CLINICAL PHARMACOLOGY REVIEW

Submission	**NDA 207027**
Submission Date	**February 24, 2015**
Generic Name	**Eltrombopag (Promacta®)**
Primary Reviewer	**Jee Eun Lee, Ph.D.**
Secondary Reviewers	**Bahru Habtemariam, Pharm.D., Nitin Mehrotra, Ph.D.**
OCPB Division	**DCP5/ DPM**
ORM division	**OHOP/DHP**
Applicant	**Novartis**
Formulation; Strength(s)	**Powder for oral suspension (PfOS); 25 mg** (b) (4)
Proposed Indication	**Treatment of** (b) (4) **pediatric patients 1 years and older with chronic immune (idiopathic) thrombocytopenia (ITP)** (b) (4)
Proposed Dosing Regimen	**Initiate at 25 mg once daily for most pediatric patients aged 1 to 5 years. Reduce initial dose in patients with hepatic impairment and/or patients of East Asian ancestry. Adjust to maintain platelet count greater than or equal to 50×10^9/L**

1. EXECUTIVE SUMMARY

Eltrombopag olamine (in short, eltrombopag) is an orally bioavailable, small molecule, thrombopoietin receptor agonist. Eltrombopag has effects in inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

Eltrombopag is currently approved for the treatment of thrombocytopenia in adults and pediatric patients older than 6 years with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The recommended starting doses of eltrombopag in adult patients are

50 mg and 25 mg once daily for patients with non-East Asian (non-EA) ancestry and East Asian (EA) ancestry, respectively. For patients with mild to severe hepatic impairment, the recommended starting dose is 25 mg once daily. The dose of eltrombopag will be titrated to maintain platelet count greater than or equal to 50×10^9/L (50 Gi/L) and the daily cap is 75 mg. The approved dosage strengths are 12.5-, 25-, 50-, 75- and 100-mg tablets.

The current submission is for powder formulation for oral suspension (PfOS) which was developed for pediatric patients 1 to 5 years of age. The efficacy and safety characteristics of eltrombopag with PfOS in patients 1 to 5 years old were evaluated in 2 pediatric trials (PETIT, PETIT2) along with older pediatric (≥6 years) who received the tablet formulation. The relative bioavailability of PfOS and the effect of high calcium meal on the pharmacokinetics of eltrombopag PfOS were evaluated in a randomized, crossover study (TRA111718). This Clinical Pharmacology review is based on the results from these three studies.

1.1. Recommendations

The Office of Clinical Pharmacology have reviewed the information submitted in the NDA and recommended approval of Promacta® (eltrombopag) for the treatment of (b) (4) pediatric patients 1 to 5 years of age with chronic immune (idiopathic) thrombocytopenia (ITP) (b) (4) We recommend a starting dose of 25 mg once daily.

Initial Dosing regimen

The recommended initial dose for pediatric patients 1 to 5 years with chronic immune (idiopathic) thrombocytopenia (ITP) is 25 mg QD. The doses will be then titrated to target platelet counts for individual patients.

Labeling

Detailed labeling recommendations are provided in Section 3.

1.2. Phase 4 Commitments

We recommend that the applicant develop 12.5 mg strength of the PfOS formulation in order to enable required dose adjustments to achieve target platelet count. Currently available dispensing unit for oral suspension is 25 mg only which is not desirable for adequate dose titration in pediatric patients.

1.3. Summary of Clinical Pharmacology Findings

The studied and the applicant's proposed initial doses of eltrombopag in pediatric patients 1 to 5 years are summarized in the table below.

