immunoglobulin, or corticosteroids) and continue to have platelets <30 $x10^9$/L. A patient who initially responded to treatment but whose response wanes and platelets fall below 30 $x10^9$/L will be considered to have a "treatment failure."

Eltrombopag Regimen

Patients randomized to eltrombopag will start at a dose based on age per the manufacturer label dosing for drug initiation. Children ages 1-5 years will begin 25 mg once daily, and children ≥6 years will begin at a dose of 50 mg once daily (25 mg once daily for patients of East-Asian ethnicity). Patients will receive education regarding proper administration and dietary restrictions, and medication compliance will be queried at each study visit. Eltrombopag dose adjustments are made in response to platelet counts, with a goal of maintaining a platelet count 50-200 $x10^9$/L, with a maximum dose of 75 mg once daily (Supplementary Table 2). A modification from the dosing label was made for maintenance dose adjustment based on investigators' clinical experience with rebound thrombocytopenia when eltrombopag is held for high platelet counts. Daily eltrombopag will be continued for 12 weeks, unless platelets do not rise $\geq$ 30 $x10^9$/L after 4 weeks at the maximum daily dose of 75 mg.

Patients randomized to the eltrombopag arm who respond will be eligible to continue the treatment throughout the 1-year duration of study participation, with guidelines given for dose adjustments during weeks 13-52 (Supplementary Table 2). 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 every 2 weeks (with investigators exercising clinical judgement with respect to wean in the context of the patient's status, including intercurrent infections). Patients who have been unable to wean off of eltrombopag by 1 year will discontinue study drug, and continuation on commercially available eltrombopag at that point is at the discretion of the investigator.

Standard Therapy Regimen

Subjects randomized to the standard therapy arm will receive one of three treatments at the discretion of the treating physician. Patients previously treated with standard management prior to study entry must be treated with a different agent than their original failed agent. For example, a patient who did not respond to steroids could receive either IVIg or anti-D if randomized to the standard treatment arm. Investigators may choose amongst the following treatment options: 1) IVIg 1 g/kg x1 dose,[25] 2) Prednisone/Prednisolone 4 mg/kg/day (Max 120 mg/day) x 4 days,[26] or 3) Anti-D immunoglobulin 75 mcg/kg x1 dose.[25] No steroids for pre-medication or adjunctive therapy may be administered with IVIg or anti-D immunoglobulin.

Efficacy Outcomes

The primary endpoint is binary, with each patient classified as either a platelet responder or a platelet non-responder. Platelet response is defined as ≥6 of 8 weeks with platelets >50 x10^9/L (whereby the 6 weeks are not required to be consecutive) during weeks 5-12 of therapy. This represents 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. If a patient requires a rescue medication at any time within the first 12 weeks of therapy, then the patient will be categorized as a non-responder.

Secondary Outcomes

Additional response outcomes include the number of rescue therapies needed during the first 12 weeks, platelet response during weeks 5-12 of study in patients who required a rescue treatment during that time, proportion of patients who do not need ongoing treatment at 12 weeks and 6 months, proportion of patients with a treatment response at one year after study enrollment, and the number of second-line therapies (treatments other than prednisone, IVIg, and anti-D globulin thought to be active in the treatment of ITP) used in weeks 13-52. Safety analyses will examine the proportion of patients with abnormal liver function tests in patients with newly diagnosed ITP treated with eltrombopag, and the proportion of patients with adverse events and serious adverse events by treatment arm. Furthermore, we will investigate changes in iron indices (serum iron, TIBC, transferrin saturation, ferritin, MCV, and hemoglobin) given the chelation properties of eltrombopag.[10,27] Secondary analyses will also include comparison of patient-related outcomes for patients treated with eltrombopag versus those treated with standard first-line agents. This includes comparison of significant bleeding (WHO Bleeding Scale ≥2[28] or Modified Buchanan Score ≥3[24]), change in Health-Related Quality of Life (HRQoL) measured by the Kids ITP Tool[29], and fatigue as measured by the parent-proxy report of the Hockenberry Fatigue Scale-Parent (FS-P)[30].

Correlative Biology Studies

Age and duration of symptoms at diagnosis are known to be associated with resolution of ITP,[31] but 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 unknown whether the development of chronic ITP could be prevented by intervention with a TPO-RA early in a patient's course. A subset of patients with chronic ITP maintained increased platelets after discontinuation of treatment with TPO-RAs.[32-34] Because of the implication of Tregs in the pathogenesis of ITP and the potential immunomodulatory effects of TPO-RAs, early use of eltrombopag may have a positive impact on the number of patients who develop chronic disease. For this reason, we will evaluate the change in percentage of $CD4^+25^+Foxp3^+$ Tregs in patients treated with eltrombopag compared to those treated with standard first-line agents. Additionally, there are likely biologic factors which influence response to TPO-RAs and other therapies that are not yet understood. Identification of biomarkers of treatment response could lead to a personalized approach to therapy, targeted to an individual patient's disease biology. If consent is obtained

for optional studies, baseline DNA samples and baseline and serial RNA samples will be banked for future correlative biology studies.

Exploratory Outcomes

Additional analyses will include comparison of patients treated with eltrombopag versus those treated with standard first-line agents using International Working Group platelet-specific endpoints.[35] Lastly, we plan to conduct a cost analysis of therapy between the two treatment arms, recognizing the large cost difference between some current first-line therapy agents such as corticosteroids and eltrombopag.

Sample Size and Statistical Plan

A total of up to 162 patients will be enrolled. For the primary objective, all randomized patients will be analyzed in an intent-to-treat (ITT) analysis of response rate for the primary objective. A patient is considered "non-informative" if he withdraws from protocol therapy and data submission prior to the 5-week platelet assessment. Non-informative patients will be classified as non-responders, and both informative and non-informative patients will be included in the ITT analysis. Non-informative patients could dilute our ability to detect a treatment effect; therefore, additional patients will be randomized to make up for the diluting effect. A conservatively high estimate of 9% of patients are anticipated to be non-informative. To obtain at least 147 informative randomized patients, we plan to enroll and randomize up to 15 additional patients (10 and 5 for the eltrombopag and standard treatment arms, respectively) for a total of up to 162. At an anticipated enrollment rate of 90 patients per year, the total accrual duration is expected to be 2 years, plus 1 year follow-up on the last patient, for a total study duration of 3 years.

The primary objective will be addressed by monitoring for evidence of efficacy or lack of efficacy (futility) using group sequential analyses, with three "looks" at the data (after one-third, two-thirds, and full accrual). In each analysis, a two-sided z-test will be used to compare the two arms in terms of the proportion of patients who have a platelet response. We will reject the null hypothesis if the upper (efficacy) monitoring boundary is crossed; in this case, it will be reasonable to conclude that the platelet response is significantly greater in patients treated with eltrombopag than standard first-line treatments. If the lower (futility) monitoring boundary is crossed in either of the two interim analyses, we will have significant evidence that eltrombopag is not more efficacious than standard first-line treatments, and the trial will be stopped early for futility. The overall type 1 error is preserved at 0.05, or 0.025 in a one-sided test. The sample size of 147 informative patients will provide 81.4% power to detect an absolute difference of 25% in the proportion of patients who are platelet responders, assuming a response rate of 75% with eltrombopag and 50% with standard first-line treatments, using a two-sided z-test with alpha=0.05 (i.e., a one-sided z-test with alpha=0.025).

Discussion

ICON is a group of 50 pediatric hematology centers in the United States, Canada, and Mexico participating in collaborative research efforts dedicated to improving the understanding,

treatment, and quality of life of pediatric patients with ITP. The consortium was established in 2012 and has previously completed a prospective observational trial of patients starting second-line therapies for ITP. PINES is the Consortium's first prospective investigational trial for newly diagnosed ITP, initiated in response to a need for alternative up-front treatment options. While many children with ITP can be safely observed while waiting for spontaneous resolution of their disease, for those who require intervention, treatment options are limited and may only transiently increase the platelet count without achieving a sustained response. An optimal therapy for patients who do warrant treatment for repeated bleeding episodes or poor quality of life would be an easy-to-administer medication with a tolerable side-effect profile that produces a sustained response until resolution.

The primary endpoint of PINES, ≥ 6 of 8 weeks with platelets >50 $x10^9$/L during weeks 5-12 of therapy, is a clinically relevant measure of platelet response suggesting sustained response to therapy. It is also a previously established endpoint for eltrombopag in pediatric ITP, used in the PETIT2 trial.[7] With a goal of 162 randomized patients, the study is powered to detect an improvement of 25% in the proportion of patients who are platelet responders in the eltrombopag arm compared to standard first-line treatments. Secondary platelet endpoints include treatment response at 1 year, with response definitions based on platelet count and time since most recent platelet active medication. Additional platelet-specific endpoints are included in exploratory objectives with International Working Group defined endpoints with a goal of being able to compare across studies.[35] Another strength of this study is the collection of patient-related outcomes data. The 2019 ASH guidelines stressed that for prioritized outcomes such as bleeding and HRQoL there is a paucity of necessary data to guide clinical practice.[5] It is critical in any contemporary interventional ITP study to assess bleeding and HRQoL in addition to platelet response, as bleeding severity, platelet count, and HRQoL scores are uncorrelated independent outcomes, each of which may impact treatment decisions.[36]

The experimental design of the trial is intended to allow for maximum clinical discretion on the part of the treating investigator, with a "real-world" approach to decision-making. Patients are eligible to enroll if they require pharmacologic treatment (for whatever reason) in the opinion of the treating hematologist, as long as they do not have severe bleeding that requires emergent intervention or concomitant therapy to achieve a rapid rise in platelet count. If the patient is randomized to the standard therapy arm, the investigator may choose among three standard treatments at protocol-specified doses. Rescue medications are allowed throughout the study, and after week 12 of the study, therapy in the standard arm or for non-responders in the eltrombopag arm is at the discretion of the investigator.

Because it is anticipated that the majority of patients will have remission of their ITP before the end of the 1-year duration of study participation, protocol-prescribed adjustments of eltrombopag during weeks 13-52 of the study lead to more aggressive weaning than would result from the manufacturer recommendations for dose adjustment in the setting of chronic ITP.

In general, pediatric patients with newly diagnosed ITP have very favorable outcomes, and as such we are loath to expose these patients to any undue risk. Because eltrombopag already has an established safety profile in the pediatric population and is an FDA-approved treatment for pediatric patients with chronic ITP, we are reassured that this is a safe therapy for patients with newly diagnosed ITP. However, because safety is paramount, we have chosen to be particularly conservative with exclusion criteria, and we have chosen stringent cut-offs of transaminases and bilirubin. Iron deficiency has been reported in two retrospective series of patients treated with eltrombopag,[10,27] and we will be able to follow this larger cohort of patients prospectively to better evaluate the incidence of this potential side effect.

A prospective randomized trial presents a unique opportunity to explore biologic differences in disease between treatment responders and non-responders as well as biologic outcomes of specific interventions. Tregs play a role in the pathogenesis of ITP, but it is not clear what impact the interactions of medical therapies with Tregs have on response, and following these over time may add to our understanding of the underlying biology of ITP development and resolution. Finally, through banking DNA and RNA samples for future studies, we anticipate possible identification of genes associated with response to therapies or RNA expression changes that correlate with disease activity that may improve our understanding of how to optimally treat pediatric patients with ITP.

We describe an in-process randomized clinical trial comparing eltrombopag to standard therapy in the treatment of pediatric patients with newly diagnosed ITP. This is the first pediatric trial investigating the use of a thrombopoietin receptor agonist for patients with newly diagnosed ITP and has the potential to transform our approach to treatment in this patient population. While the primary outcome of this study is sustained platelet response during weeks 5-12 of treatment, the clinical implications surpass platelet count alone. The possibility of a limited course of a TPO-RA in the newly diagnosed phase that could bridge the time to spontaneous resolution of disease may diminish bleeding episodes and improve quality of life for these patients.

Patient and public involvement: Patients were not directly involved in the design of this study, although the consortium meets regularly with ITP patient advocacy group members and leaders, including the Platelet Disorder Support Association (PDSA), in order to understand needs and priorities of the patients. The PDSA has disseminated information about the trial to its members via website, and results and lay summary will be provided to patient groups and the public after trial completion.

Ethics and dissemination

The study protocol, informed consent and assent forms, and surveys have been approved by the central IRB at Baylor University/Texas Children's Hospital (see Supplemental materials). The study protocol was approved on January 28, 2019 and this manuscript details the protocol in the latest version v4.0 approved on October 16, 2019.

Participating consortium sites have either executed a reliance agreement to rely on the central IRB or have obtained approval from their local IRBs. Data management for the study is through

an InForm database managed by the Data Coordinating Center, Boston Children's Hospital. Data will be entered electronically at the participating sites. Study sites will be monitored at 6-month intervals by a team from the Data Coordinating Center, with audits to review and verify data recorded on CRFs against source documents. De-identified study information and study documents are sent via secure file transfer systems.
SAEs are reported to the central IRB and local IRBs as well as to Novartis.

The trial design and rationale has been presented in poster form at a national meeting. Following trial completion, results of the study will be submitted for peer review for publication in a scientific journal. The writing committee will consist of members of the trial steering committee, site investigators, and ICON consortium members. The full protocol and dataset will be publicly available upon request after completion and publication of planned analyses.

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EJN: Advisory boards: Genentech, NovoNordisk, Novartis; Honoraria: Octapharma; DSMB service: Bayer, ApoPharma, Acceleron, Imara; Consultancies: Pfizer, Celgene. RJK: Speaker: Takeda, Biogen Canada LMT, Octapharma, Pfizer; Consultancies: Agios, Amgen Inc., Hoffman-LaRoche LTD, Takeda, NovoNordisk Canada Inc. CMB: Research funding: Novartis. WBL: DSMB member: ArQule, Inc, Jubliant Draximage, Inc. CN: Research funding: PDSA. The remaining authors have no competing interests.

