CLINICAL REVIEW

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Trade Name	Promacta®
Therapeutic Class	Thrombopoietin Agonist
Applicant	Glaxo SmithKline
Formulation(s)	Tablet
Dosing Regimen	50 mg once daily
Indication(s)	Chronic ITP
Intended Population(s)	Pediatric patients ≥6 years old with chronic ITP

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Regular approval is recommended for eltrombopag for the treatment of thrombocytopenia in pediatric patients ≥6 years old with chronic idiopathic thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The dose proposed is as follows:

- The starting dose is 50 mg orally once daily. If the platelet count is less than 50 Gi/L following two weeks of treatment, the dose is increased to 75 mg once daily. If the platelet count is 200-400 Gi/L, the dose is decreased by 25 mg. If the platelet count is > 400 Gi/L, the dose is held until platelet count is <150 Gi/L and reinstated at a daily dose reduced by 25 mg.
- For patients of East Asian ancestry, the starting dose is 25 mg orally once daily. The dose of eltrombopag in this patient population may be increased to 50 mg orally once daily if the platelet count is less than 50,000/mcl after 2 weeks, then the dose adjusted as above.

The rationale for this recommendation is based on the following information:

- The efficacy of the proposed therapy in terms of increasing platelet counts in pediatric patients with ITP is supported by the pivotal studies TRA108062 and TRA115450. The studies were randomized, double-blind, placebo-controlled, multicenter, multinational trials. These trials provide substantial evidence of effectiveness as the evidence is from adequate and well-controlled trials.
- Both trials also showed favorable efficacy in clinically relevant endpoints including the reduced need for rescue medications or platelet transfusions and the reduction in baseline ITP medications.
- The pivotal trials failed to show efficacy in terms of a reduction or prevention of overall bleeding in patients with ITP. However, the trials did show a reduction in clinically significant bleeding defined as Grade 2 to 4 on the WHO Bleeding Scale.
- The safety profile in pediatric patients in similar to that seen in adult patients. The common AEs that occurred more frequently in patients treated with eltrombopag than patients treated with placebo were upper respiratory tract infection, nasopharyngitis, cough, diarrhea, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, AST increased, and rhinorrhea. These AEs tended to be low grade, and SAEs were uncommon. There were no deaths in either pediatric trial, and evaluation of AEs of special interest did not reveal any

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safety signal in pediatric patients treated with eltrombopag. The safety monitoring was appropriate and acceptable to identify the important safety concerns.

- Other AEs of special interest with the adult eltrombopag experience including hepatotoxicity, cataracts, thromboembolic events and bone marrow toxicity did not occur in pediatric patients receiving eltrombopag.

1.2 Risk Benefit Assessment

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic ITP in children is caused by a combination of accelerated platelet destruction by the reticuloendothelial system, coupled with impairment of platelet production. Thrombocytopenia results in an increased risk of bleeding. • The incidence of acute ITP in children is 2.5-5.3/100,000 children with the highest incidence rates in 1-7 year old (mean 5.7 years). • Chronic ITP is defined as a duration of thrombocytopenia of >6 months. Approximately 15-30% of cases of acute ITP in children become chronic. • The rate of chronic ITP among children is more common in adolescents.	If untreated, chronic ITP can lead to serious and life-threatening bleeding.
Unmet Medical Need	• Currently available treatments for chronic ITP in children are targeted towards decreasing the rate of platelet destruction predominantly by immune modulation. Immune suppression with these efforts can lead to an increase risk of infections. • Standard of care in this disease is heterogeneous depending on the severity of bleeding symptoms, platelet count nadir and risk of bleeding, and a patient's individual response to therapy. • Current treatments include IVIG, anti-D immunoglobulin, steroids, rituximab, and other immunosuppressants. Refractory patients may undergo splenectomy in an effort to reduce platelet destruction. • Romiplostim is a TPO-R antagonist which is indicated to treat adults with chronic ITP, but has not been adequately studied in children. • Many of the commonly used drug therapies are parenterally administered. Parenteral administration can complicate drug administration, sometimes requiring additional health care visits and increase the risk of infection.	The treatment armamentarium would benefit greatly from a new therapeutic option that is more efficacious, well tolerated, and orally administered. There is a specific unmet medical need for patients refractory to available treatments or with intolerable side effects to current therapies.
Clinical Benefit	• Eltrombopag is indicated for the treatment of thrombocytopenia in pediatric patients 6 years and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. • The efficacy of the proposed therapy in terms of increasing platelet counts in pediatric patients with ITP is supported by the pivotal studies TRA108062 and TRA115450 with a total of 159 pediatric patients treated in the randomized period (108 in the eltrombopag	These trials were adequate and well-controlled. Eltrombopag treatment resulted in a clinically relevant sustained increase in platelet

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	arm). • The studies were randomized, double-blind, placebo-controlled, multicenter, multinational trials. • The primary efficacy endpoint for TRA108062 was the proportion of subjects achieving platelet counts ≥50 Gi/L at least once between weeks 1 and 6 of the randomized period. The primary efficacy endpoint for TRA115450 was the proportion of subjects achieving platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between weeks 5 to 12 of the randomized period • Combined data from both trials showed that 62% of patients had a platelet count ≥50 Gi/L at any time in the first 6 weeks of treatment and 38% of patients were sustained responders. • Treatment with Eltrombopag led to a reduced use of rescue therapies (including steroids and platelet transfusions), reductions in baseline ITP therapies, as well as a trend towards reduction of severe bleeding events.	count in a substantial percentage of pediatric patients in all age groups. Baseline and rescue medications used to treat chronic ITP and platelet transfusions have inherent risks, and reduction in these therapies provides advantages for patients. Patients with chronic ITP experience bleeding which interferes with their quality and quantity of life. A reduction in bleeding is an important outcome for patients with this disease.
Risk	• The safety database includes 157 pediatric patients in the randomized period of both trials (107 patients receiving eltrombopag) and 171 pediatric patients exposed to at least one dose of eltrombopag. A total of 128 patients were treated with eltrombopag for ≥24 weeks. • The safety database includes 61 patients from cohort 1 (ages 12-17), 70 patients from cohort 2 (ages 6-11) and 40 patients from cohort 3 (ages 1-5). • The common adverse reactions (ARs) that occurred more frequently in patients treated with eltrombopag were upper respiratory tract infection, nasopharyngitis, cough, diarrhea, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, AST increased, and rhinorrhea. • ARs that occurred more often in the patients treated with eltrombopag were generally low grade and reversible. Severe adverse reactions were less common in the eltrombopag arm than the placebo arm. • ARs that led to discontinuation of study treatment were similar between arms (2.8% for eltrombopag and 2% for placebo) • Serious ARs that led to discontinuation of study treatment were lower in the eltrombopag arm (0.9%, versus 2% in the placebo arm). • There were no deaths in either pediatric trial, and evaluation of ARs of special interest did not reveal any safety signal in pediatric patients treated with eltrombopag.	Treatment of pediatric patients with eltrombopag did not reveal any new safety signal. The safety profile of eltrombopag in pediatric patients was consistent with that seen in adults. AEs in pediatric patients were generally low grade and tolerable or reversible after discontinuing the drug.
Risk Management	• The safety concerns associated with eltrombopag treatment in pediatric patients are well documented. • The risk of hepatotoxicity is described, and signs and symptoms	Labelling indicates that approval for the tablet is for patients ≥6 years

	are included in the Medication Guide. • Based on animal data, eltrombopag may cause fetal harm. Pregnancy testing was required prior to study enrollment.	old. Limitations of use indicate that eltrombopag should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding A waiver for study in pediatric patients <age 1 will be granted since patients require 6 to 12 months for the diagnosis of chronic ITP. There are no new safety signals that would indicate the need for a REMS or PMR/PMC.
Benefit-Risk Summary and Assessment The benefit-risk profile for eltrombopag in pediatrics is favorable. Eltrombopag showed efficacy in all pediatric age cohorts. The drug was generally safe and low-grade AEs were well tolerated. SAEs were uncommon and there were no new safety signals in the pediatric population.		

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended because the safety profile is acceptable. There are no existing REMS for Promacta under the approved indications.

1.4 Recommendations for Postmarket Requirements and Commitments

No new PMRs or PMCs are recommended.

2 Introduction and Regulatory Background

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2.1 Product Information

Eltrombopag is an orally bioavailable, small molecule thrombopoietin (TPO) receptor agonist. Eltrombopag interacts with the transmembrane domain of the human TPO-receptor and initiates a signaling cascade that induces proliferation and differentiation from bone marrow progenitor cells resulting in an increased production of platelets.

Promacta® (eltrombopag) is FDA approved for the treatment of:

- Thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- Thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
- Patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

This supplement provides the clinical data for treatment of children with chronic ITP ages 1-17 years. The currently marketed formulation is a tablet for oral administration which was used for the older cohorts, ages 6-17 years, and will be the basis for this approval. The proposed indication for this supplement therefore is the treatment of thrombocytopenia in pediatric patients 6 years and older with chronic immune (idiopathic) thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The CMC information on (b) (4) (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Immune (idiopathic) thrombocytopenia (ITP) is caused by a combination of accelerated platelet destruction by the reticuloendothelial system, coupled with impairment of platelet production. In children, ITP is often preceded by a viral illness or other immune stimulant such as allergic reactions or immunizations (particularly MMR), and is found to be seasonal[1]. The incidence of acute ITP in children is 2.5-5.3/100,000 children[2] with the highest incidence rates in 1-7 year old (mean 5.7 years)[3]. Chronic ITP is defined as a duration of thrombocytopenia of >6 months. While children are more likely than adults to have acute ITP resolve spontaneously, approximately 15-30% of cases become chronic. The rate of chronic ITP among children is more common in adolescents[1].

The reduced number of circulating platelets in ITP leads to an increased risk of bleeding. Patients commonly experience bruising, petechiae, and purpura. The incidence of bleeding is difficult to quantify, but a recent review by Neunert et al estimated the rates of severe bleeding in children with ITP. Intracranial hemorrhage (ICH) occurred in 0.4% of children with ITP, predominately in children with chronic ITP. The definition of severe (non-ICH) bleeding has not been standardized across trials, but is estimated to occur in 20.2% of children, and predictors were severe thrombocytopenia (platelet counts <10-20 Gi/L), newly-diagnosed ITP, and previous minor bleeding[4].

Currently available treatments for chronic ITP in children are targeted towards decreasing the rate of platelet destruction predominantly by immune modulation[1, 3]. Standard of care in this disease is heterogeneous depending on the severity of bleeding symptoms, platelet count nadir and risk of bleeding, and a patient's individual response to therapy. The medications commonly used for the treatment of chronic ITP in children are listed in Table 1, and other non-drug interventions are listed in Table 2. The only treatments that are FDA-approved for the treatment of chronic ITP in children are anti-D immunoglobulin (WinRho® for children and adults and Rhophylac® labeled for adults with literature references for treatment in children) and IVIG (Privigen® for patients ≥15 years old).

Table 1: Available medications for the treatment of chronic ITP in children

Therapy	Target
IVIG	Immune-modulation
Anti-D immunoglobulin	Immune-modulation
Steroids	Immunosuppression
Rituximab	Anti-CD20
Danazol, azathioprine, cyclosporine A	Other immunosuppressants
Eltrombopag*, romiplostim*	TPO-receptor agonists

*Currently only approved for use in adults

Table 2: Other interventions in the treatment of chronic ITP in children

Intervention
Observation only
Splenectomy
Platelet transfusions

To date, TPO receptor agonists are the only treatment targeted at increasing platelet production which is known to be decreased in chronic ITP. The increase in platelet production will have to overwhelm the increased platelet destruction to result in a rise in the platelet count. Romiplostim (Nplate®) is a TPO receptor agonist which is approved for use in adults with chronic ITP based upon "Durable Platelet Response" defined as at

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least 6 weekly platelet counts ≥50 Gi/L during the last 8 weeks of the study in the absence of rescue medications.

2.3 Availability of Proposed Active Ingredient in the United States

Promacta is presently marketed in the United States as a tablet for oral administration. Promacta received accelerated approval in November 2008 for the treatment of chronic ITP in adults, and regular approval in February 2011 for the same indication. The indication of treatment of thrombocytopenia in patients with chronic Hepatitis C was added in November 2011, and the indication of treatment of cytopenias in severe aplastic anemia was added in August 2014. The prescribing information for eltrombopag includes the following warnings and precautions with hepatic decompensation included in a Boxed Warning:

- Hepatic Decompensation in Patients with Chronic Hepatitis C.
- Hepatotoxicity: Monitor liver function before and during therapy.
- Thrombotic/Thromboembolic Complications: Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA. Monitor platelet counts regularly.

2.4 Important Safety Issues With Consideration to Related Drugs

Romiplostim (Nplate®) is a TPO receptor agonist approved by the FDA for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Romiplostim is an Fc-peptide fusion protein (peptibody) that activates the TPO receptor leading to increased platelet production. The prescribing information for romiplostim includes the following warnings and precautions:

- In some patients with MDS, Nplate increases blast cell counts and increases the risk of progression to acute myelogenous leukemia.
- Thrombotic/thromboembolic complications may result from increases in platelet counts with Nplate use. Portal vein thrombosis has been reported in patients with chronic liver disease receiving Nplate.
- If severe thrombocytopenia develops during Nplate treatment, assess patients for the formation of neutralizing antibodies.

The most common adverse reactions for romiplostim are arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia.

The risk of thrombotic/thromboembolic events is thought to be a class effect for TPO receptor agonists. In adult studies of eltrombopag in patients with chronic hepatitis C and thrombocytopenia, 3% of patients treated with eltrombopag experienced a thrombotic event compared to 1% in patients treated with placebo. There were no thrombotic events in either pediatric study in this review (see Section 7). Regarding the

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other Nplate warnings, eltrombopag is not indicated for use in patients with MDS and eltrombopag should not cause formation of neutralizing antibodies because it is a small molecule and not a biologic product.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The FDA Office of Orphan Products Development granted Orphan Drug Designation in May 2008 for eltrombopag for the treatment of ITP (ODA # 07-2519).