Population	Studied dose	Applicant's proposed dose
Non-East Asian ancestry	0.7, 1.2 and 1.5 mg/kg daily	25 mg daily
East Asian ancestry	0.5 and 0.8 mg/kg daily	(b) (4)

We do not agree with the sponsor's proposal [redacted] (b) (4). Since the majority of patients in clinical trials required doses of greater than 50 mg to achieve target platelet count, a starting daily dose of 25 mg (QD) for all pediatric patients ages 1-5 is recommended. Our recommendation is intended to simplify the dosing regimen and minimize the number of dose titration required to achieve target platelet count. Furthermore, the reviewers have concerns [redacted] (b) (4)

1.3.1. Biopharmaceutics

Although in vitro dissolution data support consistent release from PfOS batches, PfOS and the tablet formulations are not bioequivalent. Administration of eltrombopag PfOS, with a maximum recommended therapeutic dose of 75 mg/day, requires reconstitution with 20 mL water [redacted] (b) (4) Stability of eltrombopag with PfOS has been demonstrated with sample processing and long-term storage.

Because PfOS is not bioequivalent to the table formulations, the applicant proposes that platelet counts be monitored weekly for 2 weeks when a patient switches between formulations. Furthermore, the applicant proposes that eltrombopag be administered at least 2 hours before and at least 4 hours after polyvalent metal cation-containing products (such as antacids, mineral supplements, and dairy) based on findings from a food effect study with PfOS (TRA111718).

Study TRA111718 also included the assessment of the relative bioavailability of PfOS compared to tablet formulation in healthy adult subjects, and found that AUC of eltrombopag was increased by 22% and Cmax by 31% compared to the tablet formulation. The population PK analysis estimated about 71% of relative bioavailability of PfOS in pediatric patients 1 to 5 years of age, however, we conclude that the results obtained from Study TRA111718 would be more reliable since the effect of PfOS on eltrombopag PK was confounded by the effect of age as only pediatric patients 1 to 5 years of age received the PfOS in the PETIT and PETIT2 trials.

1.3.2. Pharmacokinetics/Pharmacodynamics

Pharmacokinetics and pharmacodynamics of eltrombopag in pediatric patients were characterized in two studies (PETIT and PETIT2) where older age group of pediatric patients (>=6 years) were also enrolled along with the target age groups. The population PK and PKPD analyses in pediatric ITP patients 1 to 17 years of age enrolled in studies PETIT and PETIT2 are summarized as followings:

- Plasma eltrombopag PK following repeat oral administration to pediatric subjects with ITP were adequately described by a 2-compartment model with first order absorption and elimination.

- Plasma eltrombopag clearance (CL/F) and volume of distribution (Q, V2/F, V3/F) parameters increased with increasing body weight. Mean plasma eltrombopag CL/F was 30% lower in East/Southeast Asian subjects compared to other races. These CL/F differences translate to mean AUC (0-tau) increases of 43% in Ease Asian subjects.

- Platelet count response following eltrombopag dosing was described by the 7-compartment life-span model (3 PK and 4 PD compartments), where the increase in platelet precursor production rate was linearly related to eltrombopag concentration.

- The majority of subjects (96%) were identified as responding to eltrombopag treatment. Platelet maturation rate constant increased with increasing age, which influenced the time to steady-state platelet count. The time to ≥80% of steady-state platelet count was 4 weeks.

- No significant covariates were identified on pharmacodynamics. No effect of formulation on pharmacodynamics of eltrombopag was detected.

1.3.3. PKPD Simulation for Justification of Initial Dosing Regimens

The applicant proposes [redacted] (b) (4) The studied dosing regimens were based on body weight (1.2 mg/kg QD for non-East Asian and 0.8 mg/kg QD for East Asian in PETIT2) while the applicant's proposed dosing regimens are [redacted] (b) (4) (25 mg QD for non-East Asian [redacted] (b) (4) The justification for the proposed dosing regimen was based on simulations with the PKPD model to predict platelet counts following various initial dosing regimens. This approach appears reasonable with adequate PKPD modeling evaluation. Considering the fact that the proposed dosing regimen is only for the initial dose and individual dose is to be titrated based on platelet counts, the proposal of initial dose based on simulation is readily agreeable.