Figure 1 Schematic diagram of study entry, randomization, primary endpoint evaluation, and follow-up

Table 1 Administration, efficacy, and potential side effects of standard therapies

	Dosing	Method of administration	Efficacy[37] (platelet[a])	Short-term Potential Side Effects
Prednisone	4 mg/kg/d x 4-7 d[b]	Oral	~70-80%	Mood changes, hyperglycemia, hypertension, weight gain
Intravenous Immunoglobulin	0.8-1 g/kg	IV	~70-80%	Headache, flu-like symptoms, allergic reaction, neutropenia, hemolytic anemia Black Box: Thrombosis, renal failure
Anti-D Immunoglobulin	50-75 µg/kg	IV	~70-80%	Anemia, fevers, nausea Black Box: intravascular hemolysis, DIC, renal failure

Abbreviations: IV, intravenous; DIC, disseminated intravascular coagulopathy
[a]Definition of platelet response varies depending on study
[b]A number of steroid regimens are used

Table 2 Published studies of eltrombopag in pediatric patients with ITP

Paper[a]	Type of Study	Patient population	Results
Giordano P et al 2020[38]	Retrospective multicenter study	386 children with chronic ITP enrolled retrospectively at 17 sites	Prevalence of eltrombopag use was 19% in patients with chronic ITP
Koca Yozgat A et al 2020[10]	Retrospective multicenter study	105 children with chronic or acute refractory ITP treated with epag	Overall response rate was 74%. 27.6% developed iron deficiency or iron deficiency anemia.
Cheng X et al 2019[39]	Single-center observational study	20 patients with severe chronic ITP treated with epag	The durable response rate was 70% (14/20)
Grace RF et al 2019[40]	Multi-center prospective observational study	120 children with ITP starting 2nd-line therapies. 20 patients treated with epag.	Increased platelet counts and HRQoL. Decrease in skin, but not non-skin, bleeding symptoms in patients on epag.
Suntsova E et al 2019[41]	Single-center retrospective analysis	23 patients with chronic ITP who failed first TPO-RA. 10 patients switched to epag.	Response rates after switching TPO-RAs were 80% (romi→ epag) and 62% (epag → romi)
Tumaini MJ et al 2019[42]	Meta-analysis	Five randomized controlled trials with total of 261 pediatric patients. 159 treated with epag.	TPO-RAs superior to placebo
Grainger JD et al 2019[43]	Multi-center RCT	82 patients with ITP >6 months who had received at least one prior treatment	Epag did not impact HRQoL as assessed by KIT
Grace RF et al 2018[44]	Multi-center prospective observational study	120 children with ITP starting 2nd-line therapies. 20 patients treated with eltrombopag.	Oral agents, including eltrombopag, were chosen for ease of administration and expected adherence (P < .001)
Leblebisatan G et al 2018[45]	Single-arm study	19 patients with chronic ITP	58% of patients responded with either increased platelet counts or decreased bleeding
Zhang J et al 2018[46]	Indirect-comparison meta-analysis	Five randomized controlled trials with total of 261 pediatric patients. 159 treated with epag.	Epag & romi similar in efficacy and safety, but decreased bleeding w/ epag.
Guo JC et al 2018[47]	Meta-analysis	Seven randomized controlled trials with total of 345 pediatric patients. 159 treated with epag.	TPO-RAs superior to placebo
Zhang J et al 2017[48]	Systematic review	Five randomized controlled trials with total of 261 pediatric patients. 159 treated with epag.	Overall response & durable platelet response increased in TPO-RAs vs placebo
Lambert MP et al 2017[27]	Retrospective chart review	12 patients with ITP treated with eltrombopag	8/11 patients developed iron deficiency during treatment with epag
Neunert C et al 2016[9]	Multicenter retrospective study	79 patients with ITP treated with TPO-RAs	89% achieved platelet count >50 x1 (no difference between epag or romi); 40% achieved stable response
Grainger JD et al 2015[7]	Multicenter RCT	92 patients with chronic ITP and platelets <30k	40% (vs 3% placebo) achieved platelet count >50 for 6/8 weeks

Bussel JB et al 2015[6]	Multicenter RCT	82 patients with ITP >6 months who had received at least one prior treatment	62% (vs 32% placebo) achieved platelet count >50 x1
Ramaswamy K et al 2014[49]	Multicenter retrospective study	33 pediatric patients with ITP who had received at least one prior treatment; 12 received eltrombopag	75% achieved platelet counts >/=50k and >/=20k above baseline for 2 consecutive weeks

Abbreviations: ITP, immune thrombocytopenia; epag, eltrombopag; HRQoL, health-related quality of life; TPO-RA, thrombopoietin receptor agonist; romi, romiplostim; RCT, randomized controlled trial; KIT, Kids ITP Tool

[a]Search was performed in PubMed using terms "eltrombopag" and either "pediatric" or "children." Clinical trials and meta-analyses were included. Papers were excluded if the patient population was anything other than pediatric patients with immune thrombocytopenia, or if they included fewer than 10 patients treated with eltrombopag.

Table 3 Protocol endpoints and statistical analysis plans

Outcome (Endpoint)	Statistical Plan
Efficacy	
1. Platelet response, defined as ≥6 of 8 non-consecutive weeks with platelets >50 x10^9/L during weeks 5-12 of therapy	Group sequential analyses, with three "looks" at the data: two interim analyses (for efficacy and futility), and a final analysis (for efficacy), using a two-sided z-test with alpha=0.05 (i.e., a one-sided z-test with alpha=0.025), to compare the two arms in terms of the proportion of patients who have a platelet response
2. Cumulative number of rescue therapies needed during the first 12 weeks of treatment	Student's t-test will be used to compare the two treatment arms
3. Platelet response during weeks 5-12 of therapy in patients who required a rescue treatment during weeks 1-2 of study	Observed proportion and 95% confidence interval will be calculated
4. No further need for treatment after 12 weeks and 6 months of study	Chi-squared test will be used to compare the two treatment arms
5. Treatment response[a] at one year of study	Chi-squared test will be used to compare the two treatment arms
6. Number of 2nd-line therapies used in weeks 13-52	Student's t-test will be used to compare the two treatment arms
Safety	
7. Abnormal liver function tests[b] (LFTs) in patients with newly diagnosed ITP treated with eltrombopag.	Frequency and proportion (with 95% confidence interval) of patients with abnormal LFTs will be calculated
8. Incidence of adverse events and serious adverse events	Adverse events will be coded by MedDRA classification term. Adverse events and serious adverse events will be tabulated by treatment group, including 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.
9. Iron indices[c] at 12 weeks, 6 months, and 1 year	Two-sided Student's t-test will be used to compare iron indices at 12 weeks, 6 months, and 1 year between the two arms
Patient-Related Outcomes Assessment	
10. 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	Chi-squared test will be used to compare the two treatment arms
11. Change in Health-Related Quality of Life (HRQoL) from a) baseline to 1 week,	KIT scores will be calculated per the methods described in Klaassen et al.[29] Spaghetti plots will be used to

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)	visualize the KIT scores over time per patient by treatment arm. Two-sided Student's t-test will be used to compare the percentage change from baseline in KIT overall score at 1 week, 4 weeks, 12 weeks, and 1 year between the two arms.
12. 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)	Fatigue scores will be calculated per the methods described in Hockenberry et al.[30] Spaghetti plots will be used to visualize the scores over time per patient by treatment arm. A two-sided Student's t-test will be used to compare the percentage change from baseline at 1 week, 4 weeks, 12 weeks, and 1 year between the two arms.
Biology	
13. Change in percentage of $CD4^+25^+Foxp3^+$ regulatory T cells (Tregs) a) from baseline to 12 weeks; and b) from baseline to 1 year	Student's t-test will be used to compare the two treatment arms

Abbreviations: LFTs, liver function tests; MedDRA, Medical Dictionary for Regulatory Activities; WHO, World Health Organization

[a]Complete response (CR) is defined as a 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 (patient 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.

[b]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)

[c]Iron, TIBC, transferrin saturation, ferritin, MCV, and hemoglobin

Table 4 Outline of study assessments

	DAY 0	72H	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	6 MONTHS	1 YEAR
PHYSICAL EXAM	x		x			x								x	x	x
BLEEDING ASSESSMENT	x		x	x	x	x								x		x
HRQOL: KIT	x		x			x								x		x
HOCKENBERRY FATIGUE SCORE	x		x			x								x		x
PROMIS	x													x		x
GLOBAL RATE OF CHANGE			x			x								x		x
PLATELET COUNT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
IRON STUDIES	x													x		x
TREGS	x													x		x
SAMPLES FOR BANKING (OPTIONAL)	x													x		x

Abbreviations: HRQOL, Health-Related Quality of Life; KIT, Kids ITP Tool; PROMIS, Patient-Reported Outcomes Measurement Information System; Tregs, Regulatory T cells

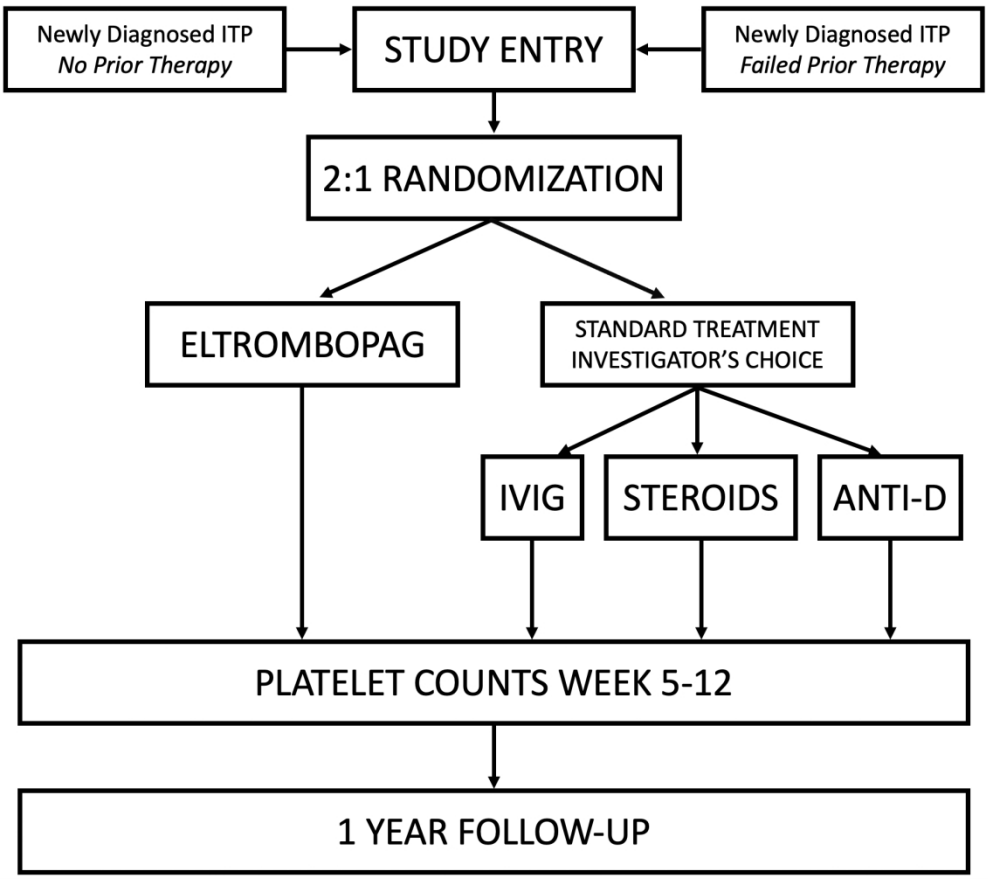

Figure 1 Schematic diagram of study entry, randomization, primary endpoint evaluation, and follow-up

Supplementary Table 1 Exclusion criteria by system

Cardiac
Prolonged QTc, with corrected QTc >450 msec
Clinically significant cardio-vascular disease (e.g., uncontrolled hypertension, history of labile hypertension)
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[a]
Gynecologic
Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.[b]
Hematology
Evans Syndrome: positive direct Coombs with evidence of active hemolysis (elevated LDH or reticulocyte count not attributable to recent treatment or bleeding)
Anticoagulant or anti-platelet agents
Thrombophilic risk factors[c]
Hepatic
AST or ALT > 2 x upper limit of normal (ULN) Total bilirubin > 1.5 x ULN Liver cirrhosis (as determined by the investigator)
Immunology
Known immediate or delayed hypersensitivity reaction to eltrombopag or its excipient
Infectious
HIV (or history of positivity) Hepatitis C (screening not required if no clinical suspicion) Active or uncontrolled infections not responding to appropriate therapy
Oncology
Any malignancy History of stem cell transplant or solid organ transplant
Ophthalmic
Baseline problems that may potentiate cataract development
Psychologic
History of alcohol and drug abuse
Renal
Creatinine > 2.5 x ULN

Abbreviations: LDH, lactate dehydrogenase; AST, aspartate transaminase; ALT, alanine transaminase; ULN, upper limit of normal; HIV, human immunodeficiency virus

[a]Defined as 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.

[b]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, female sterilization, male sterilization,

barrier methods, or use of oral, injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other hormonal contraception with similar efficacy. 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.

[c]Subjects for whom the potential benefits of participating in the study outweigh the potential risks of thromboembolic events, as determined by the investigator

Supplementary Table 2 Dose adjustment nomogram for eltrombopag

PLATELET COUNT RESULT	DOSE ADJUSTMENT OR RESPONSE
Weeks 1-12	
< 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.
> 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)
Weeks 13-52	
< 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.
> 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.

Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	10
Funding	#4	Sources and types of financial, material, and other support	5, 14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1, 5
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4, Table 2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4, 6, Table 1
Objectives	#7	Specific objectives or hypotheses	4, Table 3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5, Figure 1
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, Table 5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6, Table 6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6, Table 6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-7, 9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4, 7-9, Table 3
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, Table 4
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7, 8, 11, Tables 3-4
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry;	11

		range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8, Table 3
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8, Table 3
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7, 11, Table 3
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	5, 11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2, 4, 5, 10
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5, 10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	1-18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	10, Table 4

Notes:

- 6a: 3-4, Table 2

- 6b: 3-4, 6, Table 1
- 8: 5, Figure 1
- 12: 4, 7-9, Table 3
- 18a: 7, 8, 11, Tables 3-4
- 22: 7, 11, Table 3
- 24: 2, 4, 5, 10
- 33: 10, Table 4

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A PHASE 3 STUDY OF ELTROMBOPAG VS. STANDARD FIRST-LINE MANAGEMENT FOR NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA (ITP) IN CHILDREN

Protocol Number: CETB115JUS33T, Version 4.0, September 23, 2019

Concise and Focused Presentation

When reading this form, please note that the words, “you” and “your” refer to the person in the study rather than to a parent or guardian, or legal representative who might sign this form on behalf of the person in the study.

Dr. XXX and her colleagues at XXX are conducting a research study in collaboration with Dr. XXX and her colleagues in the Baylor College of Medicine Department of Pediatrics. This is a research study for patients diagnosed with immune thrombocytopenia (ITP), a condition that results in low platelets and possibly bleeding due to antibodies your body makes against your platelets. You are being invited to participate in this study because you have been identified to as having ITP.

The purpose of this study is to investigate the safety and effectiveness of eltrombopag in treating children and adolescents with newly diagnosed ITP.

If you choose to participate, you will be on study for about 1 year. You will be randomly assigned to receive the study drug eltrombopag or standard therapy.

During your participation you will have study procedures weekly for 12 weeks and then about monthly or less often for up to 1 year.

The following procedures will be performed:

- Physical exam
- Complete a Bleeding assessment
- Review your medical record.
- Ask how you are feeling and if you have had any side effects from therapy
- Ask you to complete some questionnaires regarding how you are feeling and your ITP
- Collect blood samples to assess your general health
- If you are a girl and have had your period, a blood or urine sample will be collected to see if you are pregnant
- Ask you about if you have been taking your study medication.

You will be asked to participate in an optional blood collection to collect blood one time for future research including genetic research.

The most common risks associated with eltrombopag treatment are headache, muscle/extremity pain, runny nose, cough, vomiting. Some more serious, but less common risks are liver enzyme elevation, blood clots.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A PHASE 3 STUDY OF ELTROMBOPAG VS. STANDARD FIRST-LINE MANAGEMENT FOR NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA (ITP) IN CHILDREN

Your participation in this study is voluntary. You may choose not to participate in this study. You may choose to receive routine care or participate in other studies.

The benefits of participating in this study may be an improvement to your ITP, and increasing the general knowledge and understanding of ITP and treatment. However, you may receive no benefit from participating.

Please find a more detailed description of procedures and risks below.

Background

This form contains the purpose of the research being conducted, the procedures involved, your responsibilities, and the risks and benefits associated with participation in the study. Please read this form and ask the Study Doctor, Dr. XXX, or Study Staff any questions you may have. If there are any words or information that you do not know, ask them to explain. Feel free to take notes, write questions or mark any part of this form.

This research is being done by members of the Pediatric ITP Consortium of North America (ICON). ICON is a group of pediatric doctors throughout the United States who in a collaborative research effort are dedicated to improving the understanding, treatment, and quality of life of pediatric patients with ITP.

This is a research study for patients diagnosed with immune thrombocytopenia (ITP), a condition that results in low platelets and possibly bleeding due to antibodies your body makes against your platelets. Platelets enable your blood to clot and stop bleeding. You are being invited to participate in this study because you have been identified to as having ITP.