A Pediatric Written Request was issued by the Agency on January 25, 2010, and was revised on November 23, 2011. The agreed-upon written request dictated the study design for both of the pediatric trials submitted with this sNDA. The written request included information on the age groups and number of patients to be studied, inclusion criteria, study objectives and endpoints, statistical analysis, and the timeframe for completing the studies. A full review of the pediatric written request and determination of eligibility for pediatric exclusivity will be included (b) (4)

An EOP2 meeting was held on March 22, 2012, regarding (b) (4)

A pre-sNDA meeting was scheduled for May 22, 2014, under IND 063293 to discuss the content, format, and acceptability of the proposed sNDA in pediatric patients with chronic ITP based on the results of the PETIT and PETIT2 studies. After reviewing the FDA's preliminary responses to GSK's pre-sNDA meeting questions sent on May 19, 2014, the Sponsor was satisfied with the preliminary responses provided by the FDA and did not feel additional discussion was needed. The responses provided agreement on the size of the safety database, format of the electronic submission of clinical information, and the content of the submission of CMC information.

2.6 Other Relevant Background Information

Eltrombopag was given marketing authorization in the EMA in March 2010 under the trade name Revolade. They have agreed upon Paediatric Investigation Plans for the study of eltrombopag in pediatric patients with chronic ITP, aplastic anemia, and thrombocytopenia secondary to chemotherapy. The results of the clinical trials in pediatric patients with chronic ITP were due to the EMA in December 2014.

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Eltrombopag was given marketing approval in Japan in October 2010 under the trade name Revolade. Eltrombopag tablets are currently registered in >90 countries around the world.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sNDA was submitted in eCTD format, and was well organized with appropriate indexing. Because the CMC information on the pediatric formulation was not available at the time of this submission, the indication sought was for those patients with ITP 6 years and older who could use the marketed tablet. Clinical trial results were provided for all patients ages 1 to 17; therefore, an information request was submitted to the Applicant to (b) (4) Most of the subgroup analyses had already been done for the separate cohorts, but needed to be combined using only the older two cohorts ages 6-11 and 12-17 years.

3.2 Compliance with Good Clinical Practices

Per the Applicant-submitted Clinical Overview: "All studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Regulatory approval was obtained from the relevant health authority where required."

Two domestic clinical sites participating in clinical trial TRA108062 were inspected by the Office of Scientific Investigations (OSI) of the FDA in support of this sNDA. Dr. James Bussel at Cornell enrolled 20 patients (29.9% of the total population for that trial), and Dr. Kerri Nottage from St Jude's Hospital in Memphis enrolled 7 patients. The final classification by OSI for Dr. Bussell is Voluntary Action Indicated (VAI). The preliminary classification of inspection for Dr. Nottage is also VAI. The study data derived from these clinical sites are considered reliable in support of the requested indication. No sites participating in clinical trial TRA115450 were inspected because the highest enrolling site enrolled only 4 patients, and only 4 patients total were enrolled in the USA. No significant impact on the trial outcome would be anticipated from violations at any one site because of the small number of patients enrolled per site.

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3.3 Financial Disclosures

The financial disclosures were reviewed and the applicant has adequately disclosed financial arrangements with clinical investigators. Dr. [redacted] (b) (6) accepted $91,000 in research funding from the Applicant. His clinical site was inspected as mentioned in Section 3.2, and no issues were revealed with the reliability of data from his site that would impact the study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was reviewed with this submission. [redacted] (b) (4)

4.2 Clinical Microbiology

Not applicable to this product.

4.3 Preclinical Pharmacology/Toxicology

There were no new pharmacology/toxicology studies provided with this sNDA. However, juvenile rat studies have been reviewed in prior submissions under the NDA. In juvenile rats dosed 3- to 5-times the maximum clinical exposure in pediatric patients with ITP dosed at 75 mg, there were no associated adverse events. In rat pups dosed from days 4 to 31 at 5-times the maximum clinical exposure, there were slight reductions in weight gain and slight decreases in red cell parameters. In rat pups dosed from days 32 to 62 at 3-times the maximum clinical exposure, there were slight decreases in red blood cell parameters, serum cholesterol and triglyceride concentrations. At poorly-tolerated doses in juvenile rats at ≥9 times the maximum clinical exposure, reductions in body weight gain or body weight loss and discoloration of skin, fur and other organs (attributed to the color of eltrombopag) were observed and reversed following an approximate 4 week off-treatment period. Ocular opacities (consistent with cataracts) were observed grossly in some pups at these high exposures during treatment with eltrombopag or during the 4 week off-treatment period. Overall, there were no findings in juvenile rats to suggest a greater risk of toxicity with

eltrombopag treatment in pediatric vs. adult ITP patients. This summary was provided by the Applicant in the Non-clinical Overview.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action was established with the initial NDA submission. No new information on MOA was provided. In brief, eltrombopag is a small molecule, non-peptide, orally active thrombopoietin receptor (TPO-R) agonist that functions in a similar manner to endogenous thrombopoietin (TPO). Eltrombopag stimulates some, but not all, signal transduction pathways known to be induced through TPO-R activation, and has proliferative, anti-apoptotic, and proliferation effects on megakaryocyte progenitors. Eltrombopag also stimulates the expansion of hematopoietic stem cells and increases in other lineages in addition to megakaryocytes.

4.4.2 Pharmacodynamics

Data from 168 pediatric subjects with chronic ITP who provided PK and platelet count data in two eltrombopag clinical studies (TRA108062 and TRA115450) were included in the population PK (PopPK) and PK/PD analyses and were described in study report 2013N181329. Exposure and PD for the oldest pediatric cohort of 12 to 17 years were similar to that of adults treated with 50 mg tablets. For the children 6 to 12 years of age, PD modeling of a dose of 50 mg provided a target platelet count of near 50 Gi/L despite higher exposure. The majority of subjects aged 6 to 17 years of age and approximately half of subjects aged 1 to 5 years of age received eltrombopag doses ≥50 mg as their final eltrombopag regimen. Overall, East/Southeast Asian subjects received lower or similar eltrombopag final doses and had higher plasma eltrombopag exposures than non-East/Southeast Asian subjects. Taken together, this information lead to a recommendation for the starting doses listed in Table 3. Simulations support dose titration every two weeks for inadequate responses. .

Table 3: Proposed starting doses in pediatric patients with chronic ITP

Age group	Ancestry	Starting dose
Ages 6 years and older	Non-East Asian	50 mg daily
	East Asian	25 mg daily
Ages 1 to 5 years old	Non-East Asian	25 mg daily
	East Asian	25 mg every other day

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4.4.3 Pharmacokinetics

Using the marketed tablet, adolescents 12 to 17 years of age had similar plasma eltrombopag exposure as adults for the same 50 mg dose. Children 1 to 11 years of age had higher exposures.

Data from a relative bioavailability study (TRA111718) conducted in healthy adult subjects comparing the Powder for Oral Suspension (PfOS) demonstrated a 22% higher bioavailability of the PfOS. In pediatric patients age 1 to 5 years with ITP, the mean relative bioavailability of the PfOS formulation was 29% lower compared to the tablet formulation. This formulation effect is confounded by age and weight because the PfOS formulation was only used in subjects 1 to 5 years of age and the tablet formulation was only used in subjects 6 to 17 years of age.

Study TRA111718 also evaluated the food effect on the PK of the PfOS. Consistent with previous food-effect data with the tablet, administration of eltrombopag PfOS with a high-calcium meal reduced plasma eltrombopag AUC(0-∞) and Cmax by 75-80%. Administration of eltrombopag 2 hours before or 2 hours after a high calcium meal attenuated the food effect, but plasma eltrombopag exposure was decreased.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Trial Identifier (Identifier of Study Report)	Trial Objective(s)	Trial Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects
TRA108062 PETIT	Efficacy, Safety, PK, PD, QoL, PGx	Dose Finding Phase: NR, OL Randomized Period: R, DB, PC Eltrombopag Only Period: OL	Subjects between 1 and <18 years of age with chronic ITP	Dose Finding Phase: Eltrombopag tablet, 12.5 mg to 75 mg (adjusted based on platelet count) once daily for children 6 to 17 years old; Eltrombopag PfOS for children 1 to 5 years old. Maximum dose of 75 mg once daily. Randomized Period: Eltrombopag 12.5 mg to 75 mg (adjusted based on platelet count) or matching PBO once daily for children 6 to 17 years old.	Dose Finding Phase: 15 eltrombopag Randomized Period: 67 (45 ELT; 22 PBO) Eltrombopag Only Period: 67 Patients were

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				Eltrombopag PfOS or matching PBO for children 1 to 5 years old. Maximum dose of 75 mg once daily. Eltrombopag Only Period: Eltrombopag tablet, 12.5 mg to 75 mg once daily. Eltrombopag PfOS to maximum dose of 75 mg once daily.	enrolled at 22 centers in 6 countries (see Table 4 for specific countries).
TRA115450 PETIT2	Efficacy, Safety, PK, PD, PGx	Randomized Period: R, DB, PC Eltrombopag Only Period: OL	Subjects between 1 and <18 years with a confirmed diagnosis of chronic ITP for at least 1 year	Randomized Period: Eltrombopag tablet,12.5 mg to 75 mg once daily (adjusted based on platelet count) or matching PBO for children 6 to 17 years old; Eltrombopag PfOS or matching PBO for children 1 to 5 years old. Maximum dose of 75 mg once daily. Eltrombopag Only Period: Eltrombopag tablet, 12.5 mg to 75 mg once daily; Eltrombopag PfOS to maximum dose of 75 mg once daily	Randomized Period: 92 (63 ELT; 29 PBO) Eltrombopag Only Period: 87 Patients were enrolled at 38 centers in 12 countries (see Table 9 for specific countries).
2013N181329 Population PK and PK/PD Analyses of Eltrombopag in Pediatric Patients with Chronic ITP	To characterize the PK profile of eltrombopag, the relationship between plasma eltrombopag concentration and blood platelet counts, the effect of covariates on PK and PD parameters, and to select appropriate initial dose and dose titration schemes based on simulations in pediatric subjects with chronic ITP	Population PK and PK/PD analysis of data across studies	Pediatric Patients with chronic ITP	Subject data from other protocol	Not applicable
TRA110087 (b) (4)	Taste and color preference for six eltrombopag powder for oral	OL, R, 6 sequence CO	Healthy volunteers	Six powder for oral suspension formulations; reconstituted with 40mL of water to achieve an	12 (no subjects consumed eltrombopag

Seq. No. 390	suspension formulations			eltrombopag concentration of 5 mg/mL Subjects were instructed to roll a 5 mL (25 mg eltrombopag) sample over the tongue for 10 to 15 seconds, and then spit out the entire sample without swallowing.	– all samples were spit out)
TRA111718 Relative Bioavailability and Food Effect (b) (4)	Relative bioavailability of eltrombopag Powder for Oral Suspension (PfOS) formulation relative to the commercial 25 mg tablet. The effect of a high calcium meal separated by 2 hours on the bioavailability of PfOS	OL, R, 5-period, balanced CO	Healthy volunteers	**Treatment A** 25 mg tablet fasted **Treatment B** 25 mg PfOS fasted **Treatment C** 25 mg PfOS with high calcium meal **Treatment D** 25 mg PfOS given 2 hours before high calcium meal **Treatment E** 25 mg PfOS given 2 hours after high calcium meal	40

OL = Open label	PD = Pharmacodynamics	PK = Pharmacokinetics	PGx = Pharmacogenetics
DB = Double-blind	CO = Cross-over	NR = Non-randomized	R = Randomized
PC = Placebo-controlled	QoL = Quality of life	RD = Rising Dose	PBO = placebo

Table provided by the Applicant with minor modifications.

5.2 Review Strategy

For this clinical efficacy supplement, extensive review of study reports and clinical data for trials TRA108062/PETIT and TRA115450/PETIT2 were completed. Applicant analyses were repeated and verified. The review notes where FDA analyses differed from Applicant analyses in the pertinent sections. The clinical package was submitted for all age cohorts from 1 to 17 years of age. However, the CMC information on the pediatric formulation was not available at the time of this submission. (b) (4) (b) (4) this sNDA will only be evaluated for labeling of the age cohorts 6 years and older who used the tablet formulation that is currently on the market. This review will comprise a full review of safety and efficacy for all age cohorts while highlighting the information needed for labeling in the indication of treatment of patients ages 6 and older. Accordingly, the PK/PD studies and bioavailability/food

effect studies that were completed at least in part using the PfOS will be summarized in this review.

The review was conducted solely by Lori Ehrlich (Medical Officer) with the exception of the review of Patient Reported Outcomes in Section 6.1.6 which was conducted by Virginia Kwitkowski (Clinical Team Leader and Associate Director for Labeling for DHP).

A pediatric Written Request (WR) was issued to the Sponsor on January 25, 2010, and was revised on November 23, 2011. Evaluation of compliance with the WR will be conducted with review of (b) (4)

The individual clinical trials TRA108062/PETIT and TRA115450/PETIT2 are described in Section 5.3 below including the study demographics and major efficacy results during the randomized period of each trial. The endpoints that could be combined across trials are presented in Section 6 including relevant endpoints that included the open-label treatment period. Analysis of results by age cohort for the primary endpoint for each trial is listed under the respective trial in Section 5.3. All other analyses for secondary endpoints by age cohort were limited to the combined efficacy information in Section 6. Safety information is provided as a combination from both trials and presented in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

TRA108062/PETIT

PETIT (**PE**diatric patients with **T**hrombocytopenia from **IT**P) was a Phase 2, three part, staggered cohort, open-label and double-blind, randomized, placebo controlled trial to investigate the efficacy, safety, tolerability and pharmacokinetics of eltrombopag in previously treated pediatric subjects with chronic ITP. The design of the trial is presented in Figure 1. The dose selection, Part 1, of the trial was 24 weeks of treatment (12 weeks for determination of appropriate dosing per age cohort and an additional 12 weeks of treatment for efficacy analysis) for a total of 15 patients across three age cohorts (aged 12 to 17 years, 6 to 11 years, and 1 to 5 years). For the dose-escalation period, patients were first enrolled from the oldest age cohort and evaluation was completed before moving to the younger groups. Patients included in the dose finding period did not participate in Parts 2 or 3 of the trial. Part 2 was a randomized period of eltrombopag versus placebo, and patients were randomized 2:1. This phase was for 7 weeks, and the primary efficacy endpoint was evaluated in the first 6 weeks to allow for one week for unblinding and data evaluation prior to initiating part 3 of the trial. Part 3 was an open-label period where all patients were allowed treatment with eltrombopag. Patients randomized to placebo in Part 2 could take eltrombopag for 24 weeks during part 3. Patients randomized to eltrombopag continued treatment for an additional 17 weeks of treatment during Part 3 for a total treatment duration of 24

Reference ID: 3765521

weeks. The trial was to evaluate the efficacy of eltrombopag treatment in addition to standard of care treatment. To that end, patients were not allowed to discontinue baseline ITP medications during the randomized period to minimize confounding from other ITP treatments. Patients could have rescue ITP medications during the randomized period for lack of efficacy.