Among those evaluated initial doses, 25 mg QD for patients with non-East Asian ancestry [redacted] (b) (4) for patients with East Asian ancestry were proposed by the applicant. For consistency in terms of dose reduction for patients with East Asian ancestry due to the lower clearance compared to patients with non-East Asian ancestry, [redacted] (b) (4) for non-East Asian may be adequate for the patients with East Asian ancestry. However, reviewers do not agree with the sponsor's proposed dose [redacted] (b) (4) for patients with East Asian ancestry. The predicted median platelet counts following 25 mg QD for 10 weeks without dose adjustment could be close to 40 Gi/L for patients with either East Asian ancestry or non-East Asian ancestry (Figure 1). As shown in Figure 1, the [redacted] (b) (4) could lead [redacted] (b) (4) in East Asian without dose titration. Nonetheless, dose is likely to increase to target platelet counts to ≥50 Gi/L but [redacted] (b) (4) dosing regimen still does not appear to be desirable. The large fluctuation created by [redacted] (b) (4) is also of concern regarding steady input of the drug for desirable drug effect. Some patients may have greater than [redacted] (b) (4) Cmax compared to Cmin with every other day dosing regimen.

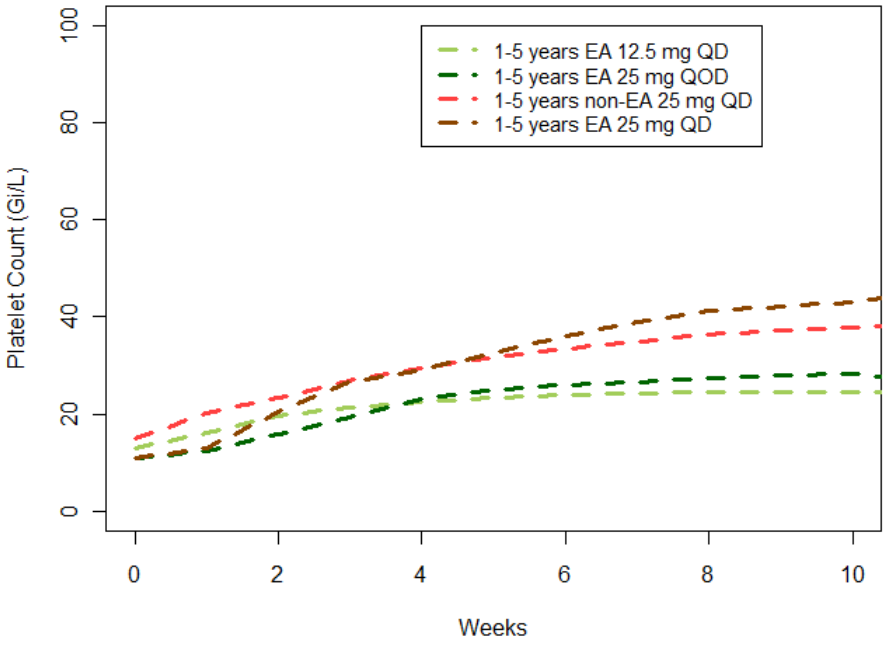


Figure 1. Predicted median platelet counts following various initial dosing regimens for 10 weeks without dose titration. EA: Patients with East Asian ancestry; non-EAT: with non-East Asian ancestry.
(Source: Reviewer's confirmatory analysis with the sponsor's PKPD model)

Moreover, 25 mg daily dose appears to be safe as a starting dose for pediatric patients 1 to 5 years old with either non-East Asian or East Asian ancestry. As shown in Table 1, over 85% of subjects ended up with final daily dose above 25 mg even none of subjects with East Asian ancestry started with dose above 25 mg. The substantial portion of patients 1 to 5 years old (48% of non-East Asian and 57% of East Asian) ended up escalating dose to above 50 mg daily dose (Table 8).