If you join this study, you will be treated with one of four treatment plans. Three of the treatment plans are the standard treatments for newly diagnosed ITP in children and adolescents. The fourth treatment plan involves a drug named eltrombopag.

Eltrombopag is a drug which is approved in over 40 countries including the United States and European Union for treatment of chronic ITP (lasting longer than 6-12 months) and other types of blood diseases, including adults and children with low platelets. Over 5000 patients have been treated with eltrombopag in clinical studies to date. Its use in this study is considered “investigational” because eltrombopag is approved by the Food and Drug Administration (FDA) to treat children with chronic ITP, but has not been studied in children with newly diagnosed ITP.

Your participation in this study is voluntary. You are free to say yes or no. If you do not want to participate, your regular medical care and legal rights will not be affected. Even if you join this study, you may stop at any time

This research study is sponsored by Baylor College of Medicine and is funded by Novartis. The investigational drug, eltrombopag, is supplied by Novartis.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A PHASE 3 STUDY OF ELTROMBOPAG VS. STANDARD FIRST-LINE MANAGEMENT FOR NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA (ITP) IN CHILDREN

Purpose

The purpose of this study is to investigate the safety and effectiveness of eltrombopag in treating children and adolescents with newly diagnosed ITP.

Procedures

The research will be conducted at the following location(s): XXX

A total of up to 162 subjects will be enrolled on this this protocol. Approximately 18 of those subjects will be enrolled at our local site.

DURATION.

There will be a total of approximately 16 study visits over a 1 year period. In addition, we will follow you for thirty days after your last dose for this study to see how you are doing.

STUDY DESIGN

If you agree to take part in the study, you will be assigned randomly (like rolling a dice) to be treated with:

- Eltrombopag
- Standard Therapy

Two out of three subjects taking part in the study will be given eltrombopag and one out of three subjects will be treated per standard therapy.

You and your study doctor(s)/team will know whether you will receive eltrombopag or standard therapy.

If you are randomized to receive the standard therapy you will be treated with one of the following three options depending on which treatment method your study doctor thinks is best for you:

- Intravenous immunoglobulin (IVIG)
- Steroids
- Anti-D immune globulin (Anti-D)

All three are standard front line treatments for treating ITP for pediatric and adolescent patients. If your study doctor determines that IVIG or Anti-D globulin is the best treatment option for you, you will receive one dose of IVIG or Anti-D through an IV. If you receive steroids, you will take them twice daily for four days by mouth.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A PHASE 3 STUDY OF ELTROMBOPAG VS. STANDARD FIRST-LINE MANAGEMENT FOR NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA (ITP) IN CHILDREN

If you are randomized to receive eltrombopag, you will take it once daily. Your dose may be modified depending on your platelet count. You will take eltrombopag for 12 weeks, with the possibility to continue therapy for up to 1 year depending on how your body responds to taking eltrombopag.

You will be required to take eltrombopag on an empty stomach, 1 hour before or 2 hours after a meal. Eltrombopag is available as a liquid and as a tablet. If you take the tablet form, you must be able to swallow the tablet(s) whole with a glass of water without chewing. The tablet should not be crushed or broken.

It is also important that you do not take the eltrombopag in the 2 hours before and 4 hours after taking any other medications, calcium-rich foods (such as, dairy products like cheese, yogurt and milk, and calcium-fortified juices), or vitamins containing minerals such as iron, calcium, aluminum, magnesium, selenium, and/or zinc. Please discuss this further with the Study Doctor as she can advise on other foods to avoid to ensure the drug is most effective.

If you vomit after taking eltrombopag, the dose should not be repeated.

Regardless of whether you are randomized to one of the standard therapies or eltrombopag, all will be referred throughout this consent as study medications.

STUDY PROCEDURES

I. SCREENING VISIT (Visit 1)

If you agree to participate in the study, you will sign a consent form and the study doctor and study staff will:

- Confirm whether you are eligible to participate in this study
- Collect information about your ITP
- Ask you about the medicines you are currently taking
- Perform a physical examination
- Examine your eyes for cataracts (clouding of the normally clear lens of the eye).
- Draw blood (about four teaspoons) to measure your blood cell counts, iron levels, liver function, and immune function, and to assess your general health if not done as part of routine medical care. If you are a female and have started your period, a blood sample may also be drawn to see if you are pregnant.
- Take a urine sample to see how your kidneys are functioning. If you are a female, have started your period, and a blood sample was not drawn to see if you are pregnant, your urine will be checked to make sure you are not pregnant.
- Ask you to complete some questionnaires about your how you feel and about your ITP.

You will be asked come back within 72 hours (+/- 24 hours) to have your platelet count checked after this visit. For this approximately ½ teaspoon of blood will be drawn. This may be done locally.

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II. Treatment Period I (Weeks 1- 12)

You will be asked to come complete a weekly study visit once every week for twelve weeks after your screening visit. Only week 4 and week 12 will be required to be done at the study site. At certain time points, labs may be done locally and questions can be asked over the phone. At these visits the study team or doctor will do all or some of the following:

- Perform a Physical exam
- Complete a Bleeding assessment
- Review your medical record and collection information from your medical record that is related to your health and/or disease history. Some examples include test results, medical procedures, pathology reports, medicines you take.
- Ask how you are feeling and if you have had any side effects from therapy
- Ask you to complete some questionnaires regarding how you are feeling and your ITP
- Collect blood samples to assess your general health
- If you are a girl and have had your period, a blood or urine sample will be collected to see if you are pregnant
- Ask you about if you have been taking your study medication. Collect your medication bottles/vials and dispense your study medication

Your platelet count will be checked weekly. If you are taking eltrombopag, your blood will be tested every two weeks to assess your liver function and iron levels in your body.

If you are receiving eltrombopag, your dosing maybe altered depending on your platelet count.

III. Treatment Period II (Weeks 13 to 52)

If you complete twelve weeks of eltrombopag, the study team will start to decrease your dose over this treatment period depending on your platelet count. If you are still taking eltrombopag at the one year mark, you will be transitioned off study, and you will continue to be treated according to your primary treating doctor.

If you are taking eltrombopag your blood will be tested monthly to assess your liver function and iron levels in your body.

If you are girl and have had your period, your urine or blood will be tested every two months if you are taking eltrombopag to see if you are pregnant.

Regardless of what medication you are receiving or received for this study, you will be asked to come for a visit at 6 month and 1 year mark. At these visits, the study team or doctor will do all or some of the following:

- Perform a physical exam
- Complete a bleeding assessment

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

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- Ask you questions and review your medical record, and collect information from your medical record that is related to your health and/or disease history. Some examples include test results, medical procedures, pathology reports, and medicines you take.
- Ask you to complete questionnaires regarding your ITP and how you are feeling
- Ask you how you are feeling and if you have had any side effects
- Collect your study medication
- Dispense your study medication
- Ask you about any medications have are currently taking
- Collect blood samples to assess your general health, clotting, iron levels, immune function and liver function.

IV. UNSCHEDULED VISITS

You may be asked to come in for additional visit(s). If you come in for an unscheduled visit, the study team or doctor will:

- Complete a physical exam
- Complete a bleeding assessment
- Collect a blood sample to assess your blood counts
- Ask you how you have been feeling and if you have had any side effects or about your medications you are currently taking

V. FOLLOW UP

We would like to keep track of your medical condition after your last dose of study drug. A member of the study team will contact you via phone or email during the month after you stop the study treatment to see how you are doing.

VI. RESCUE MEDICAITONS

If you have bleeding while participating in this study, please call your study doctor or team right away. If you have a bleed, platelets drop after initial response or you do not respond to treatment, the study doctor may give you a rescue medication such as IVIG, steroids, and/or Anti- D. If you the study doctor decides that you may need a different type of rescue medication, you will be removed from the study and treated per standard of care.

VII. SUBJECT RESPONSIBILITIES

- Come to required study visits
- Bring your empty study medication vials to each visits

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- Take you study medication as prescribed
- Tell your doctor about any medications or treatments you undergo while participating on this study
- Complete study questionnaires

Potential Risks and Discomforts

SIDE EFFECTS OF ELTROMBOPAG:

The side effects listed below have been seen in younger patients (under the age of 18) who have received eltrombopag treatment for ITP.

Very Common Side Effects:

These may affect more than 1 in 10 people treated with eltrombopag:

- Chest Infection (upper respiratory tract infection)
- Fever (Pyrexia)
- Abdominal Pain
- Cough

The following side effects have been reported to be associated with treatment with eltrombopag in patients with a different disease called severe aplastic anemia (SAA).

Very Common Side Effects:

These may affect more than 1 in 10 people treated with eltrombopag:

- Rash
- Cough
- Headache
- Runny nose
- Abdominal pain
- Diarrhea
- Nausea
- Joint pain
- Increase in some liver enzymes (transaminases)

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- Pain in arms, legs, hands and feet
- Dizziness
- Feeling very tired (fatigue)
- Fever

Progression of underlying disease or progression to a new myelodysplastic syndrome (MDS) and/or new acute myelogenous leukemia (AML, a type of blood cancer) has occurred in patients with MDS, AML, and severe aplastic anemia (SAA). In some patients with these diseases who are treated with eltrombopag, changes in bone marrow cells may occur and in some cases this may indicate a worsening/progression to cancer. The role of eltrombopag in these changes is not known. These changes have also been seen in patients with SAA alone, and with other drugs in the same class of compounds as eltrombopag. During this study, your blood will be periodically examined for signs of these changes.

Other possible side effects of Eltrombopag:

The following side effects have been reported to be associated with treatment with eltrombopag.

Liver problems:

Eltrombopag may damage the liver and cause serious, even life threatening, illness. This is specific to patients with hepatitis C. Blood tests will be done to check your liver before you start taking eltrombopag and during treatment. Your doctor will order the blood tests and any other tests required. In some cases Eltrombopag treatment may need to be stopped. Tell your doctor right away if you notice any of these signs and symptoms of liver problems:

- yellowing of the skin or the whites of the eyes (jaundice)
- unusual darkening of the urine
- unusual tiredness
- right upper stomach area pain

Bleeding after you stop treatment:

When you stop taking eltrombopag, your blood platelet count may temporarily drop back down to what it was before starting eltrombopag or lower. These effects are most likely to happen within 4 weeks after stopping. The lower platelet counts may increase the risk of bleeding. Tell your doctor or pharmacist if you develop any bruising or bleeding symptoms after stopping eltrombopag.

High platelet counts with a higher chance for blood clots:

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You could have a higher chance of getting a blood clot if your platelet count is too high during treatment with eltrombopag, but blood clots can occur with normal or even low platelet counts. Blood clots are more common in adults who have other risks for developing blood clots. The Study Doctor will check the blood platelet counts, and change the dose or stop eltrombopag if the platelet counts get too high. Tell your doctor right away if you have signs and symptoms of a blood clot in the leg, such as swelling or pain/tenderness of one leg.

Cataracts:

In animal studies, it was found that high doses of eltrombopag caused the development of cataracts (a clouding of the lens in the eyes). Following studies on patients with immune thrombocytopenia did not confirm this finding. Regardless, you will be checked for cataracts at baseline and during the study, and a visit to a doctor specializing in cataracts will be scheduled if you are determined to be at higher risk of developing cataracts.

Contraception and pregnancy-Female Subjects

If you are pregnant or nursing a child you cannot participate in this research study. You must confirm, to the best of your knowledge that you are not now pregnant and do not intend to become pregnant during the research study. You will take a pregnancy test before the research begins. The results of the pregnancy test are confidential and will be given to you by one of the study nurses or doctors in private.

There are no adequate and well-controlled studies of eltrombopag in pregnant women. The effect of eltrombopag on human pregnancy is unknown. While you are on study and for 7 days after the last dose of study treatment it is important that you use a highly effective form of birth control if you are sexually active and can become pregnant.

Examples of highly effective birth control methods are:

- Total abstinence (no sexual relations), when this is in line with your preferred and usual lifestyle. Periodic abstinence methods are not acceptable! Some terms used to describe periodic abstinence methods are: calendar, ovulation, symptothermal, post-ovulation. Please note that the withdrawal method is also not acceptable.

- Female sterilization, when you have already been surgically sterilized prior to the research study by surgical removal of both ovaries (woman's reproductive system that stores and releases eggs for fertilization and produces female sex hormones), total hysterectomy (surgical removal of the uterus and cervix), or tubal ligation (getting your "tubes tied") at least 6 weeks before taking study treatment.

- Your male partner has already been sterilized and has the appropriate documentation. Your sterilized male partner should be your sole partner.

- 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

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hormone contraception (in case of oral contraception you should have been using the same pill on a stable dose for a minimum of 3 months before taking study treatment).

Please discuss with the Study Doctor the most appropriate birth control method that also respects your cultural and religious preferences. If you become pregnant or suspect you are pregnant (for example, because of a late menstrual period) during study treatment or within 7 days after completing study treatment, you must inform the Study Doctor immediately, and you have to stop ongoing study treatment immediately. You will not be allowed to continue study treatment if you are pregnant. The Study Doctor will medically follow your pregnancy until delivery to monitor safety.

Contraception and Pregnancy- Male Subjects

The effects of the study drug on sperm are unknown. In addition, it is unknown if participation in this research could result in harm to a fetus. You should not father a baby while taking part in this research and for the period of 7 days following stopping of study treatment. If you have a female partner who is able to become pregnant, one or both of you must use some form of highly effective birth control. During the research, if your partner becomes pregnant, or if there is a chance that she is pregnant, you should contact the Study Doctor immediately so that we may provide medical assistance and counseling.

PROCEDURE RISKS:

Blood Draw: Drawing blood causes discomfort. A bruise may appear for a few days at the spot where the needle was inserted. There is a slight chance of infection. This is very unlikely. There is also a small risk of dizziness and fainting with blood draws. These risks are minimized by the use of trained personnel to draw your blood.

Loss of Confidentiality:

How will my privacy be protected?

We will not give information that identifies you to anyone without your permission, except as required by law. This project takes many steps to protect the privacy of people who take part. Research records are separate from medical records. We will not place any information from this project in your medical records.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Representatives of Baylor College of Medicine and Texas Children's Hospital
- Novartis and its authorized agents

- Agents of the Food and Drug Administration (FDA) and other government agencies involved in keeping research safe for people.
- Boston Children's Hospital- Data Coordinating Center
- Data Safety Monitoring Board
- The Institutional Review Board

Potential Benefits

The benefits of participating in this study may be: improvement to your ITP, and increasing the knowledge and understanding of ITP and treatment. However, you may receive no benefit from participating.

Alternatives

You may choose to not participate in this study.

Subject Withdrawal from a Study

Taking part in research is always a choice. If you decide to take part in this study, you can change your mind at any time. Please tell the Study Doctor or study staff if you decide to temporarily or permanently stop taking your study medication. You will be asked to return to the study site as soon as possible for a check-up.

If you decide to participate in the optional banking sub-study, and decide later that you would no longer like to participate in this study, we will destroy any leftover samples. We will not be able to withdraw your samples from studies that have already begun since we cannot get the samples back once they have been shared with other researchers. If you change your mind, and would like to withdraw from the study, we ask that you inform the research team using the contact information provided above.

Investigator Withdrawal of Subject from a Study

The investigator or sponsor may decide to stop you from taking part in this study at any time. You could be removed from the study for reasons related only to you (for example, if you move to another city, if you do not take your study medication, or if you have a serious reaction to your study medication) or because the entire study is stopped. The sponsor, investigator, drug supplier, Food and Drug Administration, or Institutional Review Board may stop the study at any time.