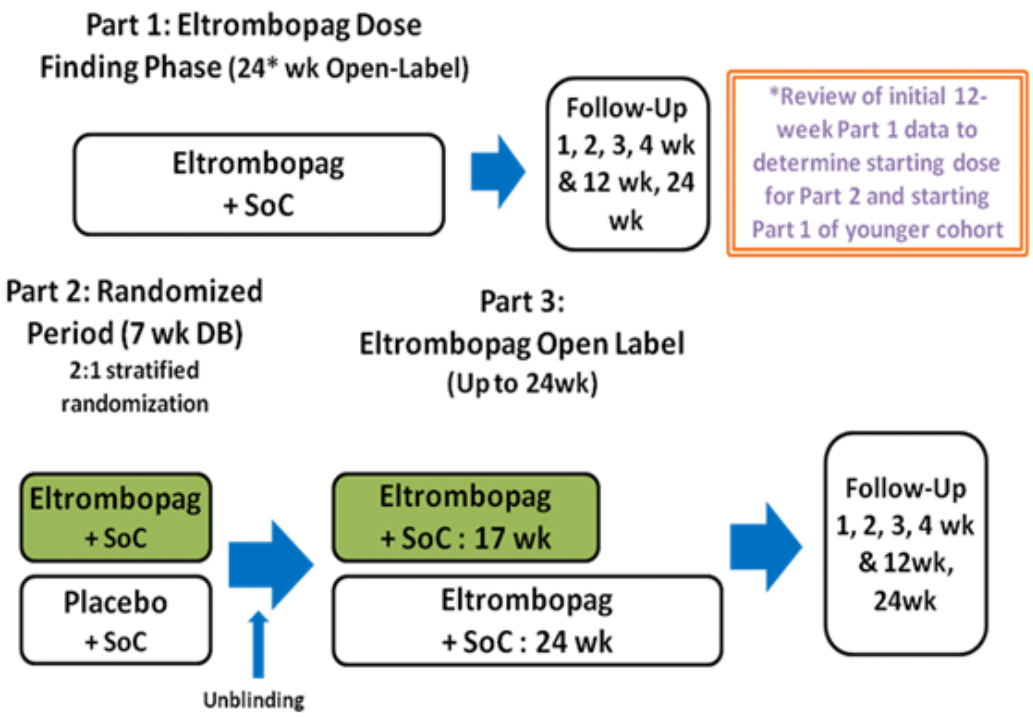

Figure 1: Design of Clinical Trial TRA108062/PETIT

Key eligibility criteria were patients ages 1 to <18 years, a confirmed diagnosis of chronic ITP for at least 6 months, and a platelet count <30 Gi/L. Subjects were refractory or relapsed after at least one prior ITP therapy, or not eligible, for a medical reason, to continue other ITP treatments. Subjects receiving concomitant ITP medication were allowed to continue with a dose that had been stable for at least 4 weeks prior to Day 1.

Trial Endpoints

Primary Endpoint: The proportion of subjects achieving platelet counts ≥50 Gi/L at least once between Days 8 and 43 (Weeks 1 and 6) of the Randomized Period.

Key Secondary Endpoints (during randomized period):

- The proportion of subjects with a sustained platelet response defined as platelet counts ≥50 Gi/L during treatment with eltrombopag in ≥60% of assessments between Weeks 2 and 6
- The proportion of patients requiring rescue ITP medications
- The ability to reduce bleeding symptoms.

Key Efficacy Endpoints (during open-label period):

- Proportion of patients achieving platelet counts ≥50 Gi/L at any time during the 24 weeks of eltrombopag treatment
- The proportion of subjects that reduced or discontinued baseline concomitant ITP medications
- The proportion of subjects that required protocol-defined rescue treatment
- The ability to reduce bleeding symptoms.

Subjects were evaluated weekly with clinical examinations and assessments including AE assessment and WHO bleeding scale, vital signs, hematology, blood chemistry, complete blood count including platelet count, and liver enzymes. Peripheral blood smears were evaluated approximately every 4 weeks for the duration of the study. Ophthalmologic exams were performed every 4 weeks while receiving eltrombopag then at 3 and 6 months after completion of the study. ECGs were not routinely monitored.

Analysis of demographic information provided for this trial showed that age, sex, ethnicity, race, and country were well balanced between the placebo and eltrombopag arms as shown in Table 4 (overall) and Table 5 (by age cohort). There were more females than males in this trial, but they were randomized equally between arms.

Table 4: PETIT trial, Demographics

	Eltrombopag (n=45) n (%)	**Placebo (n=22) n (%)**	**Total (n=67) n (%)**
Age			
Median (years)	9	10	10
Mean years (SD)	9.1 (4.3)	9.6 (4.7)	9.3 (4.4)
Range (years)	1-17	2-17	1-17
Sex			
Male	18 (40.0)	9 (40.9)	27 (40.3)
Female	27 (60.0)	13 (59.1)	40 (59.7)
Ethnicity			
Hispanic or Latino	3 (6.7)	3 (13.6)	6 (9.0)
Not Hispanic or Latino	42 (93.3)	19 (86.4)	61 (91.0)
Race			

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White	40 (88.9)	20 (90.9)	60 (89.6)
Asian	2 (4.4)	2 (9.1)	4 (6.0)
Black	1 (2.2)	0 (0)	1 (1.5)
Multiple	2 (4.4)	0 (0)	2 (3.0)
Country			
United States	24 (53.3)	14 (63.6)	38 (56.7)
Spain	9 (20.0)	4 (18.2)	13 (19.4)
Great Britain	6 (13.3)	1 (4.6)	7 (10.5)
Canada	5 (11.1)	1 (4.6)	6 (9.0)
Netherlands	0 (0)	2 (9.1)	2 (3.0)
France	1 (2.2)	0 (0)	1 (1.5)

Table 5: PETIT trial, Demographics by age cohort

	Cohort 1 (12-17 yo)		**Cohort 2 (6-11 yo)**		**Cohort 3 (1-5 yo)**	
	ELT (n=16) n (%)	**PLB (n=8) n (%)**	**ELT (n=19) n (%)**	**PLB (n=9) n (%)**	**ELT (n=10) n (%)**	**PLB (n=5) n (%)**
Age						
Median (years)	13	14.5	9	10	3.5	3
Mean yrs (SD)	13.7 (1.6)	14.6 (1.7)	8.2 (1.9)	8.6 (2.2)	3.3 (1.3)	3.6 (1.3)
Range (years)	12-17	13-17	6-11	6-11	1-5	2-5
Sex						
Male	8 (50.0)	5 (62.5)	5 (26.3)	1 (11.1)	5 (50.0)	3 (60.0)
Female	8 (50.0)	3 (37.5)	14 (73.7)	8 (88.9)	5 (50.0)	2 (40.0)
Ethnicity						
Hisp or Lat	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)	3 (30.0)	1 (20.0)
Not Hisp or Lat	16 (100)	6 (75.0)	19 (100)	9 (100)	7 (70.0)	4 (80.0)
Race						
White	15 (93.8)	7 (87.5)	17 (89.5)	8 (88.9)	8 (80.0)	5 (100)
Asian	0 (0.0)	1 (12.5)	1 (5.3)	1 (11.1)	1 (10.0)	0 (0.0)
Black	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)

Baseline disease characteristics for the PETIT trial are presented in Table 6 (overall) and Table 7 (by age cohort). Baseline platelet count, time from ITP diagnosis, and ITP medication use at baseline were all balanced between treatment arms. The 5 patients in the trial who had a prior splenectomy as part of their ITP treatment were randomized to the eltrombopag arm. The impact of this imbalance is discussed in the combined efficacy analysis in Section 6.1.7.

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Table 6: PETIT trial, Baseline disease characteristics

	Eltrombopag (n=45) n (%)	Placebo (n=22) n (%)	Total (n=67) n (%)
Baseline platelet count, ≤15 Gi/L	23 (51.1)	11 (50.0)	34 (50.8)
Time from ITP diagn., ≥12 mo	37 (82.2)	20 (90.9)	57 (85.1)
ITP medication at baseline	5 (11.1)	2 (9.1)	7 (10.5)
Previous splenectomy	5 (11.1)	0 (0)	5 (7.5)

Table 7: PETIT trial, Baseline disease characteristics by age cohort

	Cohort 1 (12-17 yo)		Cohort 2 (6-11 yo)		Cohort 3 (1-5 yo)	
	ELT (n=16) n (%)	PLB (n=8) n (%)	ELT (n=19) n (%)	PLB (n=9) n (%)	ELT (n=19) n (%)	PLB (n=5) n (%)
Baseline platelets, ≤15 Gi/L	7 (43.8)	4 (50.0)	11 (57.9)	6 (66.7)	11 (57.9)	1 (20.0)
Time from diagnosis, ≥12 mo	15 (93.8)	8 (100)	17 (89.5)	7 (77.8)	17 (89.5)	5 (100)
ITP meds at baseline	2 (12.5)	0 (0.0)	1 (5.3)	2 (22.2)	1 (5.3)	0 (0.0)
Previous splenectomy	3 (18.8)	0 (0.0)	2 (10.5)	0 (0.0)	2 (10.5)	0 (0.0)

The primary efficacy endpoint for PETIT was the percentage of patients who had a platelet response (platelet count ≥50 Gi/L without rescue therapy) at least once between weeks 1 and 6 of the randomized period. At all weeks following initiation of the randomized medication, more patients in the eltrombopag group had a platelet response compared to the eltrobopag group as shown in Figure 2. Further, Table 8 shows that all cohorts have a higher percentage of responders in patients treated with eltrombopag compared to placebo except for the youngest cohort 3. In the small numbers of patients in cohort 3, there were more patients with a response at least once, but these responses were not sustained in the placebo group as discussed below.

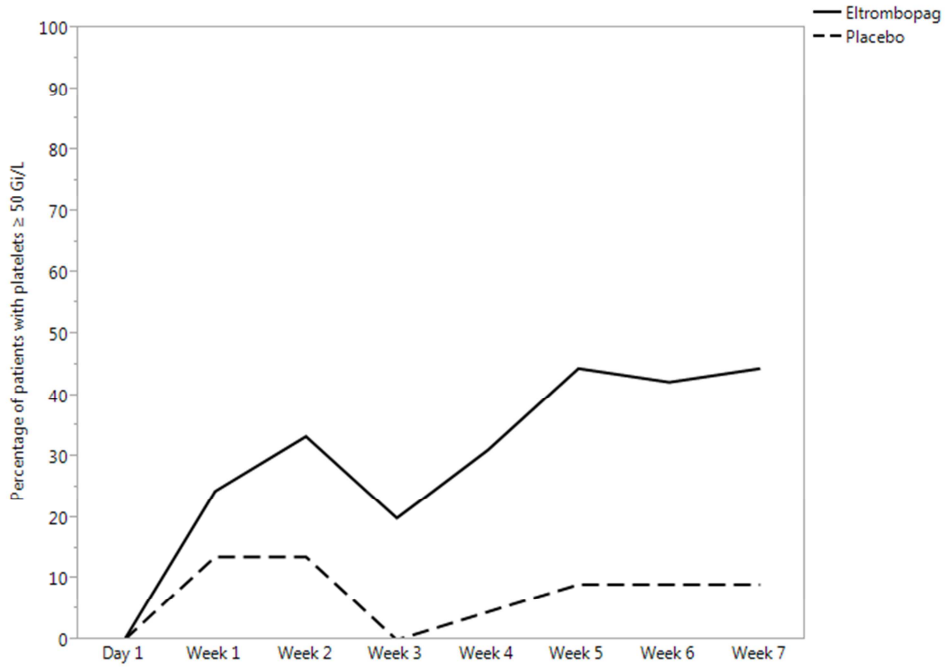

Figure 2: PETIT trial, Percent patients with platelets ≥50 Gi/L by week, ITT population

Table 8: PETIT trial, Patients with platelet count ≥50 Gi/L at least once in weeks 1 to 6 of the randomized period, n (%)

Age Cohort	Eltrombopag	Placebo
Overall*	28/45 (62.2%)	7/22 (31.8%)
Cohort 1 (12-17 years)	10/16 (62.5%)	0/8 (0%)
Cohort 2 (6-11 years)	12/19 (63.2%)	3/9 (33.3%)
Cohort 3 (1-5 years)	6/10 (60.0%)	4/5 (80%)

*p-value = 0.011

For labeling in this supplement, only Cohorts 1 and 2 were included. In those two cohorts combined, eltrombopag responders were 22/35 (62.9%), and placebo responders were 3/17 (17.6%).

For the PETIT trial, the shorter duration of the randomized period did not allow for the same definition of a sustained responder as in the longer PETIT2 trial described below. In this trial, the most comparable definition was the proportion of subjects with platelet counts ≥50 Gi/L in ≥60% of assessments between Days 15 and 43 (weeks 2 to 6) of the Randomized Period, which is a response in at least 3 of those 5 weeks. More patients treated with eltrombopag were considered a sustained responder (16/45, 35.6%) than in the patients treated with placebo (0/22, 0%). In fact, there were no sustained responders in the placebo group. In cohort 3 (age 1 to 5 years), 30% (3/10) patients were sustained responders compared to none in the placebo group, so despite there being more patients in the placebo group who had a platelet count ≥50 Gi/L at least once in the first 6 weeks, these patients did not have ongoing responses.

Other secondary endpoints are discussed in the combined efficacy information in Section 6.

TRA115450/PETIT2

PETIT2 (**PE**diatric patients with **T**hrombocytopenia from **IT**P 2) was a Phase 3, two-part, double-blind, randomized, placebo-controlled and open-label trial to investigate the efficacy, safety and tolerability of eltrombopag in pediatric subjects with previously treated chronic ITP. The design of the trial is presented in Figure 3. Part 1 was a randomized period of eltrombopag versus placebo where patients were randomized 2:1. This phase was for 13 weeks. The primary efficacy was evaluated in the first 12 weeks to allow for one week for unblinding and data evaluation prior to initiating part 2 of the trial. Part 2 was an open-label period where all patients were allowed treatment with eltrombopag for 24 weeks regardless of the arm to which they were randomized in part 1. Therefore, patients randomized to eltrombopag could be treated for a total of 37 weeks. Similar to the PETIT trial, the study treatment was in addition to standard of care treatment, and patients were not allowed to discontinue baseline ITP medications during the randomized period to minimize confounding from other ITP treatments. Patients could have rescue ITP medications during the randomized period for lack of efficacy.