Subject Costs and Payments

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs if you are

receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer.

If you are randomized to one of the standard of care therapies, you or your insurance will be responsible for the cost of the medication. If you are randomized to receive eltrombopag, Novartis will provide eltrombopag and the administration of eltrombopag at no cost to you.

In return for your time, effort and travel expenses, you will be paid for taking part in this study. We will give you a prepaid debit card worth $25 after each on-site study visit. We will give you separate instructions on how to use the debit card.

Research Related Injury

It is important that you tell your study doctor, Dr. XXX, or one of her colleagues, if you feel that you have been injured as a result of taking part in this study. You can tell the doctor in person or call her at (XXX) XXX-XXXX.

> **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to your insurer just like any other medical costs, or covered by the University of California depending on a number of factors. The University, Baylor College of Medicine, and Novartis do not normally provide any other form of compensation for injury.

CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

OPTIONAL BANKING SUB-STUDY

If you decide to participate, the study team will collect an additional 2 ½ teaspoons of blood during your screening visit, week 12 visit, and end of study visit for future research. If in the event of sample processing failure, the study team may re-collect a sample during a later study visit.

Blood will be stored for future use in a biobank. A biobank collects, stores, and distributes biological samples and health information.

The purpose of this collection is to make your samples available for use in research for studies related to ITP and related diseases after this current study is completed. Biobanks are especially useful to learn about diseases, possible treatments, including the role that specific genes play in human diseases.

The samples will be stored indefinitely at Texas Children's Hospital.

One of the methods researchers might use to study your samples is called whole exome or genome sequencing for analyzing your DNA and RNA expression studies. This allows them to look at some

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A PHASE 3 STUDY OF ELTROMBOPAG VS. STANDARD FIRST-LINE MANAGEMENT FOR NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA (ITP) IN CHILDREN

or all of your genetic code. Researchers may also use other methods to study your samples as they are developed. Studying genes along with health information will help us to better understand what causes certain diseases. It may also help us to understand how different patients respond to treatment. This knowledge could help us to develop new treatments.

"DNA" is short for deoxyribonucleic acid. DNA stores information in the form of a code. This is the code that you inherit from your parents and that you pass on to your children. Parts of DNA that have complete messages are known as "genes." Genes give the instructions for building the proteins that make our bodies work.

"RNA" is short for ribonucleic acid. RNA delivers DNA's genetic code to the part of a cell that makes proteins. RNA also helps control which genes are turned on or off at one point in time.

The goal of DNA and RNA studies are to look for genetic connections which may explain how to identify, prevent, and treat health problems. For example, the data from these studies may be use to find out:

- Who is more likely to develop a certain illness, such as asthma, cancer, or diabetes, or a condition like high blood pressure or obesity;
- What genes affect the progress of a certain disease or condition; and
- What genes may affect treatments which now may or may not work in certain people.

Genomic research will not directly benefit you, but could lead to a greater understanding of the interaction between genes and health. This knowledge could help others in the future.

Your samples may also be analyzed for certain markers and how they correlate to treatment or related diseases.

We will remove your name and any other information that could directly identify you from your materials. We will replace this information with a unique study code. We will keep a master list that links your study code to your materials. Only certain study staff can access this master list. We will keep health information and research data on secure computers. These computers have many levels of protection.

Your samples will be stored for future use. Any future research performed on your samples will not be allowed unless proof of Institutional Review Board (IRB) approval is obtained to ensure that any future research is conducted ethically, and the rights and safety of study subjects are protected. If the study is approved, we might give a part of your sample and information to the researchers.

Any data or samples that are sent to other researchers will contain only a unique identifying number; they will NOT contain personal identifiers such as your name or address. Data and samples will be kept indefinitely, allowing researchers in the future to ask new questions about blood diseases and treatment.

You should not expect to get personal results from research done through the biobank. Researchers will study samples and information from many people; it will take many years before they know if the results have any meaning.

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You can revoke the use of your samples for future use at any time by notifying Dr. XXX in writing at XXX. Any data or information collected prior to you revoking your samples will not be destroyed; however, no further information will be collected.

WHO WILL HAVE ACCESS TO MY GENETIC INFORMATION?

Researchers can do more powerful studies when they share with each other the information they get from studying human samples. They share this information with each other by putting it into scientific databases. These databases store information from many studies conducted in many different places. Researchers can then study the combined information to learn even more about health and many different diseases.

There are different kinds of databases; some are publicly accessible and some are restricted. Anyone on the Internet can access publicly accessible databases. Only researchers who apply and are approved can access restricted databases. There are many restricted databases; some are maintained by BCM, some are maintained by the federal government, and some are maintained by private companies. Some of your genetic and health information could be placed into one or more of these publicly accessible or restricted databases.

Your name and other information that could directly identify you (such as address or social security number) will not be placed into any scientific database. However, because your genetic information is unique to you, there is a chance that someone could trace the information back to you or your close biological relatives. The risk of this happening is very small, but may grow in the future.

Researchers will always have a duty to protect your privacy and to keep your information confidential.

Clinically Relevant Research Results

The results generated from this research study are not expected to have any clinical relevance to you.

Sharing and Future Research Studies with Identifiable Private Information

Information that identifies you may be removed from your identifiable private information collected as part of this research, and after such removal, your information may be used for future research studies or distributed to another investigator for future research studies without additional consent/authorization from you.

Sharing and Future Research Studies with Identifiable Biospecimens

Information that identifies you may be removed from your identifiable biospecimens collected as part of this research, and after such removal, your biospecimens may be used for future research studies or distributed to another investigator for future research studies without additional consent/authorization from you.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

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Genome Sequencing Potential

Your identifiable biospecimens(s) will be or may be sequenced in whole or in part so that your genetic information can be compared to others' genetic information.

What are the potential privacy risks?

We will take many steps to protect your privacy, but because your DNA/RNA is unique to you, it is possible but unlikely that someone could trace it back to you. There is also a risk that someone could get access to the data we have stored about you. If those data suggested something serious about your health, it could be misused. For example, it could be used to make it harder for you to get or keep a job or insurance. There are laws against this kind of misuse, but they may not give full protection. There may also be other unforeseen privacy risks.

Your privacy and the confidentiality of your data are very important to us; we will make every effort to protect them.

Researchers who study your sample and information will not know who you are. We will give them only barcode numbers; we will not give them any information that directly identifies you. The researchers must sign an agreement that they will not try to find out who you are. There are laws that protect against unauthorized access to your information. There is also a Federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

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Please read the sentence below and think about your choice. After reading the sentence, check the line next to “Yes” or “No” and initial the corresponding line to indicate your answer.

I may have additional samples of blood taken for future research during the screening visit, week 12 visit, and end of study visit. My samples may be stored and used for future research, including genetic, and results of this research may be released into separate databases.

Yes:_____Initials:_____

No:_____Initials:_____

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form and the Experimental Subjects Bill of Rights to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The study investigator, Dr. XXX, and/or someone she appoints in her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff at XXX-XXX-XXXX during the day and after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is XXX-XXX-XXXX. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

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ASSENT FOR CHILDREN 7-12 YEARS OLD

I have explained the study to _____(print name of child here) in language he/she can understand, and the child has agreed to be in the study.

_____ _____

Signature of Person Conducting Assent Discussion Date

_____

Name of Person Conducting Assent Discussion (print)

CONSENT

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form and the Experimental Subjects Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in this study, you should sign below.

_____ _____

Subject's Signature for Consent Date

_____ _____

Investigator or Designee Obtaining Consent Date

_____ _____

Witness (if applicable) Date

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A PHASE 3 STUDY OF ELTROMBOPAG VS. STANDARD FIRST-LINE MANAGEMENT FOR NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA (ITP) IN CHILDREN

_____ _____

Translator (if applicable) Date

The person being considered for this study is unable to consent for himself/herself because he/she is a minor. By signing below, you are giving your permission for your child to be included in this study.

_____ _____

Legally Authorized Representative (Parent or Guardian) Date

BMJ Open

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

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Primary Subject Heading:	Haematology (incl blood transfusion)
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Keywords:	HAEMATOLOGY, PAEDIATRICS, Clinical trials < THERAPEUTICS

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Title: A Phase 3 Randomized Trial of Eltrombopag vs. Standard First-Line Pharmacologic Management for Newly Diagnosed Immune Thrombocytopenia (ITP) in Children: Study Protocol

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ABSTRACT

Introduction: Immune thrombocytopenia (ITP) is an acquired disorder of low platelets and risk of bleeding. Although many children can be observed until spontaneous remission, others require treatment due to bleeding or impact on health-related quality of life. Standard first line therapies for those who need intervention include corticosteroids, intravenous immunoglobulin, and anti-D globulin, though response to these agents may be only transient. Eltrombopag is an oral thrombopoietin receptor agonist approved for children with chronic ITP who have had an insufficient response to corticosteroids, IVIg, or splenectomy. This protocol paper describes an ongoing open-label, randomized trial comparing eltrombopag to standard first-line management in children with newly diagnosed ITP.

Methods and Analysis: Randomized treatment assignment is 2:1 for eltrombopag versus standard first-line management and is stratified by age and by prior treatment. The primary endpoint of the study is platelet response, defined as ≥3 of 4 weeks with platelets >50 $x10^9$/L during weeks 6-12 of therapy. Secondary outcomes include number of rescue therapies needed during the first 12 weeks, proportion of patients who do not need ongoing treatment at 12 weeks and 6 months, proportion of patients with a treatment response at one year, and number of second-line therapies used in weeks 13-52, as well as changes in regulatory T cells, iron studies, bleeding, health-related quality of life, and fatigue. A planned sample size of up to 162 randomized pediatric patients will be enrolled over 2 years at 20 sites.

Ethics and Dissemination: The study has been approved by the centralized Baylor University Institutional Review Board. The results are expected to be published in 2023.

Trial Registration Number: NCT03939637

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a multicenter randomized controlled trial that will provide valuable information about the efficacy of eltrombopag for newly diagnosed children with ITP.
- The primary endpoint is a well-defined definition of platelet response similar to that used in other ITP trials, while the secondary endpoints include important assessments of patient-related outcomes, including bleeding scores, fatigue, and health-related quality of life, all of which may be more significant to patients than a platelet count alone.
- Correlative biology studies will allow exploration of biologic differences between patients with ITP who are responders and non-responders, as well as biologic mechanisms related to outcomes of specific interventions and the natural history of the disease in children receiving treatment.
- A limitation of this study is that patients who are managed with a close observation approach are not included or compared to those who require treatment.
- An additional limitation of this study is the lack of a uniform definition of “requiring treatment,” which is left to the discretion of individual investigators; however, this allows for a “real-world” approach and ultimately the potential for broader applicability of trial results to clinical practice.

Introduction

Immune thrombocytopenia (ITP) is the most common autoimmune cytopenia in children, causing an often severely reduced platelet count, variable bleeding symptoms, and reduction in health-related quality of life (HRQoL) related to activity restrictions, frequent medical visits and interventions, anxiety from risk of bleeding, and fatigue.[1-3] In an era when the fields of hematology and immunology are advancing rapidly with the development of drugs targeted to underlying disease mechanisms, the available treatments for newly diagnosed ITP remain non-specific, with no novel or targeted therapies introduced in the past 30 years.[4]

Many children with ITP can be closely observed without treatment until they experience spontaneous remission.[5] Others require pharmacologic treatment for moderate bleeding or HRQoL limitations. While many therapies exist for treatment of chronic ITP, the treatment of newly diagnosed ITP is generally limited to close observation and three first-line medications: corticosteroids, intravenous immunoglobulin (IVIg), and anti-D globulin. Each of these agents has either undesirable side effects, challenging logistics of administration, or both (Table 1).

Table 1 Administration, efficacy, and potential side effects of standard therapies

	Dosing	Method of administration	Efficacy[6] (platelet[a])	Short-term Potential Side Effects
Prednisone	4 mg/kg/d x 4-7 d[b]	Oral	~70-80%	Mood changes, hyperglycemia, hypertension, weight gain
Intravenous Immunoglobulin	0.8-1 g/kg	IV	~70-80%	Headache, flu-like symptoms, allergic reaction, neutropenia, hemolytic anemia Black Box: Thrombosis, renal failure
Anti-D Immunoglobulin	50-75 µg/kg	IV	~70-80%	Anemia, fevers, nausea Black Box: intravascular hemolysis, DIC, renal failure

Abbreviations: IV, intravenous; DIC, disseminated intravascular coagulopathy
[a]Definition of platelet response varies depending on study
[b]A number of steroid regimens are used

Furthermore, they act only transiently to raise the platelet count, and in children with ongoing ITP, the platelet count will decrease days to weeks after the medication is given.

Eltrombopag is an oral, small-molecule, nonpeptide thrombopoietin receptor agonist (TPO-RA). It initiates thrombopoietin receptor signaling by interacting with the transmembrane domain of the receptor, inducing proliferation and differentiation of cells in the megakaryocytic lineage. Eltrombopag is currently approved for children ages ≥1 year with chronic ITP who have had an insufficient response to corticosteroids, IVIg, or splenectomy. Safety and efficacy were established in the PETIT[7] and PETIT2[8] trials. Forty percent of patients who received eltrombopag vs 3% of patients randomized to placebo in the PETIT2 trial achieved the primary outcome, ≥ 6 of 8 non-consecutive weeks with platelets >50 x10^9/L during weeks 5-12 of therapy (odds ratio 18.0, 95% CI, 2.3-140.9; p=0.0004).[8] The drug was approved by the US FDA in 2015[9] and the European Medicines Agency in 2016 for children with chronic ITP. The majority

of the literature to date evaluating the use of eltrombopag in the pediatric population has been in the setting of chronic ITP (Table 2),

Table 2 Published studies of eltrombopag in pediatric patients with ITP

Paper[a]	Type of Study	Patient population	Results
Giordano P et al 2020[10]	Retrospective multicenter study	386 children with chronic ITP enrolled retrospectively at 17 sites	Prevalence of eltrombopag use was 19% in patients with chronic ITP
Koca Yozgat A et al 2020[11]	Retrospective multicenter study	105 children with chronic or acute refractory ITP treated with epag	Overall response rate was 74%. 27.6% developed iron deficiency or iron deficiency anemia.
Cheng X et al 2019[12]	Single-center observational study	20 patients with severe chronic ITP treated with epag	The durable response rate was 70% (14/20)
Grace RF et al 2019[13]	Multi-center prospective observational study	120 children with ITP starting 2nd-line therapies. 20 patients treated with epag.	Increased platelet counts and HRQoL. Decrease in skin, but not non-skin, bleeding symptoms in patients on epag.
Suntsova E et al 2019[14]	Single-center retrospective analysis	23 patients with chronic ITP who failed first TPO-RA. 10 patients switched to epag.	Response rates after switching TPO-RAs were 80% (romi→ epag) and 62% (epag → romi)
Tumaini MJ et al 2019[15]	Meta-analysis	Five randomized controlled trials with total of 261 pediatric patients. 159 treated with epag.	TPO-RAs superior to placebo
Grainger JD et al 2019[16]	Multi-center RCT	82 patients with ITP >6 months who had received at least one prior treatment	Epag did not impact HRQoL as assessed by KIT
Grace RF et al 2018[17]	Multi-center prospective observational study	120 children with ITP starting 2nd-line therapies. 20 patients treated with eltrombopag.	Oral agents, including eltrombopag, were chosen for ease of administration and expected adherence (P < .001)
Leblebisatan G et al 2018[18]	Single-arm study	19 patients with chronic ITP	58% of patients responded with either increased platelet counts or decreased bleeding
Zhang J et al 2018[19]	Indirect-comparison meta-analysis	Five randomized controlled trials with total of 261 pediatric patients. 159 treated with epag.	Epag & romi similar in efficacy and safety, but decreased bleeding w/ epag.
Guo JC et al 2018[20]	Meta-analysis	Seven randomized controlled trials with total of 345 pediatric patients. 159 treated with epag.	TPO-RAs superior to placebo
Zhang J et al 2017[21]	Systematic review	Five randomized controlled trials with total of 261 pediatric patients. 159 treated with epag.	Overall response & durable platelet response increased in TPO-RAs vs placebo
Lambert MP et al 2017[22]	Retrospective chart review	12 patients with ITP treated with eltrombopag	8/11 patients developed iron deficiency during treatment with epag
Neunert C et al 2016[23]	Multicenter retrospective study	79 patients with ITP treated with TPO-RAs	89% achieved platelet count >50 x1 (no difference between epag or romi); 40% achieved stable response

Grainger JD et al 2015[8]	Multicenter RCT	92 patients with chronic ITP and platelets <30k	40% (vs 3% placebo) achieved platelet count >50 for 6/8 weeks
Bussel JB et al 2015[7]	Multicenter RCT	82 patients with ITP >6 months who had received at least one prior treatment	62% (vs 32% placebo) achieved platelet count >50 x1
Ramaswamy K et al 2014[24]	Multicenter retrospective study	33 pediatric patients with ITP who had received at least one prior treatment; 12 received eltrombopag	75% achieved platelet counts >/=50k and >/=20k above baseline for 2 consecutive weeks

Abbreviations: ITP, immune thrombocytopenia; epag, eltrombopag; HRQoL, health-related quality of life; TPO-RA, thrombopoietin receptor agonist; romi, romiplostim; RCT, randomized controlled trial; KIT, Kids ITP Tool
[a]Search was performed in PubMed using terms "eltrombopag" and either "pediatric" or "children." Clinical trials and meta-analyses were included. Papers were excluded if the patient population was anything other than pediatric patients with immune thrombocytopenia, or if they included fewer than 10 patients treated with eltrombopag.

although multicenter retrospective studies document that pediatric hematologists are using TPO-RAs off-label in some cases of newly diagnosed ITP.[11,23] Eltrombopag has been studied prospectively for adults with newly diagnosed ITP 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.[25] In a second study, 76% of steroid-nonresponsive patients had a durable response to eltrombopag after 3 months of therapy.[26] TPO-RAs may, therefore, be a safe and efficacious first-line therapy for newly diagnosed ITP patients who require treatment.

The issue of long-term expense of a drug that costs thousands of dollars monthly and requires ongoing use has been both a practical and conceptual hurdle for use of TPO-RAs in children since their launch, but that thinking has evolved to consider that early in the course of illness the majority of cases of pediatric ITP will eventually resolve. While standard therapies like steroids, or when appropriate, observation only, are much less expensive than TPO-RAs, a few courses of IVIg may rival the cost of a short course of eltrombopag, as well as require IVs and inpatient stays with associated complications that yield additional expense.

Eltrombopag has the potential to change the landscape of newly diagnosed ITP for children. The earliest randomized trial in children with newly diagnosed ITP took place in 1984 comparing prednisone to observation.[27] Since that time only a handful of additional randomized trials have been conducted in this population, with the majority comparing IVIg to Anti-D immunoglobulin.[28-35] The most recent randomized trial, conducted in 2018, was unable to show any long-term benefit to IVIg compared to observation.[36] No trial to date has investigated a novel agent for this patient population in a randomized manner. As an oral outpatient therapy which can be continued until ITP has remitted, eltrombopag has clear benefits over the transiently effective current first-line options. In addition, eltrombopag may have fewer side effects than standard therapies. However, the early response rate in the newly diagnosed setting is not known. We therefore describe here our design of an ongoing randomized trial investigating the up-front use of eltrombopag in pediatric patients with ITP: PINES (*P*ediatric *I*TP

*N*ewly diagnosed patients *E*ltrombopag vs *S*tandard therapy) Study, NCT03939637. The trial was FDA-approved in January 2019, and the first site opened to enrollment in May 2019. With this publication we aim to provide researchers and funding agencies with early-stage information about this novel clinical trial which contributes to the gap in randomized trials for patients with pediatric newly diagnosed ITP. Ultimately, we hope that this will allow for transparency and collaboration with other research consortiums, as well as dissemination of knowledge about the study to patients not treated at PINES sites, which may encourage them to explore engagement in research protocols with their physicians.

Methods and Analysis

Study Objectives and Hypothesis

The primary objective of the trial is 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 pharmacologic treatment. The primary endpoint, platelet response, is defined as ≥ 3 of 4 non-consecutive weeks with platelets >50 x10^9/L during weeks 6-12 of therapy. We hypothesize that children with newly diagnosed ITP treated with eltrombopag will have an increased likelihood of a sustained platelet response as compared with those treated with standard therapy. The endpoints and statistical analysis plans of the primary and secondary objectives are listed in Table 3.

Table 3 Protocol endpoints and statistical analysis plans

Outcome (Endpoint)	**Statistical Plan**
Efficacy	
1. Platelet response, defined as ≥3 of 4 non-consecutive weeks with platelets >50 x10^9/L during weeks 6-12 of therapy	Group sequential analyses, with three "looks" at the data: two interim analyses (for efficacy and futility), and a final analysis (for efficacy), using a two-sided z-test with alpha=0.05 (i.e., a one-sided z-test with alpha=0.025), to compare the two arms in terms of the proportion of patients who have a platelet response
2. Cumulative number of rescue therapies needed during the first 12 weeks of treatment	Student's t-test will be used to compare the two treatment arms
3. Platelet response during weeks 6-12 of therapy in patients who required a rescue treatment during weeks 1-2 of study	Observed proportion and 95% confidence interval will be calculated
4. No further need for treatment after 12 weeks and 6 months of study	Chi-squared test will be used to compare the two treatment arms
5. Treatment response[a] at one year of study	Chi-squared test will be used to compare the two treatment arms
6. Number of 2nd-line therapies used in weeks 13-52	Student's t-test will be used to compare the two treatment arms
Safety	

7. Abnormal liver function tests[b] (LFTs) in patients with newly diagnosed ITP treated with eltrombopag.	Frequency and proportion (with 95% confidence interval) of patients with abnormal LFTs will be calculated
8. Incidence of adverse events and serious adverse events	Adverse events will be coded by MedDRA classification term. Adverse events and serious adverse events will be tabulated by treatment group, including 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.
9. Iron indices[c] at 12 weeks, 6 months, and 1 year	Two-sided Student's t-test will be used to compare iron indices at 12 weeks, 6 months, and 1 year between the two arms
Patient-Related Outcomes Assessment	
10. 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	Chi-squared test will be used to compare the two treatment arms
11. 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)	KIT scores will be calculated per the methods described in Klaassen et al.[37] Spaghetti plots will be used to visualize the KIT scores over time per patient by treatment arm. Two-sided Student's t-test will be used to compare the percentage change from baseline in KIT overall score at 1 week, 4 weeks, 12 weeks, and 1 year between the two arms.
12. 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)	Fatigue scores will be calculated per the methods described in Hockenberry et al.[38] Spaghetti plots will be used to visualize the scores over time per patient by treatment arm. A two-sided Student's t-test will be used to compare the percentage change from baseline at 1 week, 4 weeks, 12 weeks, and 1 year between the two arms.
Biology	
13. Change in percentage of $CD4^+25^+Foxp3^+$ regulatory T cells (Tregs) as a proportion of CD4 cells a) from baseline to 12 weeks; and b) from baseline to 1 year	Student's t-test will be used to compare the two treatment arms

Abbreviations: LFTs, liver function tests; MedDRA, Medical Dictionary for Regulatory Activities; WHO, World Health Organization

[a]Complete response (CR) is defined as a 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 (patient may have received a second-line therapy, excluding rituximab or splenectomy), disease stability at 1 year is defined as platelets >/=50x10^9/L but <150 x10^9/L >/= 3 months after discontinuing most recent platelet active medication.
[b]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)
[c]Iron, TIBC, transferrin saturation, ferritin, MCV, and hemoglobin

In addition, exploratory objectives will include comparisons by treatment arm of other platelet-related endpoints, patient-related outcomes, and cost of therapy. By obtaining data on patient-related outcomes such as health-related quality of life we will be able to assess the potential impact of differences in drug delivery such as dietary restrictions, need for daily medication administration, and potential impact of infusion therapy.

Overview of Study Design and Oversight

The PINES Study is a national, multicenter, randomized, open-label, standard therapy-controlled trial. The study was designed to align with usual care for children with newly diagnosed ITP (Figure 1). The screening period occurs from the time of diagnosis up until 3 months from the first low platelet count. Randomization and initiation of treatment occurs at the baseline visit, and follow up visits occur at week 1, and 1, 3, 6, and 12 months from enrollment. Biweekly platelet counts are obtained from baseline through week 12. Patients will be followed for a total of 1 year from enrollment. Planned study visits and assessments are outlined in Table 4.

Table 4 Outline of study assessments

	DAY 0	72H	W1	W2	W3	W4	W6	W8	W10	W12	6 MONTHS	1 YEAR
PHYSICAL EXAM	x		x			x				x	x	x
BLEEDING ASSESSMENT	x		x	x	x	x				x		x
HRQOL: KIT	x		x			x				x		x
HOCKENBERRY FATIGUE SCORE	x		x			x				x		x
PROMIS	x									x		x
GLOBAL RATE OF CHANGE			x			x				x		x
PLATELET COUNT	x	x	x	x		x	x	x	x	x	x	x
IRON STUDIES	x									x		x
TREGS	x									x		x

SAMPLES FOR BANKING (OPTIONAL)	x		x	x

Abbreviations: HRQOL, Health-Related Quality of Life; KIT, Kids ITP Tool; PROMIS, Patient-Reported Outcomes Measurement Information System; Tregs, Regulatory T cells

The study is being conducted at 20 national sites through the Pediatric ITP Consortium of North America (ICON). Participating sites are listed on clinicaltrials.gov.

The trial is designed and led by a Steering Committee that includes academic investigators from ICON and statisticians from Dana-Farber/Boston Children's Cancer and Blood Disorders Center, the coordinating center for ICON. The Steering Committee will ensure transparent management of the study, recommend and approve study modifications, and develop recommendations for publications of study results. The trial is operated under an IND held by Baylor College of Medicine, cross-filed with Novartis. Novartis is providing funding for this investigator-initiated trial and supplies the drug used on the eltrombopag arm. An independent Data Safety Monitoring Committee (DSMC) monitors patient safety and outcomes at intervals during the study and makes recommendations to the Steering Committee regarding ongoing trial conduct. The
protocol was reviewed and approved by regulatory authorities, a central institutional review board at Baylor College of Medicine, and institutional review boards at individual institutions. The study is registered at clinicaltrials.gov (NCT03939637). This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines[39] (see SPIRIT checklist in Supplementary Document 1).

Study Population, Randomization, and Stratification

The study population includes children ages 1 to <18 years with newly diagnosed ITP (<3 months from first abnormal platelet count). At time of study screening, patients must have a platelet count <30 x10^9/L and require pharmacologic treatment from the perspective of the treating clinician. A platelet count of <30 x10^9/L was selected in order to provide a real-world approach to treatment in which patients often receive treatment based not on a platelet count threshold but rather for bleeding history or secondary to disease impact on HRQoL, both of which may occur at a higher platelet count. Recognizing that there will be variation in physician practice with regards to treatment as well as heterogeneity in the reasons for treatment (bleeding, platelet count, HRQoL, etc.) we have elected to apply randomized trial design to help balance this variability between the two treatment groups. Patients who have previously received a TPO-RA are excluded. As we do not want to impede appropriate critical care management, patients with severe bleeding, defined as overall Grade 4 or 5 bleeding,[40] or bleeding requiring emergent treatment will be excluded. Patients are excluded if they have known secondary ITP (for instance due to lupus, common variable immunodeficiency, or autoimmune lymphoproliferative disorder). Additional exclusion criteria are outlined in Supplementary Table 1. All patients and/or their parents or legal guardians must sign a written informed consent and assent when applicable.

Patients who meet all of the inclusion and none of the exclusion criteria will be enrolled and randomly assigned to receive eltrombopag or standard therapy in a 2:1 ratio. Central randomization at study enrollment will occur via the online InForm system, with randomization allocation delivered only to the enrolling site study staff. Randomization will utilize blocking and will be stratified by the age of the patient (1-<6, 6-<12, and 12-<18 years) and by prior treatment status. "Upfront treatment" refers to patients within 10 days of ITP diagnosis who have not received previous pharmacologic treatment. This allows for a reasonable window from time of diagnosis to enrollment as well as for proper time to confirm the diagnosis and rule out other transient causes of thrombocytopenia. The "treatment failure" stratum is for patients who have received standard initial management (observation >10 days, IVIg, Anti-D immunoglobulin, or corticosteroids) and continue to have platelets <30 $x10^9$/L. A patient who initially responded to treatment but whose response wanes and platelets fall below 30 $x10^9$/L will be considered to have a "treatment failure."

Eltrombopag Regimen

Patients randomized to eltrombopag will start at a dose based on age per the manufacturer label dosing for drug initiation. Children ages 1-5 years will begin 25 mg once daily, and children ≥6 years will begin at a dose of 50 mg once daily (25 mg once daily for patients of East-Asian ethnicity). Patients will receive education regarding proper administration and dietary restrictions, and medication compliance will be queried at each study visit. Eltrombopag dose adjustments are made in response to platelet counts, with a goal of maintaining a platelet count 50-200 $x10^9$/L, with a maximum dose of 75 mg once daily (Supplementary Table 2). A modification from the dosing label was made for maintenance dose adjustment based on investigators' clinical experience with rebound thrombocytopenia when eltrombopag is held for high platelet counts. Daily eltrombopag will be continued for 12 weeks, unless platelets do not rise $\geq$ 30 $x10^9$/L after 4 weeks at the maximum daily dose of 75 mg.

Patients randomized to the eltrombopag arm who respond will be eligible to continue the treatment throughout the 1-year duration of study participation, with guidelines given for dose adjustments during weeks 13-52 (Supplementary Table 2). 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 every 2 weeks (with investigators exercising clinical judgement with respect to wean in the context of the patient's status, including intercurrent infections). Patients who have been unable to wean off of eltrombopag by 1 year will discontinue study drug, and continuation on commercially available eltrombopag at that point is at the discretion of the investigator.

Standard Therapy Regimen

Subjects randomized to the standard therapy arm will receive one of three treatments at the discretion of the treating physician. Patients previously treated with standard management prior to study entry must be treated with a different agent than their original failed agent. For example, a patient who did not respond to steroids could receive either IVIg or anti-D if randomized to the standard treatment arm. Investigators may choose amongst the following treatment options: 1) IVIg 1 g/kg x1 dose,[41] 2) Prednisone/Prednisolone 4 mg/kg/day (Max 120

mg/day) x 4 days,[42] or 3) Anti-D immunoglobulin 75 mcg/kg x1 dose.[41] No steroids for pre-medication or adjunctive therapy may be administered with IVIg or anti-D immunoglobulin.