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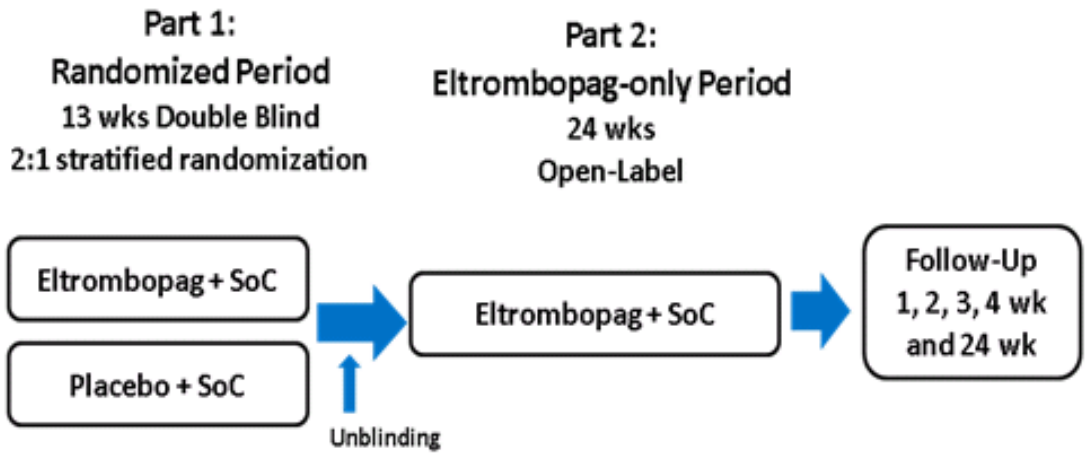

Figure 3: Design of Clinical Trial TRA115450/PETIT2

The key eligibility criteria were the same as PETIT except the patient must have had the diagnosis of ITP for at least 1 year.

Trial Endpoints

Primary Efficacy Endpoint: The proportion of subjects on eltrombopag, compared to placebo, achieving platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 to 12 of Randomized Period.

Key Secondary Endpoints (during randomized period):

- The proportion of subjects that achieved platelet counts ≥50 Gi/L at any time during the first 6 weeks and first 12 weeks
- The proportion of patients requiring rescue ITP medications
- The ability to reduce bleeding symptoms.

Key Efficacy Endpoints (during open-label period):

- Proportion of patients achieving platelet counts ≥50 Gi/L at any time during Part 2
- The proportion of subjects that reduced or discontinued baseline concomitant ITP medications
- The proportion of subjects that required protocol-defined rescue treatment
- The ability to reduce bleeding symptoms.

Subjects were evaluated weekly with clinical examinations and assessments including AE assessment and WHO bleeding scale, vital signs, hematology, blood chemistry, complete blood count including platelet count, and liver enzymes. Peripheral blood smears were evaluated approximately every 4 weeks for the duration of the study. Ophthalmologic exams were performed every 4 weeks while receiving eltrombopag

then at 3 and 6 months after completion of the study. ECGs were not routinely monitored.

Analysis of demographic information provided for this trial showed that age, sex, ethnicity, race, and country were well balanced between the placebo and eltrombopag arms as shown in Table 9 (overall) and Table 10 (by age cohort). There were a higher number of Asian patients in this trial compared to the PETIT trial due to the sites of enrollment, but these patients were balanced between the treatment arms.

Table 9: PETIT2 trial, Demographics

	Eltrombopag (n=63) n (%)	**Placebo (n=29) n (%)**	**Total (n=92) n (%)**
Age			
Median (years)	9	9	9
Mean years (SD)	9.4 (4.4)	9.8 (4.0)	9.5 (4.3)
Range (years)	1-17	4-17	1-17
Sex			
Male	33 (52.4)	15 (51.7)	48 (52.2)
Female	30 (47.6)	14 (48.3)	44 (47.8)
Ethnicity			
Hispanic or Latino	6 (9.5)	1 (3.5)	7 (7.6)
Not Hispanic or Latino	57 (90.5)	28 (96.6)	85 (92.4)
Race			
White	41 (65.1)	19 (65.5)	60 (65.2)
Asian	21 (33.3)	10 (34.5)	31 (33.7)
Black	1 (1.6)	0 (0)	1 (1.1)
Country			
United States	3 (4.8)	1 (3.4)	4 (4.4)
Thailand	17 (27.0)	9 (31.0)	26 (28.3)
Russia	7 (11.1)	6 (20.7)	13 (14.1)
Italy	9 (14.3)	3 (10.3)	12 (13.0)
Czech Republic	3 (4.8)	4 (13.8)	7 (7.6)
Great Britain	5 (7.9)	2 (6.9)	7 (7.6)
Israel	6 (9.5)	1 (3.4)	7 (7.6)
Germany	4 (6.4)	1 (3.4)	5 (5.4)
Argentina	3 (4.8)	1 (3.4)	4 (4.4)
Spain	3 (4.8)	0 (0)	3 (3.3)
Hong Kong	1 (1.6)	1 (3.4)	2 (2.2)
Taiwan	2 (3.2)	0 (0)	2 (2.2)

Table 10: PETIT2 trial, Demographics by age cohort

	Cohort 1 (12-17 yo)		Cohort 2 (6-11 yo)		Cohort 3 (1-5 yo)	
	ELT (n=24) n* (%)	PLB(n=10) n (%)	ELT (n=25) n* (%)	PLB(n=13) n (%)	ELT (n=14) n (%)	PLB (n=6) n (%)
Age						
Median (years)	14	14	8	9	4	5
Mean yrs (SD)	14.1 (1.8)	14.3 (2.1)	8.0 (1.7)	8.7 (1.7)	3.6 (1.2)	4.7 (0.5)
Range (years)	12-17	12-17	6-11	6-11	1-5	4-5
Sex						
Male	15 (62.5)	7 (70.0)	12 (48.0)	6 (46.2)	6 (42.9)	2 (33.3)
Female	9 (37.5)	3 (30.0)	13 (52.0)	7 (53.8)	8 (57.1)	4 (66.7)
Ethnicity						
Hisp or Lat	0 (0.0)	0 (0.0)	2 (8.0)	1 (7.7)	4 (28.6)	0 (0.0)
Not Hisp or Lat	24 (100)	10 (100)	23 (92.0)	12 (92.3)	10 (71.4)	6 (100)
Race						
White	16 (66.7)	7 (70.0)	16 (64.0)	8 (61.5)	9 (64.3)	4 (66.7)
Asian	7 (29.2)	3 (30.0)	9 (36.0)	5 (38.5)	5 (35.7)	2 (33.3)
Black	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*In the original data sets from the Applicant, 16-year-old patient 781 was mistakenly placed into Cohort 2. This was corrected in a response to information request.

Baseline disease characteristics for the PETIT2 trial are presented in Table 11 (overall) and Table 12 (by age cohort). Baseline platelet count was balanced between treatment arms. The time from ITP diagnosis of less than or greater than 12 months was not applicable to this trial as the entry criteria required a diagnosis of at least 1 year. There were more patients who were on baseline ITP medications randomized to the eltrombopag group, and the 4 patients in the trial who had a prior splenectomy as part of their ITP treatment were all randomized to the eltrombopag arm. The impacts of these two imbalances are discussed in the combined efficacy analysis in Section 6.1.7.

Table 11: PETIT2 trial, Baseline disease characteristics

	Eltrombopag (n=63) n (%)	Placebo (n=29) n (%)	Total (n=92) n (%)
Baseline platelet count, ≤15 Gi/L	38 (60.3)	19 (65.5)	57 (62.0)
Time from ITP diagn., ≥12 mo*	n/a	n/a	n/a
ITP medication at baseline	13 (20.6)	1 (3.4)	14 (15.2)
Previous splenectomy	4 (6.3)	0 (0.0)	4 (4.3)

*Trial included only patients with chronic ITP for ≥12 months

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Table 12: PETIT2 trial, Baseline disease characteristics by age cohort

	Cohort 1 (12-17 yo)		Cohort 2 (6-11 yo)		Cohort 3 (1-5 yo)	
	ELT (n=23) n (%)	PLB(n=10) n (%)	ELT (n=26) n (%)	PLB(n=13) n (%)	ELT (n=14) n (%)	PLB (n=6) n (%)
Baseline platelets, ≤15 Gi/L	15 (65.2)	4 (40.0)	16 (61.5)	10 (76.9)	7 (50.0)	5 (83.3)
Time from diagn, ≥12 mo*	n/a	n/a	n/a	n/a	n/a	n/a
ITP meds at baseline	3 (13.0)	0 (0.0)	6 (23.1)	0 (0.0)	4 (28.6)	1 (16.7)
Previous splenectomy	2 (8.7)	0 (0.0)	1 (3.8)	0 (0.0)	1 (7.1)	0 (0.0)

*Trial included only patients with chronic ITP for ≥12 months

The primary efficacy endpoint for PETIT2 was the percentage of sustained responders defined as proportion of subjects on eltrombopag achieving platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 to 12 of Randomized Period. A higher proportion of patients in the eltrombopag group achieved a sustained platelet response in all age cohorts as shown in Table 13.

Table 13: PETIT2 trial, Patients achieving a sustained response

Age Cohort	Eltrombopag	Placebo
Overall*	26/63 (41.3%)	1/29 (3.4%)
Cohort 1 (12-17 years)	10/24 (41.7%)	1/10 (10%)
Cohort 2 (6-11 years)	11/25 (44.0%)	0/13 (0%)
Cohort 3 (1-5 years)	5/14 (35.7%)	0/6 (0%)

*p-value < 0.001

For labeling in this supplement, only Cohorts 1 and 2 were included. In those two cohorts combined, eltrombopag sustained responders were 21/49 (42.9%), and placebo sustained responders were 1/23 (4.3%).

For PETIT2, patients were analyzed to be responders at any time in the first 6 weeks of the trial to allow comparison with PETIT. The analysis was also extented to patient who responded in the first 12 week of the trial. Those results are reflected in Figure 4. Consistent with the results of the PETIT trial, more patients in PETIT2 who were randomized to receive eltrombopag had a platelet response in the first 6 weeks (40/63, 63.5%) or in the first 12 weeks (47/63, 74.6%) compared to patient randomized to receive placebo in the first 6 weeks (5/29, 17.2%) or in the first 12 weeks (6/29, 20.7%).

The initial data from the Applicant did not count patient 343 in the PETIT2 trial as a sustained responder or a responder during the first 6 weeks because his baseline

platelet count was 38 Gi/L. On screening labs on day -2, the patient had a platelet count of 28 Gi/L, so he qualified for enrollment in the trial. Per the Applicant's guidelines, for any patients whose baseline platelet count was ≥30 Gi/L, the subject's assessments will be classified as a negative response until their platelet count falls below 30Gi/L. Once a subject's platelet count has fallen below 30 Gi/L any subsequent assessments will be classified as a positive response if the platelet count is ≥50Gi/L (unless they are taking a rescue medication). Patient 343 was randomized to eltrombopag treatment, and he had a response to 66 Gi/L by week 2 and a maximum response of 404 Gi/L at week 4. At his week 4 assessment, his study drug was held for a platelet count of >400 Gi/L and he subsequently dropped to 2 Gi/L by week 6. He was not considered a responder by the Applicant's criteria until after the study drug was held and he had a count <30 Gi/L at week 6. After restarting the study drug, he again had a robust response to eltrombopag with a platelet count of 139 in week 7. Given his robust initial response with a rise in his platelet count of more than 300 Gi/L, we considered him a responder in the first 6 weeks and a sustained responder in addition to being a responder in the first 12 weeks as previously assessed. We asked the Applicant to revise the label to include this patient as a sustained responder.

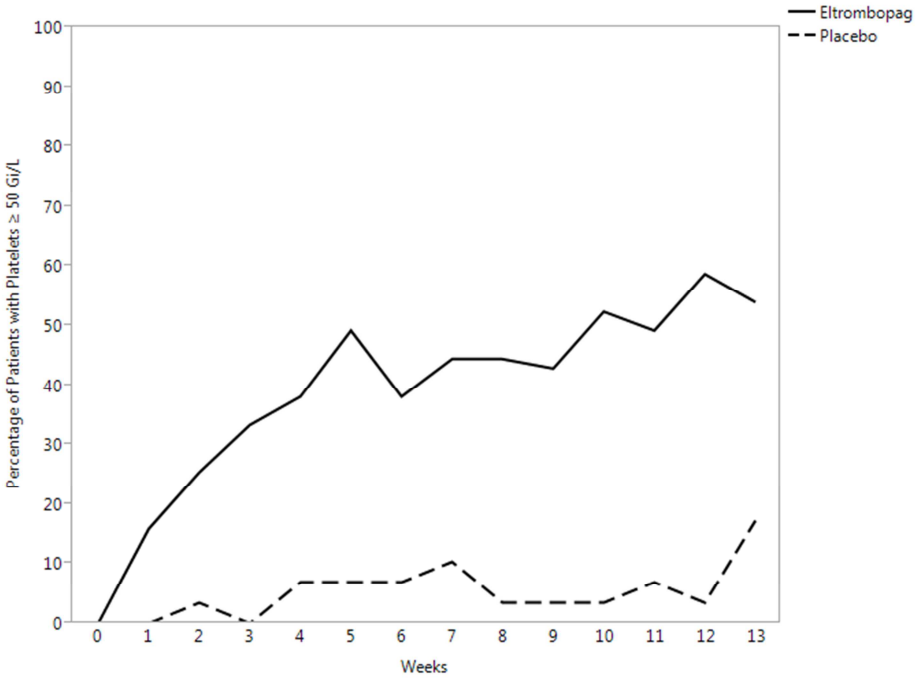

Figure 4: PETIT2 trial, Percentage of patients with platelets ≥50 Gi/L by week in the randomized period, ITT population

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6 Review of Efficacy

Efficacy Summary

Both pediatric clinical trials met their primary efficacy endpoint, and eltrombopag was shown to be efficacious in raising the platelet counts of pediatric patients ages 1 to 17 with chronic ITP. Evaluation of the secondary endpoints in both studies also favored eltrombopag over placebo. Pooled data from both trials from similar endpoints supported the individual study results. In both studies, the cohort 1 (12 to 17 years) had the highest proportion of responders with fewer responders in cohort 2 (6 to 11 years), and even fewer in the youngest cohort 3 (1 to 5 years); however, the drug was active in all age groups.

6.1 Indication

The proposed indication is "Promacta for the treatment of thrombocytopenia in adult and pediatric patients 6 years and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy." The proposed indication is acceptable because it is supported by the results of the PETIT and PETIT2 trials.