Efficacy Outcomes

The primary endpoint is binary, with each patient classified as either a platelet responder or a platelet non-responder. Platelet response is defined as ≥3 of 4 weeks with platelets >50 $x10^9$/L (whereby the 3 weeks are not required to be consecutive) during weeks 6-12 of therapy. The primary endpoint for this study was initially defined as ≥6 of 8 weeks platelets >50 $x10^9$/L, and was chosen in part because it is a previously defined primary endpoint in a prior ITP study.[8] The COVID-19 pandemic introduced safety and logistics concerns for the conduct of clinical research, however, particularly with respect to study assessments done for research purposes only that would require additional exposure to clinic or lab settings during shelter-in-place restrictions. The study DSMC therefore recommended a change to the primary endpoint to a clinically equivalent definition that would require fewer lab assessments as a measure to prioritize patient safety during the pandemic and in order to minimize missing data if subjects were unable to complete a study assessment due to pandemic-related safety concerns. The primary endpoint represents 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. While rescue therapies (steroids, IVIg, or anti-D globulin) are permitted during the study, patients who require a rescue medication at any time within the first 12 weeks of therapy will be categorized as a non-responder.

Secondary Outcomes

Additional response outcomes include the number of rescue therapies needed during the first 12 weeks, platelet response during weeks 6-12 of study in patients who required a rescue treatment during that time, proportion of patients who do not need ongoing treatment at 12 weeks and 6 months, proportion of patients with a treatment response at one year after study enrollment, and the number of second-line therapies (treatments other than prednisone, IVIg, and anti-D globulin thought to be active in the treatment of ITP) used in weeks 13-52. Safety analyses will examine the proportion of patients with abnormal liver function tests in patients with newly diagnosed ITP treated with eltrombopag, and the proportion of patients with adverse events and serious adverse events by treatment arm. Furthermore, we will investigate changes in iron indices (serum iron, TIBC, transferrin saturation, ferritin, MCV, and hemoglobin) given the chelation properties of eltrombopag.[11,22] Secondary analyses will also include comparison of patient-related outcomes for patients treated with eltrombopag versus those treated with standard first-line agents. This includes comparison of significant bleeding (WHO Bleeding Scale ≥2[43] or Modified Buchanan Score ≥3[40]), change in Health-Related Quality of Life (HRQoL) measured by the Kids ITP Tool[37], and fatigue as measured by the parent-proxy report of the Hockenberry Fatigue Scale-Parent (FS-P)[38].

Correlative Biology Studies

Age and duration of symptoms at diagnosis are known to be associated with resolution of ITP,[44] but 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 unknown whether the development of chronic ITP could be prevented by intervention with a TPO-RA early in a patient's course. A subset of patients with chronic ITP maintained increased platelets after discontinuation of treatment with TPO-RAs.[45-47] Because of the implication of Tregs in the pathogenesis of ITP and the potential immunomodulatory effects of TPO-RAs, early use of eltrombopag may have a positive impact on the number of patients who develop chronic disease. For this reason, we will evaluate the change in percentage of $CD4^{+}25^{+}Foxp3^{+}$ Tregs in patients treated with eltrombopag compared to those treated with standard first-line agents. Additionally, there are likely biologic factors which influence response to TPO-RAs and other therapies that are not yet understood. Identification of biomarkers of treatment response could lead to a personalized approach to therapy, targeted to an individual patient's disease biology. If consent is obtained for optional studies, baseline DNA samples and baseline and serial RNA samples will be banked for future correlative biology studies.

Exploratory Outcomes

Additional analyses will include comparison of patients treated with eltrombopag versus those treated with standard first-line agents using International Working Group platelet-specific endpoints.[48] Lastly, we plan to conduct a cost analysis of therapy between the two treatment arms, recognizing the large cost difference between some current first-line therapy agents such as corticosteroids and eltrombopag.

Sample Size and Statistical Plan

A total of up to 162 patients will be enrolled. For the primary objective, all randomized patients will be analyzed in an intent-to-treat (ITT) analysis of response rate for the primary objective. A patient is considered "non-informative" if he withdraws from protocol therapy and data submission prior to the 5-week platelet assessment. Non-informative patients will be classified as non-responders, and both informative and non-informative patients will be included in the ITT analysis. Non-informative patients could dilute our ability to detect a treatment effect; therefore, additional patients will be randomized to make up for the diluting effect. A conservatively high estimate of 9% of patients are anticipated to be non-informative. To obtain at least 147 informative randomized patients, we plan to enroll and randomize up to 15 additional patients (10 and 5 for the eltrombopag and standard treatment arms, respectively) for a total of up to 162. At an anticipated enrollment rate of 90 patients per year, the total accrual duration is expected to be 2 years, plus 1 year follow-up on the last patient, for a total study duration of 3 years.

The primary objective will be addressed by monitoring for evidence of efficacy or lack of efficacy (futility) using group sequential analyses, with three "looks" at the data (after one-third, two-thirds, and full accrual). In each analysis, a two-sided z-test will be used to compare the two arms in terms of the proportion of patients who have a platelet response. We will reject the null hypothesis if the upper (efficacy) monitoring boundary is crossed; in this case, it will be reasonable to conclude that the platelet response is significantly greater in patients treated with eltrombopag than standard first-line treatments. If the lower (futility) monitoring boundary is crossed in either of the two interim analyses, we will have significant evidence that

eltrombopag is not more efficacious than standard first-line treatments, and the trial will be stopped early for futility. The overall type 1 error is preserved at 0.05, or 0.025 in a one-sided test. The sample size of 147 informative patients will provide 81.4% power to detect an absolute difference of 25% in the proportion of patients who are platelet responders, assuming a response rate of 75% with eltrombopag and 50% with standard first-line treatments, using a two-sided z-test with alpha=0.05 (i.e., a one-sided z-test with alpha=0.025).

Discussion

ICON is a group of 50 pediatric hematology centers in the United States, Canada, and Mexico participating in collaborative research efforts dedicated to improving the understanding, treatment, and quality of life of pediatric patients with ITP. The consortium was established in 2012 and has previously completed a prospective observational trial of patients starting second-line therapies for ITP. PINES is the Consortium's first prospective investigational trial for newly diagnosed ITP, initiated in response to a need for alternative up-front treatment options. While many children with ITP can be safely observed while waiting for spontaneous resolution of their disease, for those who require intervention, treatment options are limited and may only transiently increase the platelet count without achieving a sustained response. An optimal therapy for patients who do warrant treatment for repeated bleeding episodes or poor quality of life would be an easy-to-administer medication with a tolerable side-effect profile that produces a sustained response until resolution.

The primary endpoint of PINES, ≥ 3 of 4 weeks with platelets >50 $x10^9$/L during weeks 6-12 of therapy, is a clinically relevant measure of platelet response suggesting sustained response to therapy. It also parallels a previously established endpoint for eltrombopag in pediatric ITP used in the PETIT2 trial.[8] With a goal of 162 randomized patients, the study is powered to detect an improvement of 25% in the proportion of patients who are platelet responders in the eltrombopag arm compared to standard first-line treatments. Secondary platelet endpoints include treatment response at 1 year, with response definitions based on platelet count and time since most recent platelet active medication. Additional platelet-specific endpoints are included in exploratory objectives with International Working Group defined endpoints with a goal of being able to compare across studies.[48] Another strength of this study is the collection of patient-related outcomes data. The 2019 ASH guidelines stressed that for prioritized outcomes such as bleeding and HRQoL there is a paucity of necessary data to guide clinical practice.[5] It is critical in any contemporary interventional ITP study to assess bleeding and HRQoL in addition to platelet response, as bleeding severity, platelet count, and HRQoL scores are uncorrelated independent outcomes, each of which may impact treatment decisions.[49]

The experimental design of the trial is intended to allow for maximum clinical discretion on the part of the treating investigator, with a "real-world" approach to decision-making. Patients are eligible to enroll if they require pharmacologic treatment (for whatever reason) in the opinion of the treating hematologist, as long as they do not have severe bleeding that requires emergent intervention or concomitant therapy to achieve a rapid rise in platelet count. If the patient is randomized to the standard therapy arm, the investigator may choose among three

standard treatments at protocol-specified doses. Rescue medications are allowed throughout the study, and after week 12 of the study, therapy in the standard arm or for non-responders in the eltrombopag arm is at the discretion of the investigator.

Because it is anticipated that the majority of patients will have remission of their ITP before the end of the 1-year duration of study participation, protocol-prescribed adjustments of eltrombopag during weeks 13-52 of the study lead to more aggressive weaning than would result from the manufacturer recommendations for dose adjustment in the setting of chronic ITP.

In general, pediatric patients with newly diagnosed ITP have very favorable outcomes, and as such we are loath to expose these patients to any undue risk. Because eltrombopag already has an established safety profile in the pediatric population and is an FDA-approved treatment for pediatric patients with chronic ITP, we are reassured that this is a safe therapy for patients with newly diagnosed ITP. However, because safety is paramount, we have chosen to be particularly conservative with exclusion criteria, and we have chosen stringent cut-offs of transaminases and bilirubin. Iron deficiency has been reported in two retrospective series of patients treated with eltrombopag,[11,22] and we will be able to follow this larger cohort of patients prospectively to better evaluate the incidence of this potential side effect.

A prospective randomized trial presents a unique opportunity to explore biologic differences in disease between treatment responders and non-responders as well as biologic outcomes of specific interventions. Tregs play a role in the pathogenesis of ITP, but it is not clear what impact the interactions of medical therapies with Tregs have on response, and following these over time may add to our understanding of the underlying biology of ITP development and resolution. Finally, through banking DNA and RNA samples for future studies, we anticipate possible identification of genes associated with response to therapies or RNA expression changes that correlate with disease activity that may improve our understanding of how to optimally treat pediatric patients with ITP.

We describe an in-process randomized clinical trial comparing eltrombopag to standard therapy in the treatment of pediatric patients with newly diagnosed ITP. This is the first pediatric trial investigating the use of a thrombopoietin receptor agonist for patients with newly diagnosed ITP and has the potential to transform our approach to treatment in this patient population. While the primary outcome of this study is sustained platelet response during weeks 6-12 of treatment, the clinical implications surpass platelet count alone. The possibility of a limited course of a TPO-RA in the newly diagnosed phase that could bridge the time to spontaneous resolution of disease may diminish bleeding episodes and improve quality of life for these patients.

Patient and public involvement: Patients were not directly involved in the design of this study, although the consortium meets regularly with ITP patient advocacy group members and leaders, including the Platelet Disorder Support Association (PDSA), in order to understand needs and priorities of the patients. The PDSA has disseminated information about the trial to

its members via website, and results and lay summary will be provided to patient groups and the public after trial completion.

Ethics and dissemination

The study protocol, informed consent and assent forms, and surveys have been approved by the central IRB at Baylor University/Texas Children's Hospital (see Supplementary Document 2). The study protocol was approved on January 28, 2019, and this manuscript details the protocol in the latest version v4.1 approved on April 26, 2021.

Participating consortium sites have either executed a reliance agreement to rely on the central IRB or have obtained approval from their local IRBs. Data management for the study is through an InForm database managed by the Data Coordinating Center, Boston Children's Hospital. Data will be entered electronically at the participating sites. Study sites will be monitored at 6-month intervals by a team from the Data Coordinating Center, with audits to review and verify data recorded on CRFs against source documents. De-identified study information and study documents are sent via secure file transfer systems.

SAEs are reported to the central IRB and local IRBs as well as to Novartis.

The trial design and rationale has been presented in poster form at a national meeting. Following trial completion, results of the study will be submitted for peer review for publication in a scientific journal. The writing committee will consist of members of the trial steering committee, site investigators, and ICON consortium members. The full protocol and dataset will be publicly available upon request after completion and publication of planned analyses.

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EJN: Advisory boards: Genentech, NovoNordisk, Novartis; Honoraria: Octapharma; DSMB service: Bayer, ApoPharma, Acceleron, Imara; Consultancies: Pfizer, Celgene. RJK: Speaker: Takeda, Biogen Canada LMT, Octapharma, Pfizer; Consultancies: Agios, Amgen Inc., Hoffman-LaRoche LTD, Takeda, NovoNordisk Canada Inc. CMB: Research funding: Novartis. WBL: DSMB member: ArQule, Inc, Jubliant Draximage, Inc. CN: Research funding: PDSA. The remaining authors have no competing interests.

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Figure 1 Schematic diagram of study entry, randomization, primary endpoint evaluation, and follow-up

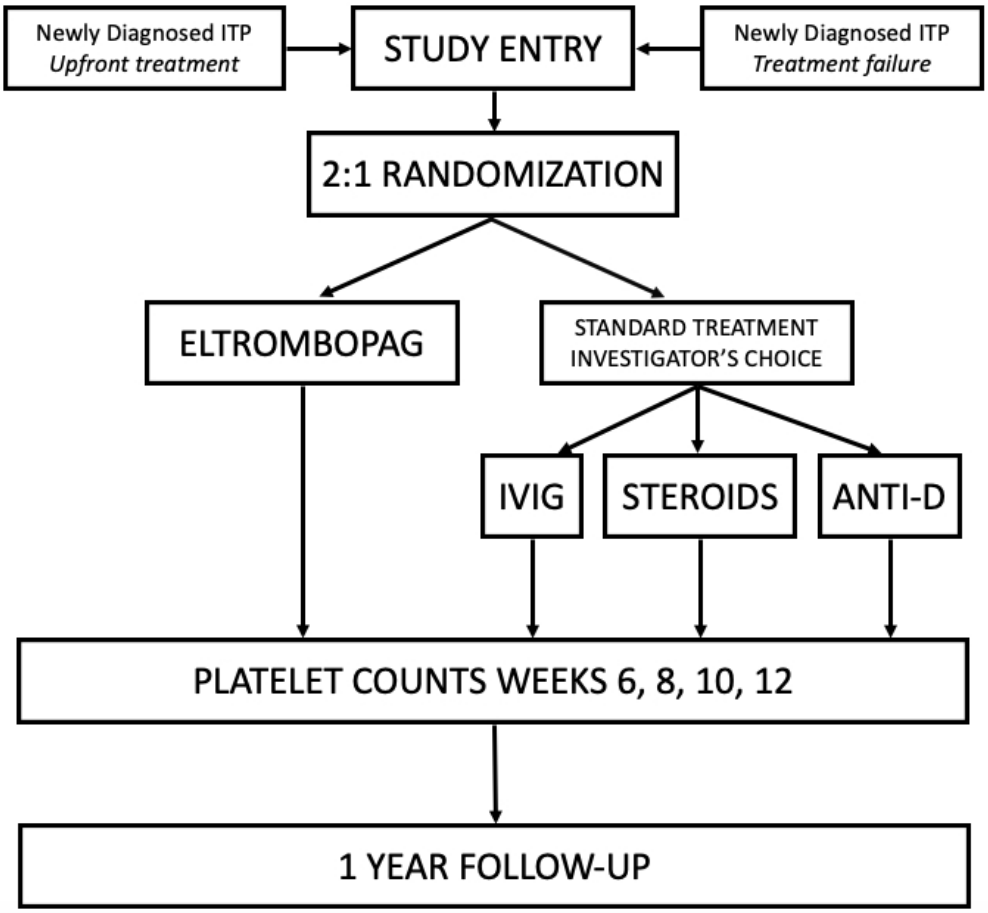

Figure 1 Schematic diagram of study entry, randomization, primary endpoint evaluation, and follow-up

239x220mm (72 x 72 DPI)

Supplementary Table 1 Exclusion criteria by system

Cardiac
Prolonged QTc, with corrected QTc >450 msec
Clinically significant cardio-vascular disease (e.g., uncontrolled hypertension, history of labile hypertension)
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[a]
Gynecologic
Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.[b]
Hematology
Evans Syndrome: positive direct Coombs with evidence of active hemolysis (elevated LDH or reticulocyte count not attributable to recent treatment or bleeding)
Anticoagulant or anti-platelet agents
Thrombophilic risk factors[c]
Hepatic
AST or ALT > 2 x upper limit of normal (ULN) Total bilirubin > 1.5 x ULN Liver cirrhosis (as determined by the investigator)
Immunology
Known immediate or delayed hypersensitivity reaction to eltrombopag or its excipient
Infectious
HIV (or history of positivity) Hepatitis C (screening not required if no clinical suspicion) Active or uncontrolled infections not responding to appropriate therapy
Oncology
Any malignancy History of stem cell transplant or solid organ transplant
Ophthalmic
Baseline problems that may potentiate cataract development
Psychologic
History of alcohol and drug abuse
Renal
Creatinine > 2.5 x ULN

Abbreviations: LDH, lactate dehydrogenase; AST, aspartate transaminase; ALT, alanine transaminase; ULN, upper limit of normal; HIV, human immunodeficiency virus

[a]Defined as 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.