6.1.1 Methods

The designs of both pediatric trials were similar, but due to the difference in duration of the randomized period during each trial, not all efficacy endpoints could be combined. Shared efficacy endpoints during the randomized period included the proportion of platelet responders at any time in the first 6 weeks, the proportion of sustained responders, the proportion of patients requiring rescue ITP medications, the ability to reduce bleeding symptoms, and the time to platelet response. Shared efficacy endpoints during the open-label portion of the trial included the proportion of patients achieving a platelet response of ≥50 Gi/L during 24 weeks of eltrombopag treatment and the proportion of subjects that reduced or discontinued baseline concomitant ITP medications.

The definition of sustained responders was different between trials, but the responders were combined for a more robust analysis of the proportion of sustained responders in the patients receiving eltrombopag compared to those receiving placebo. In PETIT, a sustained responder was defined as a subject who achieved platelet counts ≥50 Gi/L in ≥ *60% of assessments between weeks 2 to 6* of the randomized treatment period. In PETIT2, a sustained responder was defined as a subject who achieved platelet counts ≥50 Gi/L for *at least 6 out of 8 weeks, between weeks 5 to 12* of the randomized period.

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A comparison of key elements of each pediatric trial is presented in Table 14.

Table 14: Comparison of key elements of PETIT and PETIT2

Design Elements	PETIT	PETIT2
Phase	2	3
Dose finding phase	24 weeks	Not included
Randomized period (2:1 ELT:PLB)	7 weeks	13 weeks
Eltrombopag only period	24 or 17 weeks duration for subjects randomized to placebo or eltrombopag, respectively	24 weeks duration
Follow up	Weekly follow-up for 4 weeks after the last dose of study treatment, or follow-up after 4 weeks if continuing post-study eltrombopag. Ocular examination 12 weeks and 24 weeks after eltrombopag open-label period	Weekly follow-up for 4 weeks after the last dose of study treatment, or follow-up after 4 weeks if continuing post-study eltrombopag. Ocular examination 24 weeks after completion of eltrombopag open-label period
Primary endpoint	The proportion of subjects achieving platelet counts ≥50 Gi/L at least once between Days 8 and 43 (Weeks 1 and 6) of the Randomized Period	The proportion of subjects on eltrombopag, compared to placebo, achieving platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 to 12 of Randomized Period

Reviewer Comments on Selection of Endpoints: Patients with ITP experience abnormally low platelet counts that increase their risk of bleeding. Bleeding can cause symptoms when associated with severe bleeding, but most children experience only mild and asymptomatic bleeding in the form of petechiae and bruising. The goal of treatment of ITP is to maintain a platelet count that is adequate to prevent bleeding, typically considered ≥50 Gi/L.

Prior approvals in ITP (in adults) were based upon similar endpoints of sustained increases in platelets. Prior approvals have not required evidence of reduced bleeding, symptomatic improvement, or prolonged survival. The endpoints for the PETIT and PETIT2 trials were agreed upon in advance of trial conduct through the Pediatric Written Request discussions. The endpoints selected are considered acceptable for regular approval by the Agency.

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Missing data during both studies were treated as negative response in the computation of the primary endpoint. The data completion rate for the primary endpoint for PETIT was 93% (62/67 pts had platelet counts available for weeks 1-6) and for PETIT2 was 92% (85/92 pts had platelet counts available for weeks 5-12). Multiple imputations by the statistics reviewer for the missing data analysis for the primary endpoints produced similar result as those provided.

6.1.2 Demographics

The combined demographics for both trials are shown in Table 15. The distribution of age, sex, ethnicity, and race was balanced between the placebo and eltrombopag groups.

Table 15: Combined trials, Demographics

	Eltrombopag (n=108) n (%)	**Placebo (n=51) n (%)**	**Total (n=159) n (%)**
Age			
Median (years)	9	10	9
Mean years (SD)	9.2 (4.4)	9.7 (4.3)	9.4 (4.3)
Range (years)	1-17	2-17	1-17
Sex			
Male	51 (47.2)	24 (47.1)	75 (47.2)
Female	57 (52.8)	27 (52.9)	84 (52.8)
Ethnicity			
Hispanic or Latino	9 (8.3)	4 (7.8)	13 (8.2)
Not Hispanic or Latino	99 (91.7)	47 (92.2)	146 (91.8)
Race			
White	81 (75.0)	39 (76.5)	120 (75.5)
Asian	23 (21.3)	12 (23.5)	35 (22.0)
Black	2 (1.9)	0 (0)	2 (1.3)
Multiple	2 (1.9)	0 (0)	2 (1.3)

The combined baseline disease characteristics for both trials are shown in Table 16. The baseline platelet count and time from ITP diagnosis are balanced between the placebo and eltrombopag arms. As discussed in the trial design, patients in PETIT2 had to have been diagnosed with ITP at least one year prior to study enrollment while those in PETIT only required 6 months, therefore the majority of patients in the combined group had been diagnosed at least one year prior to the study. The

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percentage of patients taking ITP medications at baseline and those with a previous splenectomy were more frequently randomized to the eltrombopag arm. The influence of this imbalance will be discussed below in the efficacy analysis in Section 6.1.7.

Table 16: Combined trials, Baseline disease characteristics

	Eltrombopag (n=108) n (%)	**Placebo (n=51) n (%)**	**Total (n=159) n (%)**
Baseline platelet count, ≤15 Gi/L	61 (56.5)	30 (58.8)	91 (57.2)
Time from ITP diagn., ≥12 mo*	100 (92.6)	49 (89.1)	149 (93.7)
ITP medication at baseline	18 (16.7)	3 (5.9)	21 (13.2)
Previous splenectomy	9 (8.3)	0 (0.0)	9 (5.7)

6.1.3 Subject Disposition

The intent-to-treat population (159 subjects) includes 67 subjects randomized in PETIT and 92 subjects randomized in PETIT2. Two subjects in PETIT were randomized to eltrombopag, but not dosed. One subject in PETIT (patient 324) was randomized to placebo but received treatment with eltrombopag in error. This patient is included in the placebo group for the ITT Population, but is included in the eltrombopag group for the Safety Population.

The majority of subjects completed the studies including the follow-up period. Overall, 19 (11.9%) subjects withdrew prematurely from the studies with a higher proportion of subjects withdrawing in the eltrombopag group (14.8% vs. 5.9%).

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints of the two pediatric trials were different (see Table 14) and described above in Section 5.3. Analyses of the efficacy endpoints for the combined trials were therefore provided in Section 6.1.5.

6.1.5 Analysis of Secondary Endpoints(s)

Where possible within the limitations of different trial designs, the efficacy results were combined. Most notably, patients with a response during the first 6 weeks of the randomized period and the patients with a sustained response during the randomized period were combined between the two trials for analysis. Consistent with the results of the individual trials, there was a robust platelet response in the first 6 weeks of eltrombopag treatment compared to placebo, see Table 17. The percentage of

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responders was slightly lower in the youngest age cohort, but there was still activity in that cohort. Notably, there were more patients in the younger cohorts who had a platelet count of ≥50 Gi/L in the placebo arm compared to the older cohorts. The platelet counts in patients with chronic ITP are more variable in the younger patients. This dilutes some of the percieved efficacy improvement in the younger cohorts for a platelet response at any time, but as shown below, the responses in the placebo group are not sustained.

Table 17: Combined trials efficacy analysis, Patients with a platelet response at least once in the first 6 weeks of the randomized period.

Age Cohort	Eltrombopag	Placebo
Overall	68/108 (63.0%)	12/51 (23.5%)
Cohort 1 (12-17 years)	26/40 (65.0%)	2/18 (11.1%)
Cohort 2 (6-11 years)	29/44 (65.9%)	6/22 (27.3%)
Cohort 3 (1-5 years)	13/24 (54.2%)	4/11 (36.4%)

Similarly, there was a robust platelet response for sustained responders in patients treated with eltrombopag compared to patients treated with placebo, see Table 18. The definition of sustained platelet responders in each trial is described in section 6.1.1. There was only slightly lower activity in the youngest age cohort compared to the older patients when evaluating a sustained response, but there is significant activity in all age cohorts.

Table 18: Combined trials efficacy analysis, Patients with sustained platelet response

Age Cohort	Eltrombopag	Placebo
Overall	42/108 (38.9%)	1/51 (2.0%)
Cohort 1 (12-17 years)	16/40 (40.0%)	1/18 (5.6%)
Cohort 2 (6-11 years)	18/44 (40.9%)	0/22 (0%)
Cohort 3 (1-5 years)	8/24 (33.3%)	0/11 (0%)

6.1.6 Other Endpoints

<u>During the randomized period</u>

Rescue treatment is defined as either a new ITP medication, an increase in dose of concomitant ITP medication from baseline, platelet transfusion, or splenectomy. Fewer patients treated with eltrombopag required rescue treatment during the randomized periods (14/108, 13.0%) compared to patients in the placebo group (16/51, 31.4%).

Note that the duration of the randomized period was 7 weeks in PETIT and 13 weeks in PETIT2. The majority of rescue treatments were the addition or of an increased dose of steroids.

The decrease in any grade bleeding was not statistically significant in either trial between placebo and eltrombopag treatment arms, but there was a statistically significant decrease in clinically significant bleeding, defined as WHO Bleeding Scale Grades 2-4, in both studies, summarized in Table 19. For the PETIT trial during the randomized period, most bleeding was WHO Grade 1 or 2. Two subjects (1 in each treatment group) reported a WHO Grade 3 bleed. No subject reported WHO Grade 4 bleeding. For the PETIT2 trial during the randomized period, no eltrombopag subject reported WHO Grade 3 bleeding. Three placebo subjects reported WHO Grade 3 bleeding, one of whom went on to have a grade 4 serious adverse event (SAE) of abdominal hemorrhage described further in Section 7.3.2.

In both trials, there was a decrease in bleeding events from baseline. In the PETIT trial, decrease from baseline to week 6 in the eltrombopag treated patients was from 20% to 2.2% and in the placebo treated patients it was from 27% to 18%. In the PETIT2 trial, the decrease in bleeding from baseline was not statistically significant, but had a higher magnitude of decrease in the eltrombopag arm of 20% (from 25% at baseline to 5% during treatment) compared to the placebo arm of 13% (from 21% at baseline to 7% during treatment).

Table 19: Combined trials efficacy analysis, Patients with bleeding events during the randomized period

	Eltrombopag (n=45) n (%)	**Placebo (n=22) n (%)**	**Odds Ratio**
Any Bleeds Grade 1-4	33 (73.3%)	20 (90.9%)	0.27 (p=0.122)
Clinically Significant Grade 2-4	12 (26.7%)	13 (59.1%)	0.21 (p=0.013)

Patient Reported Outcomes during the randomized period

Most symptoms of ITP are from bleeding, but are also considered signs (purpura, petechiae, nosebleeds, gingival/oral mucocutaneous bleeding, hematuria, melena, and heavy menstrual bleeding). Bleeding can be both patient reported and measured objectively via physical examination and laboratory testing. ITP does not appear to cause other systemic symptoms.

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NDA 022291, S-015 contains the results from two randomized, placebo-controlled trials: TRA108062/PETIT and TRA115450/PETIT2. The Study Endpoints and Labeling Development (SEALD) staff was consulted on March 6, 2015. They were asked to evaluate the reliability of the Kids' ITP Tools (KIT) questionnaire and results for labeling claims. There were no proposed labeling claims, but our intention was to evaluate the information in case any claims were supported or warranted so that the patient's perspective could inform the clinical benefit of eltrombopag in the indicated population.

Instrument Review:

The Kids' ITP Tools (KIT) is a questionnaire developed (starting in 1997) by the Canadian Children's Platelet Study Group designed to measure the health-related quality of life of children with ITP. Early in development, the instrument was referred to as "the disease-specific health-related quality-of-life instruments"[5]. Eighty-eight children with acute or chronic ITP (and their parents) participated in the development of the KIT instrument[6]. The instrument for children with ITP was designed in self-assessment (for children 7 and older) and proxy-assessment formats (for those younger than 7). The instrument development work was published in 2003 by Bernard et al[6]. The ITP-Child Quality-of-Life Questionnaire includes five domains: treatment side effect-related, intervention-related, disease-related, activity-related, and family-related.

The child instrument includes 26 items plus one open-ended question and uses an 8 item Likert scale with text anchors (0-not at all, 1-Hardly at all, 2-A little bit, 3-Some, 4-Quite a bit, 5-A lot, 6- A great deal, and 9-not applicable). The recall period was 7 days for chronic ITP and 2 days for acute ITP. The instrument items are listed in Table 20.

As ITP does not appear to cause systemic symptoms (outside of symptoms caused by bleeding), the instrument appears to measure impacts distal to the actual direct effects of the disease itself.

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Table 20: Kids' ITP Tools, Children's instrument items

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The Parent Instrument also contains 26 items and a single open-ended item. The SEALD team was consulted to review the Kids' ITP Tools for possible labeling of descriptive claims. The Applicant did not propose any labeling claims for this secondary endpoint. The SEALD consult response by Michelle Campbell concluded that the evidence submitted by the Applicant is inadequate to demonstrate that the KIT is adequate to reliably measure health-related QoL in children with chronic idiopathic ITP. No data on the psychometrics of the instrument were provided, so the SEALD consult concluded that the KIT single overall score represents a multidimensional concept. Also, the results from the PETIT trial showed that the KIT did not meet the minimally important difference of improvement from baseline of at least one half of the standard deviation of the baseline score. The Applicant concluded that the KIT may not have been sensitive enough to show change in the PETIT trial.

Endpoint Positioning: Secondary endpoint without control of the Type I error rate. Trial TRA108062/PETIT included the following patient reported objectives and secondary endpoints:

Table 21: PETIT trial, Patient reported objectives and secondary endpoints

Objectives	Endpoints
To assess the impact of eltrombopag on the incidence and severity of bleeding symptoms when administered in previously treated pediatric subjects with chronic ITP.	The ability to reduce bleeding symptoms associated with ITP based on the WHO Bleeding Scale.
To evaluate the impact of eltrombopag on the quality of life of previously treated pediatric subjects with chronic ITP.	The impact of eltrombopag on the quality of life (subject and care giver reported outcomes) using the Kid's ITP Tools (KIT) questionnaire

Assessment of Bleeding Symptoms (TRA108062/PETIT)

The Time and Events Table in protocol TRA108062 (Section 4.3.1, amendment 05) states that the WHO Bleeding Scale was administered during Part 2 (randomized, placebo-controlled period) at the following time points: Screening, Day 1, and weekly from week 1 through 7. This instrument was also scheduled during the open-label period, but as PRO assessments may be biased when administered when patients or investigators are aware of the treatment assignment, only the blinded period will be discussed here. The protocol states that "the evaluation of bleeding symptoms will be done using the WHO bleeding scale, and should be the first clinical interaction to take place at each visit; bleeding should be assessed before reviewing the platelet count to avoid bias" (Section 7.4, amendment 05).