[b]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, female sterilization, male sterilization,

barrier methods, or use of oral, injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other hormonal contraception with similar efficacy. 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.

[c]Subjects for whom the potential benefits of participating in the study outweigh the potential risks of thromboembolic events, as determined by the investigator

Supplementary Table 2 Dose adjustment nomogram for eltrombopag

PLATELET COUNT RESULT	DOSE ADJUSTMENT OR RESPONSE
Weeks 1-12	
< 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.
> 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)
Weeks 13-52	
< 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.
> 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.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	10
Funding	#4	Sources and types of financial, material, and other support	5, 14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1, 5
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4, Table 2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4, 6, Table 1
Objectives	#7	Specific objectives or hypotheses	4, Table 3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5, Figure 1
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, Table 5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6, Table 6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6, Table 6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-7, 9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4, 7-9, Table 3
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, Table 4
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory	7, 8, 11, Tables 3-4

		tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8, Table 3
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8, Table 3
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7, 11, Table 3
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	5, 11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2, 4, 5, 10
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5, 10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	1-18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	10, Table 4

Notes:

- 6a: 3-4, Table 2
- 6b: 3-4, 6, Table 1
- 8: 5, Figure 1
- 12: 4, 7-9, Table 3
- 18a: 7, 8, 11, Tables 3-4
- 22: 7, 11, Table 3
- 24: 2, 4, 5, 10
- 33: 10, Table 4 This checklist was completed on 15. September 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

CONSENT FORM HIPAA Compliant

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

ICON 3

H-42131- A PHASE 3 STUDY OF ELTROMBOPAG VS. STANDARD FIRST-LINE MANAGEMENT FOR NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA (ITP) IN CHILDREN

Concise and Focused Presentation

This is a research study for patients diagnosed with immune thrombocytopenia (ITP), a condition that results in low platelets and possibly bleeding due to antibodies your body makes against your platelets. You are being invited to participate in this study because you have been identified to as having ITP .

The purpose of this study is to investigate the safety and effectiveness of eltrombopag in treating children and adolescents with newly diagnosed ITP.
If you choose to participate, you will be on study for about 1 year. You will be randomly assigned to receive the study drug eltrombopag or standard therapy.

During your participation you will have study procedures weekly for 12 weeks and then about monthly or less often for up to 1 year.
The following procedures will be performed:
- Physical exam
- Complete a Bleeding assessment
- Review your medical record.
- Ask how you are feeling and if you have had any side effects from therapy
- Ask you to complete some questionnaires regarding how you are feeling and your ITP
- Collect blood samples to assess your general health
- If you are a girl and have had your period, a blood or urine sample will be collected to see if you are pregnant
- Ask you about if you have been taking your study medication.

You will be asked to participate in an optional blood collection to collect blood one time for future research including genetic research.
The most common risks associated with eltrombopag treatment are headache, muscle/extremity pain, runny nose, cough, vomiting. Some more serious, but less common risks are liver enzyme elevation, blood clots.

Your participation in this study is voluntary. you may choose not to participate in this study. You may choose to receive routine care or participate in other studies.

The benefits of participating in this study may be an improvement to your ITP and increasing the general knowledge and understanding of ITP and treatment. However, you may receive no benefit from participating.

Please find a more detailed description of procedures and risks below.

Background

When reading this form, please note that the words, "you" and "your" refer to the person in the study rather than to a parent or guardian, or legal representative who might sign this form on behalf of the person in the study.

CONSENT FORM HIPAA Compliant

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

ICON 3

H-42131- A PHASE 3 STUDY OF ELTROMBOPAG VS. STANDARD FIRST-LINE MANAGEMENT FOR NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA (ITP) IN CHILDREN

This form contains the purpose of the research being conducted, the procedures involved, your responsibilities, and the risks and benefits associated with participation in the study. Please read this form and ask the Study Doctor and Study Staff any questions you may have. If there are any words or information that you do not know, ask them to explain. Feel free to take notes, write questions or mark any part of this form.

This research is being done by members of the Pediatric ITP Consortium of North America (ICON). ICON is a group of pediatric doctors throughout the United States who in a collaborative research effort are dedicated to improving the understanding, treatment, and quality of life of pediatric patients with ITP.

This is a research study for patients diagnosed with immune thrombocytopenia (ITP), a condition that results in low platelets and possibly bleeding due to antibodies your body makes against your platelets. Platelets enable your blood to clot and stop bleeding. You are being invited to participate in this study because you have been identified as having ITP.

If you join this study, you will be treated with one of four treatment plans. Three of the treatment plans are the standard treatments for newly diagnosed ITP in children and adolescents. The fourth treatment plan involves a drug named eltrombopag.

Eltrombopag is a drug which is approved in over 40 countries including the United States and European Union for treatment of chronic ITP (lasting longer than 6-12 months) and other types of blood diseases, including adults and children with low platelets. Over 5000 patients have been treated with eltrombopag in clinical studies to date. Its use in this study is considered "investigational" because eltrombopag is approved by the Food and Drug Administration (FDA) to treat children with chronic ITP, but has not been studied in children with newly diagnosed ITP.

Your participation in this study is voluntary. You are free to say yes or no. If you do not want to participate, your regular medical care and legal rights will not be affected. Even if you join this study, you may stop at any time

This research study is sponsored by Baylor College of Medicine and is funded by Novartis. The investigational drug, eltrombopag, is supplied by Novartis.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Purpose

The purpose of this study is to investigate the safety and effectiveness of eltrombopag in treating

children and adolescents with newly diagnosed ITP.

Procedures

The research will be conducted at the following location(s):
Baylor College of Medicine, Boston Children's Hospital - Massachusetts, Children's Hospital Colorado, Children's Hospitals and Clinics -- Minneapolis/St. Paul - Minnesota, Duke University - North Carolina, Lurie Childrens Hospital of Chicago, Nationwide Childrens Hospital , Oregon Health and Science University, St. Jude Children's Research Hospital - Tennessee, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, The Children's Hospital of Philadelphia (CHOP) - Pennsylvania, University of California: San Fran, and University of Florida.

A total of up to 162 subjects will be enrolled on this this protocol. Approximately 20 of those subjects will be enrolled at our local site.

DURATION.

There will be a total of approximately 16 study visits over a 1 year period. In addition, we will follow you for thirty days after your last dose for this study to see how you are doing.

STUDY DESIGN

If you agree to take part in the study, you will be assigned randomly (like rolling a dice) to be treated with:

- Eltrombopag
- Standard Therapy

Two out of three subjects taking part in the study will be given eltrombopag and one out of three subjects will be treated per standard therapy.

You and your study doctor(s)/team will know whether you will receive eltrombopag or standard therapy.

If your are randomized to receive the standard therapy you will be treated with one of the following three options depending on which treatment method your study doctor thinks is best for you.

- Intravenous immunoglobulin (IVIG)
- Steroids
- Anti-D immune globulin (Anti-D)

All three are standard front-line treatments for treating ITP for pediatric and adolescent patients. If your study doctor determines that IVIG or Anti-D globulin is the best treatment option for you, you will receive one dose of IVIG or Anti-D through an IV. If you receive steroids, you will take them twice daily for four days by mouth.

If you are randomized to receive eltrombopag, you will take it once daily. Your dose may be modified depending on your platelet count. You will take eltrombopag for 12 weeks, with the possibility to continue therapy for up to 1 year depending on how your body responds to taking eltrombopag.

You will be required to take eltrombopag on an empty stomach, 1 hour before or 2 hours after a meal. Eltrombopag is available as a liquid and as a tablet. If you take the tablet form, you must be able to swallow the tablet(s) whole with a glass of water without chewing. The tablet should not be crushed or broken.

It is also important that you do not take the eltrombopag in the 2 hours before and 4 hours after taking any other medications, calcium-rich foods (such as, dairy products like cheese, yogurt and milk, and calcium-fortified juices), or vitamins containing minerals such as iron, calcium, aluminum, magnesium, selenium, and/or zinc. Please discuss this further with the Study Doctors as they can advise on other foods to avoid to ensure the drug is most effective.

If you vomit within 30 minutes of taking eltrombopag, the dose should be repeated.

Regardless of whether you are randomized to one of the standard therapies or eltrombopag, all will be referred throughout this consent as study medications.

STUDY PROCEDURES

I. SCREENING VISIT (Visit 1)

If you agree to participate in the study, you will sign a consent form and the study doctor and study staff will:

- Confirm whether you are eligible to participate in this study
- Collect information about your ITP
- Ask you about the medicines you are currently taking
- Perform a physical examination
- Examine your eyes for cataracts (clouding of the normally clear lens of the eye).
- Draw blood (about four teaspoons) to measure your blood cell counts, iron levels, liver function, and immune function, and to assess your general health if not done as part of routine medical care. If you are a female and have started your period, a blood sample may also be drawn to see if you are pregnant.
- Take a urine sample to see how your kidneys are functioning. If you are a female, have started your period, and a blood sample was not drawn to see if you are pregnant, your urine will be checked to make sure you are not pregnant.
- Ask you to complete some questionnaires about your how you feel and about your ITP.

You will be asked come back within 72 hours (+/- 24 hours) to have your platelet count checked after this

visit. For this approximately ½ teaspoon of blood will be drawn.

II. Treatment Period I(Weeks 1- 12)

You will be asked to come complete study visits during the twelve weeks after your screening visit. Only week 4 and week 12 will be required to be done at the study site, and in some cases these may be done by telehealth. At certain time points, labs may be done locally and questions can be asked over the phone. At these visits the study team or doctor will do all or some of the following:

- Perform a Physical exam
- Complete a Bleeding assessment
- Review your medical record and collection information from your medical record that is related to your health and/or disease history. Some examples include test results, medical procedures, pathology reports, medicines you take.
- Ask how you are feeling and if you have had any side effects from therapy
- Ask you to complete some questionnaires regarding how you are feeling and your ITP
- Collect blood samples to assess your general health
- If you are a girl and have had your period, a blood or urine sample will be collected to see if you are pregnant
- Ask you about if you have been taking your study medication. Collect your medication bottles/vials and dispense your study medication

Your platelet count will be checked at weeks 1, 2, 4, 6, 8, 10, and 12. If you are taking eltrombopag, your blood will be tested every two weeks to assess your liver function.

If you are receiving eltrombopag, your dosing maybe altered depending on your platelet count.

III. Treatment Period II (Weeks 13 to 52)

If you complete twelve weeks of eltrombopag, the study team will start to decrease your dose over this treatment period depending on your platelet count. If you are still taking eltrombopag at the one year mark, you will be transitioned off study, and you will continue to be treated according to your primary treating doctor.

If you are taking eltrombopag your blood will be tested monthly to assess your liver function and iron levels in your body.

If you are girl and have had your period, your urine or blood will be tested every two months if you are taking eltrombopag to see if you are pregnant.

Regardless of what medication you are receiving or received for this study, you will be asked to come for a visit at 6 month and 1 year mark. At these visits, the study team or doctor will do all or some of the

following:

- Perform a physical exam
- Complete a bleeding assessment
- Ask you questions and review your medical record, and collect information from your medical record that is related to your health and/or disease history. Some examples include test results, medical procedures, pathology reports, and medicines you take.
- Ask you to complete questionnaires regarding your ITP and how you are feeling
- Ask you how you are feeling and if you have had any side effects
- Collect your study medication
- Dispense your study medication
- Ask you about any medications have are currently taking
- Collect blood samples to assess your general health, clotting, iron levels, immune function and liver function.

III. UNSCHEDULED VISITS

You may be asked to come in for additional visit(s). If you come in for an unscheduled visit, the study team or doctor will:

- Complete a physical exam
- Complete a bleeding assessment
- Collect a blood sample to assess your blood counts
- Ask you how you have been feeling and if you have had any side effects or about your medications you are currently taking

IV. FOLLOW UP

We would like to keep track of your medical condition after your last dose of study drug. A member of the study team will contact you via phone or email during the month after you stop the study treatment to see how you are doing.

V. RESCUE MEDICATIONS

If you have bleeding while participating in this study, please call your study doctor or team. If you have a bleed, platelets drop after initial response or you do not respond to treatment, the study doctor may give you a rescue medication such as IVIG, steroids, and/or Anti- D. If the study doctor decides that you need a different type of rescue medication, you will no longer receive your assigned study treatment, and you will be treated per standard of care. You will still be followed on the study, however, to collect information about your platelet counts, bleeding symptoms, and ITP.

VI. SUBJECT RESPONSIBILITIES

- Come to required study visits
- Bring your empty study medication vials to each visit
- Take you study medication as prescribed
- Tell your doctor about any medications or treatments you undergo while participating on this study
- Complete study questionnaires

VII. OPTIONAL BANKING SUB-STUDY

If you decide to participate, the study team will collect an additional 2 ½ teaspoons of blood during your screening visit, week 12 visit, and end of study visit for future research. If in the event of sample processing failure, the study team may re-collect a sample during a later study visit.

Blood will be stored for future use in a biobank. A biobank collects, stores, and distributes biological samples and health information.

The purpose of this collection is to make your samples available for use in research for studies related to ITP and related diseases after this current study is completed. Biobanks are especially useful to learn about diseases, possible treatments, including the role that specific genes play in human diseases.

The samples will be stored at Texas Children's Hospital.

One of the methods researchers might use to study your samples is called whole exome or genome sequencing for analyzing your DNA and RNA expression studies. This allows them to look at some or all of your genetic code. Researchers may also use other methods as they are developed. Studying genes along with health information will help us to better understand what causes certain diseases. It may also help us to understand how different patients respond to treatment. This knowledge could help us to develop new treatments.

"DNA" is short for deoxyribonucleic acid. DNA stores information in the form of a code. This is the code that you inherit from your parents and that you pass on to your children. Parts of DNA that have complete messages are known as "genes." Genes give the instructions for building the proteins that make our bodies work.

"RNA" is short for ribonucleic acid. RNA delivers DNA's genetic code to the part of a cell that makes proteins. RNA also helps control which genes are turned on or off at one point in time.

The goal of DNA and RNA studies are to look for genetic connections which may explain how to identify, prevent, and treat health problems. For example, the data from these studies may be used to find out:

- Who is more likely to develop a certain illness, such as asthma, cancer, or diabetes, or a condition like high blood pressure or obesity;
- What genes affect the progress of a certain disease or condition; and
- What genes may affect treatments which now may or may not work in certain people.

Genomic research will not directly benefit you, but could lead to a greater understanding of the interaction between genes and health. This knowledge could help others in the future.

Your samples may also be analyzed for certain markers and how they correlate to treatment or related diseases.

We will remove your name and any other information that could directly identify you from your materials. We will replace this information with a unique study code. We will keep a master list that links your study code to your materials. Only certain study staff can access this master list. We will keep health information and research data on secure computers. These computers have many levels of protection.

Your samples will be stored for future use. Any future research performed on your samples will not be allowed unless proof of Institutional Review Board (IRB) approval is obtained to ensure that any future research is conducted ethically, and the rights and safety of study subjects are protected. If the study is approved, we might give a part of your sample and information to the researchers.