Neither the protocol nor the Clinical Study Report state exactly how the WHO Bleeding Scale was administered: whether the patient filled out a form or whether the clinician asked questions of the patient and filled out the form (either directly as reported by the patient or with interpretation). The Case Report Form for the WHO Bleeding Scale (page 19 of 227 of the Annotated CRF) requests the "date assessed" and "indicate the subject's bleeding severity". Because bleeding is considered an observable sign, and not a symptom that patients feel, this was most likely a Clinician Reported Outcome informed by patient reports of bleeding.

The bleeding symptoms endpoint was evaluated using the "WHO Bleeding Scale" (Appendix 1 of protocol TRA108062, amendment 05) and is reproduced below:

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Table 22: WHO Bleeding Scale

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

Per the Clinical Study Report, during the randomized period, the odds of any clinically significant bleeding (Grades 2-4) were lower in eltrombopag treated subjects (26.7%) than in placebo treated subjects (59.1%) (p=0.013). The odds of any bleeding (Grades 1-4) were also lower in eltrombopag treated subjects (73.3%) than in placebo treated subjects (90.9%); but this effect was not statistically significant.

The incidence of any grade bleeding reported at baseline in both treatment groups was the same (80%). By week 5, the proportion of eltrombopag subjects reporting any bleeding decreased to 35.6% and decreased further to 22.2% at Week 6. The placebo treated subjects reported any bleeding at a rate of >68% at each visit during the 6 week randomized period. While both treatment arms achieved a decrease in bleeding after starting the trial, the magnitude of change from baseline to Week 6 was greater in the eltrombopag group compared with the placebo group.

The same pattern was observed with regards to clinically significant bleeding (Grades 2-4) which was similar at baseline between treatment arms (20% for eltrombopag and 27.3% for placebo). Throughout the 6 week treatment period, clinically significant bleeding (Grades 2-4) occurred in <16% of eltrombopag subjects compared with 18-36% of placebo treated patients. By Week 6, the proportion of subjects reporting clinically significant bleeding decreased to 2.2% for the eltrombopag arm and 18% for the placebo arm.

Conclusion on WHO Bleeding Score findings: Eltrombopag treatment reduced the incidence of all grade and clinically significant bleeding during the randomized treatment period. The endpoint does not appear to have been assessed entirely as a patient reported outcome.

Assessment of Quality of Life (TRA108062/PETIT)

The QoL assessments using the Kid's ITP Tools (KIT) questionnaire were administered during the randomized period at screening, Day 1, Weeks 1-7. The questionnaire was also administered during the open label period, but for the reasons mentioned above those results will not be discussed here. The most relevant time period to assess patient reports is during the randomized blinded period.

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Per the Applicant, during the randomized double-blind period, the mean baseline KIT scores were similar across cohorts in patients randomized to receive eltrombopag (Cohort 1: 76.8, Cohort 2: 66.4, Cohort 3: 78.2). Patients randomized to receive placebo reported total KIT scores that were higher than the patients randomized to eltrombopag (Cohort 1: 83.9, Cohort 2: 71, Cohort 3: 82.6). The minimally important difference is estimated as 6.9, 9.2, and 5.9, respectively for Cohorts 1 to 3. The analysis of the KIT scores for all age groups combined is presented in Table 23. Additionally, in the randomized period, KIT scores were similar between patient and parental scores, between baseline and after 6 weeks of therapy. These findings suggest either that little change occurred in HRQoL after 6 weeks of therapy with eltrombopag, or that the instrument itself is insensitive to change.

Table 23: PETIT trial, Analysis of change in total KIT score from baseline to week 6 of the randomized period, ITT Population

	Placebo (N=22)	**Eltrombopag (N=45)**
Baseline KIT Score Mean (SD)	N=15 76.37 (17.1)	N=20 74.24 (14.4)
Change from Baseline to Week 6 KIT total score Mean (SD)	1.90 (8.5)	3.44 (9.6)
Model-Adjusted change from baseline in KIT total score at week 6 Mean (SD)	1.84 (2.5)	3.36 (2.0)
Difference from Placebo Mean (95% CI) P-value	-1.52 (-8.10, 5.06) 0.641	

Conclusion on findings from KIT (HRQoL): The KIT instruments were developed in a population of pediatric patients with ITP using qualitative methods of item generation. The population involved in item generation would be considered similar enough to the PETIT trial population. However, the Applicant did not provide adequate evidence of follow-up evaluations of content validity and construct validity that would make them acceptable to provide substantial evidence for labeling purposes.

In addition, the KIT results were not available in all randomized patients (15 out of 22 in the placebo arm and 20 out of 45 on the eltrombopag arm). No discussion was provided in the Applicant's submission for this missing data.

The FDA recognizes the importance of Health Related Quality of Life for children with ITP, so the instrument and data generated were evaluated (by SEALD and Virginia Kwitkowski) to attempt to identify anything that would not be misleading that could be

placed in the label. Given the information available about the instruments as well as the results generated, nothing acceptable for inclusion in the label could be identified.

During the open-label period

Patients were not allowed to discontinue baseline ITP medications during the randomized period. During the eltrombopag-only, open-label period of both trials, patients were allowed to discontinue baseline ITP medications if appropriate based on their platelet counts on treatment and decreased risk of bleeding. Twenty-eight subjects were taking baseline ITP meds at the start of the open-label period for both trials. Of those patients, 4 (14.2%) discontinued all baseline ITP meds, and 14 (50%) had a sustained reduction or discontinuation of baseline meds.

As further confirmation of the continued responses over a longer duration of treatment with eltrombopag, the percentage of patients with responses during 24 weeks of treatment were evaluated over both trials including the open-label periods of eltrombopag treatment, see Figure 5. After the initial month of treatment, approximately 50-70% of patients with assessments had a platelet count ≥50 Gi/L. There was a substantial amount of missing laboratory data over this time period, and over time this could reflect that patients who are not having any signs of low platelets (i.e. petechiae, nose bleeds, etc.) and are no longer coming in for weekly laboratory tests. For that reason, this analysis was done as the percentage of patients with a platelet response per the number of evaluable assessments. If reported as the number of patients who are still receiving eltrombopag regardless of the availability of results from that week, the response is 25-45% after the initial month of treatment.

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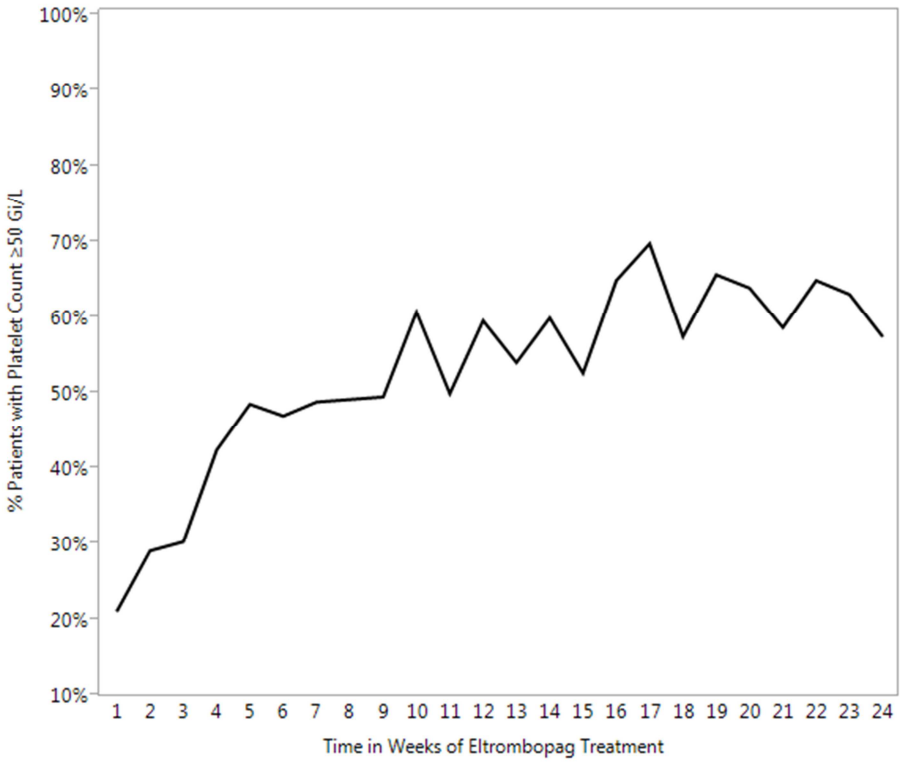

Figure 5: Combined trials, Percentage of patients with assessments who had platelets ≥50 Gi/L

6.1.7 Subpopulations

Additional subgroup analyses were done for patient demographics and baseline disease characteristics using the results of both PETIT and PETIT2 combined data. The odds ratio for response is shown in Figure 6 with corresponding numbers of responders shown in Table 24 for patients with a response at least once during the first 6 weeks of the randomized period. For sustained responders, the numbers of responders during the randomized period in each subgroup is shown in Table 25.

For a response in the first 6 weeks, all subset analyses favored treatment with eltrombopag except for in patients who were taking ITP medications at baseline which was equivocal. However, the number of patients treated with placebo in this subgroup was so small as to make the calculation of an odds ratio uninterpretable. Importantly, only patients treated with eltrombopag were sustained responders in this subgroup, and for sustained responders, an odds ratio could not be calculated because no patients in the placebo arm were sustained responders. The need for ITP medications at baseline likely reflects a population of patients where their disease is more refractory to treatments aimed at reducing platelet destruction. More patients were randomized to

the eltrombopag treated group in both studies (combined n=21, 18 in eltrombopag treated group and 3 in placebo treated group). The low number of patients in the placebo treated group did not allow for calculation of an odds ratio between groups. However, in the eltrombopag treated group, 12 patients (66.7%) were responders in the first 6 weeks, and 9 patients (50%) were sustained responders which is similar to the performance of patients who were not on baseline ITP medications with response rates of 62.2% and 36.7%, respectively.

In both studies, all patients who had a previous splenectomy (n=5 in PETIT and n=4 in PETIT2) were randomly assigned to receive eltrombopag. Of those 9 patients, 7 (77.8%) were responders at least once during the first 6 weeks, and 3 (33.3%) were sustained responders (defined differently in the two trials, see section 6.1.1 above). These proportions of responders, though evaluated in a small number of patients, are similar to the responders in the first 6 weeks and sustained responders in the patients who did not have a prior splenectomy when treated with eltrombopag, 61.6% and 23.5%, respectively. The effect of splenectomy on the efficacy of eltrombopag is difficult to predict, but likely reflects the refractoriness of these patients to treatments aimed at reducing platelet destruction. In that case, an increase in platelet production by eltrombopag may not be able to overcome the destruction, but there was still similar efficacy in analysis of this very small sample size in patients with a prior splenectomy.

Odds ratio for many of the subgroups either had small numbers of patients making them difficult to interpret or could not be analyzed because the response rates in the placebo group were zero or close to zero, particularly in analysis of patients with a sustained response.

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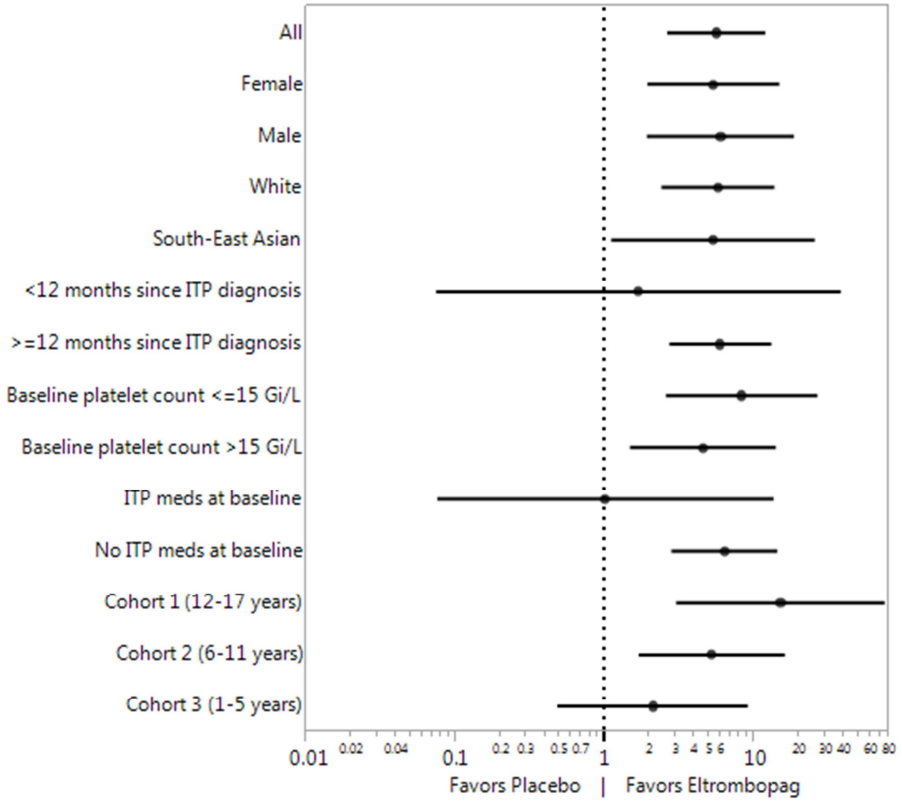

Figure 6: Combined trials efficacy analysis, Odds ratio of patients with a platelet response of >50 Gi/L in the first 6 weeks of the randomized period by subgroup

Table 24: Combined trials efficacy analysis, Subgroup analysis of patients with a platelet response of ≥50 Gi/L in the first 6 weeks of the randomized period

	Eltrombopag	Placebo
All	68/108 (63.0%)	12/51 (23.5%)
Sex		
Female	37/57 (64.9%)	7/27 (25.9%)
Male	31/51 (60.8%)	5/24 (20.8%)
Race		
White	51/81 (63.0%)	9/39 (23.1%)
South-East Asian	14/22 (63.6%)	3/12 (25.0%)
Other	3/5 (60.0%)	0/0
Time since ITP diagnosis		
<12 months since ITP diagnosis	5/8 (62.5%)	1/2 (50.0%)
≥12 months since ITP diagnosis	63/10 (63.0%)	11/49 (22.4%)
Baseline platelet count		
Baseline platelet count ≤15 Gi/L	34/61 (55.7%)	4/30 (13.3%)

Baseline platelet count >15 Gi/L	33/44 (75.0%)	8/20 (40.0%)
Missing baseline platelet count	1/3 (33.3%)	0/1 (0.0%)
ITP meds at baseline		
Yes	12/18 (66.7%)	2/3 (66.7%)
No	56/90 (62.2%)	10/48 (20.8%)
Previous splenectomy		
Yes	7/9 (77.8%)	0/0
No	61/99 (61.6%)	12/51 (23.5%)
Age cohort		
Cohort 1 (12-17 years)	26/40 (65.0%)	2/18 (11.1%)
Cohort 2 (6-11 years)	29/44 (65.9%)	6/22 (27.3%)
Cohort 3 (1-5 years)	13/24 (54.2%)	4/11 (36.4%)

Table 25: Combined trials efficacy analysis, Subgroup analysis of patients with a sustained response during the randomized period

	Eltrombopag	Placebo
All	42/108 (38.9%)	1/51 (2.0%)
Sex		
Female	26/57 (45.6%)	0/27 (0%)
Male	16/51 (31.4%)	1/24 (4.2%)
Race		
White	32/81 (39.5%)	1/39 (2.6%)
South-East Asian	8/22 (36.4%)	0/12 (0%)
Other	2/5 (40.0%)	0/0
Time since ITP diagnosis		
<12 months since ITP diagnosis	3/8 (37.5%)	0/2 (0.0%)
≥12 months since ITP diagnosis	39/100 (39.0%)	1/49 (2.0%)
Baseline platelet count		
Baseline platelet count ≤15 Gi/L	16/61 (26.2%)	0/30 (0%)
Baseline platelet count >15 Gi/L	25/44 (56.8%)	1/20 (5.0%)
Missing baseline platelet count	1/3 (33.3%)	0/1 (0%)
ITP meds at baseline		
Yes	9/18 (50.0%)	0/3 (0%)
No	33/90 (36.7%)	1/48 (2.1%)
Previous splenectomy		
Yes	3/9 (33.3%)	0/0
No	39/99 (39.4%)	1/51 (2.0%)
Age cohort		
Cohort 1 (12-17 years)	16/40 (40.0%)	1/18 (5.6%)
Cohort 2 (6-11 years)	18/44 (40.9%)	0/22 (0%)
Cohort 3 (1-5 years)	8/24 (33.3%)	0/11 (0%)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing information was provided in Section 4.4.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There was no evidence of persistence of efficacy. For the patients who did not receive post-treatment eltrombopag after completion of the trials, the median platelet counts returned to baseline within 2 weeks.

No tolerance effects were observed during the trial with similar efficacy results in the first 6 weeks of PETIT, the second 6 weeks of PETIT2, and the last 12 weeks of eltrombopag only treatment in both trials.

6.1.10 Additional Efficacy Issues/Analyses

The time to platelet response was defined as the time to first platelet count ≥50 Gi/L in the absence of rescue treatment. This was not a pre-specified endpoint. The median time to platelet response for patients receiving eltrombopag was 16 days (range: 7 to 44 days) and for patients receiving placebo was 28 days (range 7 to 43 days). While the range of time to response was similar for each group, the number of patients receiving placebo who had a platelet response was much lower than in the eltrombopag arm, and fewer responses were sustained, so this information should be interpreted with caution. See Table 26.

Table 26: Combined trials efficacy analysis, Time to treatment response during the randomized period

Days from first dose to response	Eltrombopag (n=108)	Placebo (n=51)
Subjects with a response, n	68	12
Mean	19.9	24.7
SD	11.3	13.1
25th quartile	8	11.25
Median	15.5	28
75th quartile	29	37.5
Min.	7	7
Max	44	43

Reference ID: 3765521

An analysis was also conducted to evaluate the time to first response only in sustained responders. This analysis is shown in Table 27 for both pediatric trials combined.

Table 27: Combined trials efficacy analysis, Time to treatment response during the randomized period for sustained responders

Days from first dose to response	Eltrombopag (n=108)	Placebo (n=51)
Subjects with a response, n	42	1
Mean	15.4	39
SD	7.6	
25th quartile	8	
Median	15	
75th quartile	22	
Min.	7	
Max	30	

For labeling purposes, the time to first response analysis was conducted on sustained responders only in the PETIT2 trial. Similar to the combined trial analysis, sustained responders in PETIT2 had a median time to first response of 15 days (interquartile range 8-22.5 days). For a more clinically meaningful analysis, this was reported in the label as the percentage of patients who had a first response within the first two weeks. For all cohorts, in the patients who were sustained responders, 61.5% (16/26) had an initial response in the first 2 weeks after starting eltrombopag (71.4% [15/21] for patients in cohorts 1 and 2 only).

7 Review of Safety

Safety Summary

The safety profile in pediatric patients in similar to that seen in adult patients. No new safety signals were identified in the pediatric pivotal trials. There was no difference in the frequency of all grade Adverse Reactions (ARs) between treatment arms in all age cohorts. The common ARs that occurred more frequently in patients treated with eltrombopag were upper respiratory tract infection, nasopharyngitis, cough, diarrhea, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, AST increased, and rhinorrhea. These ARs tended to be low grade, and Serious Adverse Reactions (SARs) were uncommon. There were no deaths in either pediatric trial, and evaluation of ARs of special interest did not reveal any safety signal in pediatric patients treated with eltrombopag.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Pediatric patients enrolled in the pivotal trials TRA108062/PETIT and TRA115450/PETIT2 were combined for the safety analysis. Details of the study designs are described in Section 5.3. The intent-to-treat population (159 subjects) includes 67 subjects randomized in PETIT and 92 subjects randomized in PETIT2. Of these, 157 subjects received at least one dose of study treatment and comprise the safety population. Two subjects in PETIT were randomized to eltrombopag, but not dosed. (Patient 93 was withdrawn due to withdrawal of consent by parent/guardian and Patient 230 no longer met the eligibility criteria.) One subject in PETIT (patient 324) was randomized to placebo but received treatment with eltrombopag in error. This patient is included in the placebo group for the ITT population, but is included in the eltrombopag group for the safety population. The numbers of patients in the safety database for each trial is described in Table 28.

Table 28: Pediatric safety database during the randomized period

Trial number	Eltrombopag	Placebo
TRA108062/PETIT		
Total	44	21
Cohort 1 (12-17 years)	16	8
Cohort 2 (6-11 years)	17	9
Cohort 3 (1-5 years)	11	4
TRA115450/PETIT2		
Total	63	29
Cohort 1 (12-17 years)	24	10
Cohort 2 (6-11 years)	25	13
Cohort 3 (1-5 years)	14	6
Combined		
Total	107	50
Cohort 1 (12-17 years)	39	18
Cohort 2 (6-11 years)	43	22
Cohort 3 (1-5 years)	25	10

The majority of patients continued the trial into the open-label phase. Evaluation of AEs was also conducted during the open-label phase for descriptive analyses without comparison to placebo.

Reference ID: 3765521

7.1.2 Categorization of Adverse Reactions

Safety data coding was evaluated by comparing the verbatim term and the MedDRA version 16.1 preferred term. There were some areas of splitting of preferred terms, but the splitting did not impact the results to the point that lumping these split events would have increased the incidence of the broader event term to be considered for the frequent AE tables. For example, abdominal pain/upper abdominal pain, headache/migraine, and URI/viral URI/respiratory tract infection/nasopharyngitis were separate categories. These categories contributed to the common ARs, and evaluation by high level terms to combine these categories is reported in Section 7.4.1. SMQ analysis was also performed using MAED, and no additional safety signals were revealed.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The two pediatric clinical trials were pooled for analysis during the randomized period for both studies. The enrollment criteria were identical across the two trials with the exception of the time from diagnosis of ITP of 6 months in PETIT and 1 year in PETIT2. The populations enrolled in each trial were similar regarding demographics and baseline disease characteristics. Though the duration of the randomized period was different for each trial, 7 weeks for PETIT and 13 weeks for PETIT2, pooling allowed for a larger database, and the incidence of AEs did not change significantly over this 6 weeks difference in duration.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

There were a total of 174 subjects enrolled in both studies (15 in the dose-finding phase of PETIT, 67 in the randomized phase of PETIT, and 92 in the randomized phase of PETIT2). There were 3 subjects who did not receive eltrombopag. Two subjects in PETIT were randomized to eltrombopag but withdrew prior to receiving any study treatment. One subject in PETIT2 was randomized to placebo but withdrew prior to the eltrombopag-only Period.

The overall safety database includes 171 pediatric chronic ITP patients treated with eltrombopag and a randomized safety database of 157 subjects (107 receiving

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eltrombopag). A total of 128 patients were treated with eltrombopag for ≥24 weeks. The safety database includes 61 patients from cohort 1 (ages 12-17), 70 patients from cohort 2 (ages 6-11) and 40 patients from cohort 3 (ages 1-5). All patients were followed for at least 30 days after completion of the trial; however, 30/67 patients in PETIT and 58/92 patients in PETIT2 continued to receive eltrombopag post-trial.

Dose and exposure for pediatric patients are summarized in Section 4.4.3 above. At the doses used in the randomized period of both pediatric trials, the exposure, durations of exposures, and responses were similar to those in the adult trials of eltrombopag treatment in patients with chronic ITP. Two of the adult trials used for labeling for the use of eltrombopag for the treatment of adults with chronic ITP evaluated the duration of treatment of 6 weeks. The third adult trials evaluated treatment over 6 months. Therefore the doses given to pediatric patients in these trials should allow for an accurate assessment of the safety of eltrombopag use in the post-marketing setting.

7.2.2 Explorations for Dose Response

The design of the pediatric trials did not allow adequate numbers of patients treated at ascending doses to evaluate for a safety signal with dose response. The PETIT trial included a dose-finding period with 15 patients with 5 patients in each age cohort.

7.2.3 Special Animal and/or In Vitro Testing

Non-clinical studies are summarized in Section 4.3 above. There were no additional animal studies provided in this sNDA, but a brief summary of the findings in juvenile rats was conducted. There were not additional *in vitro* tests provided.

7.2.4 Routine Clinical Testing

In both studies during the randomized period, subjects were evaluated weekly with clinical assessment including AE assessment and WHO bleeding scale, vital signs, hematology, blood chemistry, complete blood count including platelet count, and liver enzymes. Peripheral blood smears were evaluated approximately every 4 weeks for the duration of the trial. Ophthalmologic exams were performed every 4 weeks while receiving eltrombopag then at 3 and 6 months after completion of the trial. ECGs were not routinely monitored.

AEs were categorized as on-therapy, post-therapy (AEs that started more than 1 day after the last dose of investigational product and up to 30 days after last dose of investigational product), or >30 days post-therapy. Routine clinical testing was adequate to assess the safety of eltrombopag in pediatric patients with chronic ITP.

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7.2.5 Metabolic, Clearance, and Interaction Workup

No relevant studies were conducted in pediatric patients.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The only other marketed TPO receptor agonists is romiplostim (Nplate®). AEs thought to be a class effect were reviewed in Section 2.4. In summary, the only relevant safety signal seen in romiplostim is the risk of thromboembolic events. There were no thromboembolic events seen in either pediatric trial. Common AEs seen in romiplostim were similar to those seen in pediatric patients treated with eltrombopag.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during either PETIT or PETIT2.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious AEs are summarized in Table 29. A higher proportion of patients in the placebo group reported SAEs than those in the eltrombopag group. With the exception of epistaxis that was reported by 2 subjects in the placebo group, there were no SAEs that were reported by more than 1 subject in either treatment group. There were no SAEs that were common to both treatment groups. The SAEs in the eltrombopag treated group tended to be infection related.

Table 29: Combined trials, Proportion of patients with serious AEs during the randomized period

	Eltrombopag (n=107) n (%)	Placebo (n=50) n (%)
Subjects with any event	9 (8.4%)	6 (12.0%)
ALT abnormal	1 (0.9%)	0
Anemia	1 (0.9%)	0
AST abnormal	1 (0.9%)	0
Febrile neutropenia	1 (0.9%)	0
Gingivitis	1 (0.9%)	0
Influenza	1 (0.9%)	0
Meningitis aseptic	1 (0.9%)	0
Neutropenia	1 (0.9%)	0
Pneumonia	1 (0.9%)	0
Pneumonia fungal	1 (0.9%)	0
Pyrexia	1 (0.9%)	0
Urinary tract infection	1 (0.9%)	0
Conjunctivitis	0	1 (2.0%)
Epistaxis	0	2 (4.0%)
Hemorrhage	0	1 (2.0%)
Hypertensive crisis	0	1 (2.0%)
Impetigo	0	1 (2.0%)
Petechiae	0	1 (2.0%)
Varicella	0	1 (2.0%)

7.3.3 Dropouts and/or Discontinuations

The majority of subjects completed the trials per protocol including the randomized period and the post-study follow up period. In the ITT Population, 19 (11.9%) subjects withdrew prematurely from the studies with a higher proportion of subjects withdrawing in the eltrombopag group (16/108, 14.8%) compared to the placebo group (3/51, 5.9%). The most common reasons for study withdrawal were withdrawal of consent (3/3 in placebo group, 6/16 in eltrombopag group) and lost to follow up (6/16 in eltrombopag group). The remaining patients in the eltrombopag group withdrew for protocol deviation (5/16) or lack of efficacy (2/16). The proportion of subjects who withdrew prematurely from the studies was similar across all age cohorts.

Three (2.8%) subjects in the eltrombopag group and 1 (2%) subject in the placebo group discontinued study treatment during the Randomized Period. In the eltrombopag group, two discontinued due to an AE (Patient 41 in PETIT2 discontinued for increased ALT/AST and Patient 775 in PETIT who discontinued for increased ALT), and one

patient was lost to follow-up (Patient 280 in PETIT was lost to follow up on day 15). The patient in the placebo arm who discontinued was due to an AE (Patient 117 in PETIT2 who had an abdominal hemorrhage, described in more detail under bleeding events in Section 7.3.5).

In total, 15 (9.7%) subjects discontinued study treatment during the eltrombopag-only period. Six were for AEs, 3 for lack of efficacy, 3 were lost to follow-up, one due to investigator decision, and 2 withdrew consent.

7.3.4 Significant Adverse Events

There were two additional medically important AEs that were not discussed elsewhere in this section.

Patient 322 in the PETIT trial developed systemic lupus erythematosus 70 days after starting treatment with eltrombopag. The event was thought to be unrelated to the study treatment, and she continued on eltrombopag treatment for several months.