Any data or samples that are sent to other researchers will contain only a unique identifying number; they will NOT contain personal identifiers such as your name or address. Data and samples will be kept indefinitely, allowing researchers in the future to ask new questions about blood diseases and treatment.

You should not expect to get personal results from research done through the biobank. Researchers will study samples and information from many people; it will take many years before they know if the results have any meaning.

You can revoke the use of your samples for future use at any time. Any data or information collected prior to you revoking your samples will not be destroyed; however, no further information will be collected.

WHO WILL HAVE ACCESS TO MY GENETIC INFORMATION?

Researchers can do more powerful studies when they share with each other the information they get from studying human samples. They share this information with each other by putting it into scientific databases. These databases store information from many studies conducted in many different places. Researchers can then study the combined information to learn even more about health and many different diseases.

There are different kinds of databases; some are publicly accessible and some are restricted. Anyone on the Internet can access publicly accessible databases. Only researchers who apply and are approved can access restricted databases. There are many restricted databases; some are maintained by BCM, some are maintained by the federal government, and some are maintained by private companies. Some of your genetic and health information could be placed into one or more of these publicly accessible or restricted databases.

Your name and other information that could directly identify you (such as address or social security number) will not be placed into any scientific database. However, because your genetic information is unique to you, there is a chance that someone could trace the information back to you or your close biological relatives. The risk of this happening is very small, but may grow in the future.

Researchers will always have a duty to protect your privacy and to keep your information confidential.

Would you like to participate in this optional sub-study for future research?

Yes:_____ Initials:_____

No: _____ Initials:_____

Clinically Relevant Research Results

The results generated from this research study are not expected to have any clinical relevance to you.

Sharing and Future Research Studies with Identifiable Private Information

Information that identifies you may be removed from your identifiable private information collected as part of this research, and after such removal, your information may be used for future research studies or distributed to another investigator for future research studies without additional consent/authorization from you.

Sharing and Future Research Studies with Identifiable Biospecimens

Information that identifies you may be removed from your identifiable biospecimens collected as part of this research, and after such removal, your biospecimens may be used for future research studies or distributed to another investigator for future research studies without additional consent/authorization from you.

Genome Sequencing Potential

Your identifiable biospecimens(s) will be or may be sequenced in whole or in part so that your genetic information can be compared to others' genetic information.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from

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ICON 3

H-42131- A PHASE 3 STUDY OF ELTROMBOPAG VS. STANDARD FIRST-LINE MANAGEMENT FOR NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA (ITP) IN CHILDREN

Baylor College of Medicine, Boston Children's Hospital - Massachusetts, Children's Hospital Colorado, Children's Hospitals and Clinics -- Minneapolis/St. Paul - Minnesota, Duke University - North Carolina, Lurie Childrens Hospital of Chicago, Nationwide Childrens Hospital , Oregon Health and Science University, St. Jude Children's Research Hospital - Tennessee, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, The Children's Hospital of Philadelphia (CHOP) - Pennsylvania, University of California: San Fran, and University of Florida to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Identifiable biospecimens
- Other: Medical Record Number

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, Boston Children's Hospital - Massachusetts, Children's Hospital Colorado, Children's Hospitals and Clinics -- Minneapolis/St. Paul - Minnesota, Duke University - North Carolina, Lurie Childrens Hospital of Chicago, Nationwide Childrens Hospital , Oregon Health and Science University, St. Jude Children's Research Hospital - Tennessee, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, The Children's Hospital of Philadelphia (CHOP) - Pennsylvania, University of California: San Fran, University of Florida, and NOVARTIS (SWITZERLAND) and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

The data coordinating center will have access to the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine, Boston Children's Hospital - Massachusetts, Children's Hospital Colorado, Children's Hospitals and Clinics -- Minneapolis/St. Paul - Minnesota, Duke University - North Carolina, Lurie Childrens Hospital of Chicago, Nationwide Childrens Hospital , Oregon Health and Science University, St. Jude Children's Research Hospital - Tennessee, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, The Children's Hospital of Philadelphia (CHOP) - Pennsylvania, University of California: San Fran, and University of Florida are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine, Boston Children's Hospital - Massachusetts, Children's Hospital Colorado, Children's Hospitals and Clinics -- Minneapolis/St. Paul - Minnesota, Duke University - North Carolina, Lurie Childrens Hospital of Chicago, Nationwide Childrens Hospital , Oregon Health and Science University, St. Jude Children's Research Hospital - Tennessee, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, The Children's Hospital of Philadelphia (CHOP) - Pennsylvania, University of California: San Fran, and University of Florida to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine, Boston Children's Hospital - Massachusetts, Children's Hospital Colorado, Children's Hospitals and Clinics -- Minneapolis/St. Paul - Minnesota, Duke University - North Carolina, Lurie Childrens Hospital of Chicago, Nationwide Childrens Hospital , Oregon Health and Science University, St. Jude Children's Research Hospital - Tennessee, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, The Children's Hospital of Philadelphia (CHOP) - Pennsylvania, University of California: San Fran, and University of Florida maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine, Boston Children's Hospital - Massachusetts, Children's Hospital Colorado, Children's Hospitals and Clinics -- Minneapolis/St. Paul - Minnesota, Duke University - North Carolina, Lurie Childrens Hospital of Chicago, Nationwide Childrens Hospital , Oregon Health and Science University, St. Jude Children's Research Hospital - Tennessee, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, The Children's Hospital of Philadelphia (CHOP) - Pennsylvania, University of California: San Fran, and University of Florida to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine, Boston Children's Hospital - Massachusetts, Children's Hospital Colorado, Children's Hospitals and Clinics -- Minneapolis/St. Paul - Minnesota, Duke University - North Carolina, Lurie Childrens Hospital of Chicago, Nationwide Childrens Hospital , Oregon Health and Science University, St. Jude Children's Research Hospital - Tennessee, TCH: Texas Children's

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ICON 3

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Hospital, TCH: Texas Children's Hospital, Clinic, The Children's Hospital of Philadelphia (CHOP) - Pennsylvania, University of California: San Fran, and University of Florida.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, NOVARTIS (SWITZERLAND) and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, data coordinating center, Data and Safety Monitoring Board, Boston Children's Hospital - Massachusetts, Children's Hospital Colorado, Children's Hospitals and Clinics -- Minneapolis/St. Paul - Minnesota, Duke University - North Carolina, Lurie Childrens Hospital of Chicago, Nationwide Childrens Hospital , Oregon Health and Science University, St. Jude Children's Research Hospital - Tennessee, TCH: Texas Children's Hospital, TCH: Texas Children's Hospital, Clinic, The Children's Hospital of Philadelphia (CHOP) - Pennsylvania, University of California: San Fran, and University of Florida may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Dr. Jenny Despotovic Clinical Care Center 6701 Fannin St. Suite 1580 Houston, TX 77030

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

SIDE EFFECTS OF ELTROMBOPAG:

The side effects listed below have been seen in younger patients (under the age of 18) who have received eltrombopag treatment for (ITP).

Very Common Side Effects:

These may affect more than 1 in 10 people treated with eltrombopag

- Upper respiratory tract infection (runny nose, cold)
- Fever (Pyrexia)
- Abdominal Pain
- Cough

The following side effects have been reported to be associated with treatment with eltrombopag in

patients with a different disease called severe aplastic anemia (SAA).

Very Common Side Effects:

These may affect more than 1 in 10 people treated with eltrombopag

- Rash
- Cough
- Headache
- Runny nose
- Abdominal pain
- Diarrhea
- Nausea
- Joint pain
- Increase in some liver enzymes (transaminases)
- Pain in arms, legs, hands and feet
- Dizziness
- Feeling very tired (fatigue)
- Fever

Progression of underlying disease or progression to a new myelodysplastic syndrome (MDS) and/or new acute myelogenous leukemia (AML, a type of blood cancer) has occurred in patients with MDS, AML, and severe aplastic anemia (SAA). In some patients with these diseases who are treated with eltrombopag, changes in bone marrow cells may occur and in some cases this may indicate a worsening/progression to cancer. The role of eltrombopag in these changes is not known. These changes have also been seen in patients with SAA alone, and with other drugs in the same class of compounds as eltrombopag. During this study, your blood will be periodically examined for signs of these changes.

Other possible side effects of Eltrombopag:

The following side effects have been reported to be associated with treatment with eltrombopag.

Liver problems:

Eltrombopag may damage the liver and cause serious, even life threatening, illness. This is specific to patients with hepatitis C. Blood tests will be done to check your child's liver before he or she starts taking eltrombopag and during treatment. Your doctor will order the blood tests and any other tests required. In some cases Eltrombopag treatment may need to be stopped. Tell your doctor right away if you notice any of these signs and symptoms of liver problems:

- yellowing of the skin or the whites of the eyes (jaundice)

- unusual darkening of the urine
- unusual tiredness
-right upper stomach area pain

Bleeding after you stop treatment:

When you stop taking eltrombopag, your blood platelet count may temporarily drop back down to what it was before starting eltrombopag or lower. These effects are most likely to happen within 4 weeks after stopping. The lower platelet counts may increase the risk of bleeding. Tell your doctor or pharmacist if you develop any bruising or bleeding symptoms after stopping eltrombopag.

High platelet counts with a higher chance for blood clots:

You could have a higher chance of getting a blood clot if your platelet count is too high during treatment with eltrombopag, but blood clots can occur with normal or even low platelet counts. Blood clots are more common in adults who have other risks for developing blood clots. The Study Doctor will check the blood platelet counts, and change the dose or stop eltrombopag if the platelet counts get too high. Tell your doctor right away if you have signs and symptoms of a blood clot in the leg, such as swelling or pain/tenderness of one leg.

Cataracts:

In animal studies, it was found that high doses of eltrombopag caused the development of cataracts (a clouding of the lens in the eyes). Following studies on patients with immune thrombocytopenia did not confirm this finding. Regardless, you will be checked for cataracts at baseline and during the study, and a visit to a doctor specializing in cataracts will be scheduled if you are determined to be at higher risk of developing cataracts.

Contraception and pregnancy-Female Subjects

If you are pregnant or nursing a child you cannot participate in this research study. You must confirm, to the best of your knowledge that you are not now pregnant and do not intend to become pregnant during the research study. You will take a pregnancy test before the research begins. The results of the pregnancy test are confidential and will be given to you by one of the study nurses or doctors in private.

There are no adequate and well-controlled studies of eltrombopag in pregnant women. The effect of eltrombopag on human pregnancy is unknown. While you are on study and for 7 days after the last dose of study treatment it is important that you use a highly effective form of birth control if you are sexually active and can become pregnant.

Examples of highly effective birth control methods are:

- Total abstinence (no sexual relations), when this is in line with your preferred and usual lifestyle. Periodic abstinence methods are not acceptable! Some terms used to describe periodic abstinence methods are: calendar, ovulation, symptothermal, post-ovulation. Please note that the withdrawal method is also not acceptable.
- Female sterilization, when you have already been surgically sterilized prior the research study by surgical removal of both ovaries (woman's reproductive system that stores and releases eggs for fertilization and produces female sex hormones), total hysterectomy (surgical removal of the uterus and cervix), or tubal ligation (getting your "tubes tied") at least 6 weeks before taking study treatment.
- Your male partner has already been sterilized and has the appropriate documentation. Your sterilized male partner should be your sole partner.
- 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 oral contraception you should have been using the same pill on a stable dose for a minimum of 3 months before taking study treatment).

Please discuss with the Study Doctor the most appropriate birth control method that also respects your cultural and religious preferences. If you become pregnant or suspect you are pregnant (for example, because of a late menstrual period) during study treatment or within 7 days after completing study treatment, you must inform the Study Doctor immediately, and you have to stop ongoing study treatment immediately. You will not be allowed to continue study treatment if you are pregnant. The Study Doctor will medically follow your pregnancy until delivery to monitor safety.

Contraception and Pregnancy- Male Subjects

The effects of the study drug on sperm are unknown. In addition, it is unknown if participation in this research could result in harm to a fetus. You should not father a baby while taking part in this research and for the period of 7 days following stopping of study treatment. If you have a female partner who is able to become pregnant, one or both of you must use some form of highly effective birth control. During the research, if your partner becomes pregnant, or if there is a chance that she is pregnant, you should contact the Study Doctor immediately so that we may provide medical assistance and counseling.

PROCEDURE RISKS:

Blood Draw: Drawing blood causes discomfort. A bruise may appear for a few days at the spot where the needle was inserted. There is a slight chance of infection. This is very unlikely. There is also a small risk of dizziness and fainting with blood draws. These risks are minimized by the use of trained personnel to draw your blood.

OPTIONAL SUB-STUDY RISKS:

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Loss of Confidentiality:

What are the potential privacy risks?

We will take many steps to protect your privacy, but because your DNA/RNA is unique to you, it is possible but unlikely that someone could trace it back to you. There is also a risk that someone could get access to the data we have stored about you. If those data suggested something serious about your health, it could be misused. For example, it could be used to make it harder for you to get or keep a job or insurance. There are laws against this kind of misuse, but they may not give full protection. There may also be other unforeseen privacy risks.

Your privacy and the confidentiality of your data are very important to us; we will make every effort to protect them.

How will my privacy be protected?

We will not give information that identifies you to anyone without your permission, except as required by law. This project takes many steps to protect the privacy of people who take part. Research records are separate from medical records. We will not place any information from this project in your medical records.

Researchers who study your sample and information will not know who you are. We will give them only barcode numbers; we will not give them any information that directly identifies you. The researchers must sign an agreement that they will not try to find out who you are. There are laws that protect against unauthorized access to your information. There is also a Federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
-Employers with 15 or more employees may not use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: improvement to your ITP, and increasing the knowledge and understanding of ITP and treatment. However, you may receive no benefit from participating.

Alternatives

You may choose to not participate in this study.

Subject Withdrawal from a Study

Taking part in research is always a choice. If you decide to take part in this study, you can change your mind at any time. Please tell the Study Doctor or study staff if you decide to temporarily or permanently stop taking your study medication. You will be asked to return to the study site as soon as possible for a check-up.

If you decide to participate in the optional banking sub-study and decide later that you would no longer like to participate in this study, we will destroy any leftover samples. We will not be able to withdraw your samples from studies that have already begun since we cannot get the samples back once they have been shared with other researchers. If you change your mind, and would like to withdraw from the study, we ask that you inform the research team using the contact information provided above

Investigator Withdrawal of Subject from a Study

The investigator or sponsor may decide to stop you from taking part in this study at any time. You could be removed from the study for reasons related only to you (for example, if you move to another city, if you do not take your study medication, or if you have a serious reaction to your study medication) or because the entire study is stopped. The sponsor, investigator, drug supplier, Food and Drug Administration, or Institutional Review Board may stop the study at any time.

Subject Costs and Payments

Most procedures used in this study will be part of standard medical care, and therefore you/your insurance company will be responsible for these costs.

If you are randomized to one of the standard of care therapies, you or your insurance will be response for the cost of the medication. If you are randomized to receive eltrombopag, Novartis will cover the cost of the study medication as it is considered "investigational" in this study.

You will not be paid for taking part in this study.

Research Related Injury

Please contact your study doctor, if you feel you have been injured as a result of taking part in this study.

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Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Novartis (drug supplier) will not pay any money to you or your medical bills.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, JENNY DESPOTOVIC, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: JENNY MCDADE DESPOTOVIC at 832-822-4362 during the day and after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

CHILD ASSENT CLAUSE

If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child's name here _____

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Legally Authorized Representative Parent or Guardian	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date