Patient 230 in the PETIT2 trial developed grade 2 hemolytic anemia during the open-label part of the trial. The AE was unresolved at the time of reporting, and was considered to be related to the study treatment.

7.3.5 Submission Specific Primary Safety Concerns

There were AEs of special interest prospectively evaluated in the pediatric population: bleeding events, hepatobiliary events, thromboembolic events, renal events, cataracts, malignancy, and bone marrow fibrosis.

<u>Bleeding events</u>

The incidence of bleeding events was an efficacy endpoint in both trials and was discussed in Section 6.1.6. There were fewer patients in the safety population with reports of bleeding events treated with eltrombopag (16.8%) compared to patients treated with placebo (36.0%) during the randomized period. The most common bleeding events reported in either treatment group were epistaxis, gingival bleeding, menorrhagia, and petechiae, all of which occurred at a higher incidence in the placebo group.

Patient 117 in PETIT2 was randomized to the placebo arm and had an abdominal hemorrhage requiring hospitalization on day 19 of study treatment. She was withdrawn from the trial by her parents, who declined further follow-up visits after Day 26.

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Hepatobiliary events

In the adult registration trials, approximately 5% of patients treated with eltrombopag had an elevation in liver enzymes or bilirubin. In the pediatric population, patients randomized to eltrombopag had a moderate increase in hepatobiliary abnormalities compared to the placebo group. In the safety population, an elevation of ALT ≥3x ULN occurred in 5 (4.7%) subjects in the eltrombopag group and no subjects in the placebo group during the randomized period. Of the 5 subjects with an elevation of ALT ≥3x ULN, 2 patients had increases in ALT ≥5x ULN, which met the protocol defined liver chemistry stopping criteria. For both subjects the elevated liver enzymes resolved following discontinuation of study treatment. For the remaining 3 patients, the elevated liver enzymes resolved either while still on treatment or after discontinuation of study treatment.

In the open-label portion of the trials, there were an additional 7 subjects with ALT ≥3x ULN. ALT and AST increases were reported in a higher proportion of East Asian Subjects. Two events occurred of concurrent elevations in ALT ≥3x ULN and bilirubin ≥1.5x ULN. However, the laboratory abnormalities were not indicative of drug induced liver injury as the bilirubin was primarily unconjugated. The subjects withdrew from eltrombopag treatment and the events resolved.

Evaluation for Hy's Law cases was defined as subject with ALT >3x ULN and TBL >2x ULN without notable increase ALP (<2xULN). No Hy's Law cases were identified in either pediatric trial during the randomized phase.

Thromboembolic events

In the adult pivotal trial of patients with thrombocytopenia and hepatitis C, thromboembolic events occurred in 3% of patients treated with eltrombopag versus 1% of patients treated with placebo. The majority were portal vein thromboses. Portal vein thrombosis also occurred in patients with thrombocytopenia and chronic liver disease in preparation for invasive procedures. In these pediatric clinical trials, there were no reports of thromboembolic events at any time during the studies.

Renal events

In the safety population, there were few events of elevated creatinine, all of the events were transient low grade elevations, and the occurrence of events was balanced between the treatment groups. All renal AEs resolved and most did not result in a dose change or interruption. One subject in the eltrombopag group had an event of creatinine increased which led to discontinuation of study treatment during the open-label period

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(Patient 742 in PETIT2). There was 1 Grade 3 SAE of hypertensive crisis that was reported in a placebo subject; no renal-related SAEs were reported in the eltrombopag group.

Cataracts

Pre-clinical animal models indicated a risk for formation of cataracts as discussed in Section 4.3. In the adult pivotal trials, the incidence rate of cataract formation was the same in both eltrombopag and placebo treatment arms at approximately 7% with a possible association in patients with thrombocytopenia and hepatitis C (7% versus 5%). In the pediatric trials, 2 subjects who had received eltrombopag were determined to have a cataract event, one patient with worsening visual acuity due to cataracts during the eltrombopag only treatment period and one patient had a bilateral incident cataract event discovered at the 24 week follow up ophthalmologic exam. Both subjects had either reported corticosteroid use as a risk factor or were receiving corticosteroids as an ongoing ITP medication. In the Safety Population, 34.6% of eltrombopag subjects and 28.0% of placebo subjects reported cataractogenic risk factors at baseline, but overall no apparent signal for cataract formation was seen in the pediatric population even with the imbalance in cataract risk factors with more in eltrombopag arm.

Malignancy

No hematologic malignancies were reported. There was one report of malignancy 20 months after the discontinuation of eltrombopag treatment. This patient was diagnosed with thyroid papillary carcinoma. The investigator considered the event unrelated to study treatment.

Bone marrow fibrosis

There were no events indicative of bone marrow fibrosis in either population at any time. Bone marrow assessments were not required during the course of the trials, but no evidence of bone marrow dysfunction was seen on laboratory evaluation or peripheral smears.

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7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 30 lists the adverse events that occurred in more than 3% of patients in the eltrombopag treated group during the randomized period. The overall occurrence of common AEs was the same in patients treated with eltrombopag compared to patients treated with placebo. The common AEs that occurred more frequently in patients treated with eltrombopag were upper respiratory tract infection, nasopharyngitis, cough, diarrhea, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, AST increased, and rhinorrhea. AEs that occurred more often in the patients treated with eltrombopag were generally low grade and reversible.

Overall, the AE profile was similar across the age cohorts and consistent with the most common AEs reported in the overall safety population (data not shown).

Table 30: Combined trials, AEs occurring in ≥3% of eltrombopag-treated patients during randomized period.

	Eltrombopag (n=107) n (%)	Placebo (n=50) n (%)
Subjects with any event	87 (81.3%)	41 (82%)
Headache	19 (17.8)	12 (24.0)
Upper respiratory tract infection	18 (16.8)	3 (6.0)
Nasopharyngitis	13 (12.2)	2 (4.0)
Cough	10 (9.4)	0
Diarrhea	10 (9.4)	1 (2.0)
Pyrexia	10 (9.4)	4 (8.0)
Rhinitis	10 (9.4)	3 (6.0)
Abdominal pain	9 (8.4)	2 (4.0)
Epistaxis	9 (8.4)	10 (20.0)
Nausea	8 (7.5)	6 (12.0)
Oropharyngeal pain	8 (7.5)	1 (2.0)
Toothache	6 (5.6)	0
Vomiting	6 (5.6)	9 (18.0)
Abdominal pain upper	5 (4.7)	5 (10.0)
Rash	5 (4.7)	1 (2.0)
AST increased	4 (3.7)	0
Rhinorrhea	4 (3.7)	0

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Table 31 lists the adverse events grouped by high level term that occurred in more than 3% of patients in the eltrombopag treated group during the randomized period. Grouping by high level term minimized the splitting of AEs that occurred during coding. A similar profile of common AEs was seen in this analysis. The common AEs that occurred more frequently in patients treated with eltrombopag in this analysis were upper respiratory tract infections, upper respiratory tract signs and symptoms, coughing and associated symptoms, diarrhea (excluding infective), febrile disorders, dental pain and sensation disorders, liver function analyses, rashes, eruptions and exanthems NEC, and lower respiratory tract and lung infections. There were no new AEs added to the list of common AEs by this analysis, but the magnitude of difference was sometimes higher between groups.

Table 31: Combined trials, AEs grouped by High Level Term occurring in ≥3% of eltrombopag-treated patients during the randomized period

	Eltrombopag (n=107) n (%)	Placebo (n=50) n (%)
Upper respiratory tract infections	39 (36.5%)	8 (16%)
Headaches NEC	19 (17.8%)	12 (24%)
Nausea and vomiting symptoms	14 (13.1%)	11 (22%)
Gastrointestinal and abdominal pains (excluding oral and throat)	13 (12.2%)	7 (14%)
Upper respiratory tract signs and symptoms	12 (11.2%)	1 (2%)
Coughing and associated symptoms	10 (9.4%)	0 (0%)
Diarrhea (excluding infective)	10 (9.4%)	1 (2%)
Febrile disorders	10 (9.4%)	4 (8%)
Nasal disorders NEC	9 (8.4%)	10 (20%)
Dental pain and sensation disorders	6 (5.6%)	0 (0%)
Liver function analyses	5 (4.7%)	0 (0%)
Rashes, eruptions and exanthems NEC	5 (4.7%)	1 (2%)
Asthenic conditions	5 (4.7%)	2 (4%)
Lower respiratory tract and lung infections	4 (3.7%)	0 (0%)
Musculoskeletal and connective tissue pain and discomfort	4 (3.7%)	2 (4%)
Skin structures and soft tissue infections	4 (3.7%)	2 (4%)
Skin injuries NEC	4 (3.7%)	3 (6%)

SMQ analysis was also performed using MAED, and no additional safety signals were revealed.

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7.4.2 Laboratory Findings

Review of hepatobiliary and renal laboratory findings were presented with the AEs of special interest in Section 7.3.5.

During the randomized period, overall abnormalities in hematology parameters were infrequent and the majority were Grade 1-2. Grade 3-4 neutropenia and lymphopenia occurred more frequently in the eltrombopag group (5/107 for neutropenia and 2/107 for lymphopenia) as compared to the placebo group (2/50 for neutropenia and 0/50 for lymphopenia). Grade 3 anemia was more common in the placebo group (3/50 patients) compared to the eltrombopag group (1/107 patients).

7.4.3 Vital Signs

In the Safety Population, vital signs in the majority of subjects were within normal limits at baseline, and no clinically significant differences were demonstrated between subjects in the eltrombopag group and subjects in the placebo group. Results were consistent across all age cohorts.

7.4.4 Electrocardiograms (ECGs)

ECGs were not collected as part of the pediatric studies.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No evaluations were conducted evaluating the dose dependency of adverse events.

7.5.2 Time Dependency for Adverse Events

The randomized period for both pediatric trials was limited in duration (7 weeks and 13 weeks, respectively), so assessments for timing of adverse reaction onset are of limited use. Generally, the profile of AEs during week 1, week 6, and week 12 of the trials were similar, though diarrhea, abdominal pain, and headache tend to be less common at week 12.

7.5.3 Drug-Demographic Interactions

There were no evident interactions between drug safety and age, gender, and weight. There were no notable differences in the incidence of AEs between East Asian and non-East Asian patients with the exception of increases in AST and ALT which were reported more frequently in East Asian patients. These AEs resolved with drug discontinuation.

7.5.4 Drug-Disease Interactions

No relevant evaluation was completed.

7.5.5 Drug-Drug Interactions

Refer to review by Clinical Pharmacology.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No hematologic malignancies were reported. There was one report of malignancy 20 months after the discontinuation of eltrombopag treatment. This patient was diagnosed with thyroid papillary carcinoma. The investigator considered the event unrelated to study treatment.

7.6.2 Human Reproduction and Pregnancy Data

There were no reported pregnancies in these trials.

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7.6.3 Pediatrics and Assessment of Effects on Growth

All patients enrolled in the trials were pediatric age. There were no evident effects on growth in the trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence of any potential for abuse or dependence.

Withdrawal and Rebound
The impact of withdrawing from study treatment was evaluated by the Applicant by evaluating the number of patients in each treatment group who had platelet counts <10 Gi/L and at least 10 Gi/L lower than baseline counts within 4 weeks after discontinuation of study drug. This analysis identified 25 patients who had baseline platelet counts of >10 Gi/L, took eltrombopag during the study, and did not receive post-treatment eltrombopag (defined as eltrombopag taken after completion of the eltrombopag-only period). Of these 25 patients, 8 patients had follow-up platelet counts <10 Gi/L and at least 10 Gi/L less than baseline platelet count for at least one assessment. Of these 8 patients, 4 patients reported five grade 1 or 2 bleeding adverse reactions during the follow-up period and 1 patient reported a Grade 2 post-therapy serious adverse reaction of epistaxis that started 21 days after the last dose of eltrombopag, and resolved 2 days later. These events were epistaxis or gingival bleeding, and all events recovered or resolved. This information was provided by the Applicant in Section 5.7 of the Integrated Summary of Safety.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

Post-marketing AE reports were summarized by the Applicant for 10,020 AEs in 4458 cases from November 20, 2008 to March 31, 2014. The age range of the patients in these reports was not provided; however, the vast majority of these would be in adults. The data reported in the post-marketing setting are consistent with the known safety profile of eltrombopag. Overall, there was no change in the nature, seriousness or frequency of reported events, based on the post-marketing data.

The AEs reported in 1% or higher cases is summarized in Table 32 as provided by the Applicant. Notably, drug ineffective, platelet count decreased, and thrombocytopenia are all indicators of lack of effectiveness and not a safety signal. There were 769 cases with a fatal outcome out of the 4458 cases reported from marketed use of eltrombopag.

(The number of overall deaths does not match the number of deaths in Table 32 below because not all deaths were reported as Adverse Events.) The deaths were primarily in elderly patients with multiple co-morbidities that likely contributed to the outcome. The majority of the deaths where the age of the patient was reported was in patients >65 years old. The other AEs in the table are already included in the safety information for eltrombopag.

Table 32: Summary of post-marketing AEs reported in ≥1% of cases

MedDRA preferred term	Adverse events, n (%)
All preferred terms	10,020 (100)
Drug ineffective	1057 (10.5)
Death	288 (2.9)
Platelet count decreased	287 (2.9)
Off label use	227 (2.3)
Fatigue	154 (1.5)
Headache	148 (1.5)
Platelet count increased	142 (1.4)
Nausea	126 (1.3)
Anemia	110 (1.1)
Deep vein thrombosis	103 (1.0)
Thrombocytopenia	98 (1.0)
Pulmonary embolism	96 (1.0)

Reference ID: 3765521

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Proposed labeling changes, including a revised indication statement for pediatric patients and the findings of the studies, are included within the sNDA. The proposed indication is: PROMACTA is indicated for the treatment of thrombocytopenia in adult and pediatric patients 6 years and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Dosing information was the same as for adult patients, and therefore did not require updating.

Common AEs seen in pediatric patients were added. Population PK information for the tablets in pediatric patients was also updated.

Topline efficacy results were added for both pediatric trials for the patients with a platelet response of ≥50 Gi/L at least once in the first 6 weeks and patients with a sustained response.

The labeling updates for this sNDA does not include any information for the (b) (4)

9.3 Advisory Committee Meeting

An advisory committee was not convened for this application because the Division has experience with the drug and selected endpoints used in the trials. The trial design and endpoints were agreed upon by the Agency in advance of trial conduct.

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/s/

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Concur.