Table 1. Subject Distribution on Starting Dose and Final Dose above 25 mg

Race	**N**	**Subjects on starting dose >=25mg (N (%))**	**Subjects on final dose >=25mg (N (%))**
Non-East Asian	31	10 (32.2)	27 (87.1)
East Asian	7	0	6 (85.7)

(Source: Reviewer's analysis)

2. QUESTION BASED REVIEW

2.1. General Attributes

2.1.1. What is the relevant background information and regulatory history?

On November 20, 2008, PROMACTA® (eltrombopag) was approved by the FDA for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The primary efficacy data supporting the approval of the ITP indication in adults were derived from 2 randomized, placebo-controlled studies of subjects treated over a 6-week period (TRA100773A, TRA100773B) and one randomized, placebo-controlled study of subjects treated for 6-months (TRA102537, a.k.a., RAISE). The studies enrolled subjects with baseline platelet counts <30 Gi/L who were refractory to, or had relapsed following standard treatment options which could have included splenectomy. The adult data demonstrated that the odds of achieving a platelet count ≥50 Gi/L in patients receiving 50 mg eltrombopag were significantly greater than those receiving placebo (OR: 8.2 in RAISE study, 22.0 in TRA100773A, and 9.6 in TRA100773B).

On June 11, 2015, eltrombopag tablet formulation was approved for adolescents and pediatric patients with 6 years of age or above (sNDA22291/S015) based on efficacy and safety from PETIT and PEIT2. In the two clinical trials, the pediatric patients 1 to 5 years of age were enrolled as a cohort and they received the PfOS formulation. The PKPD modeling and simulations were performed with data including this younger age group of patients to support the starting dose.

2.1.2. What are the proposed indications?

The proposed indication is the treatment of [redacted] (b) (4) pediatric patients 1 year of age and older with chronic immune (idiopathic) thrombocytopenia (ITP) [redacted] (b) (4)

2.1.3. What are the proposed dosing regimens?

The reviewers' recommended starting dose of eltrombopag is 25 mg daily for pediatric patients with 1 to 5 year of age.

2.2. What are the design features of the clinical studies to support the clinical pharmacology findings?

The application is based on two clinical studies, TRA108062 (PETIT) and TRA115450 (PETIT2). Subjects were enrolled into age cohorts: Cohort 1: 12 to 17 years, Cohort 2: 6 to 11 years, Cohort 3: 1 to 5 years. Subjects received eltrombopag for at least 24 weeks. Subjects underwent weekly visits until platelet counts were stable and then underwent monthly visits thereafter.

Patients older than 6 years received tablets, and starting doses ranged from 25 to 50 mg once daily. East Asian subjects initiated eltrombopag at ~ 30 to 50% lower doses.

Patients 1 to 5 years old with non-East Asian ancestry received 0.7 or 1.5 mg/kg daily dose and while those with East Asian ancestry received 0.5 or 0.8 mg/kg daily dose in PETIT. For the PETIT2 trial, the

starting doses for non-East Asian and East Asian ancestry patients were 1.2 mg/kg and 0.8 mg/kg daily, respectively. Doses were increased at 2-week intervals if platelet counts were <50 Gi/L; the maximum eltrombopag dose was 75 mg once daily. Doses were decreased at any time platelet counts were >200 Gi/L and dosing was interrupted when platelet counts were >400 Gi/L

Serial PK samples were collected at Week 6 in PETIT, and a single PK sample was collected at all visits in both PETIT and PETIT2 studies. Platelet counts were collected at all visits.

The followings summarize the study design features of PETIT and PETIT2.

2.2.1. PETIT

PETIT was a Phase 2, three part, staggered cohort, open-label, double-blind, randomized, placebo controlled study to investigate the efficacy, safety, tolerability and PK of eltrombopag in previously treated pediatric subjects with chronic ITP. The first part of the study was open-label, dose finding, and Part 2 was randomized, placebo-controlled and the Part 3 was open-label with eltrombopag only (Figure 2).

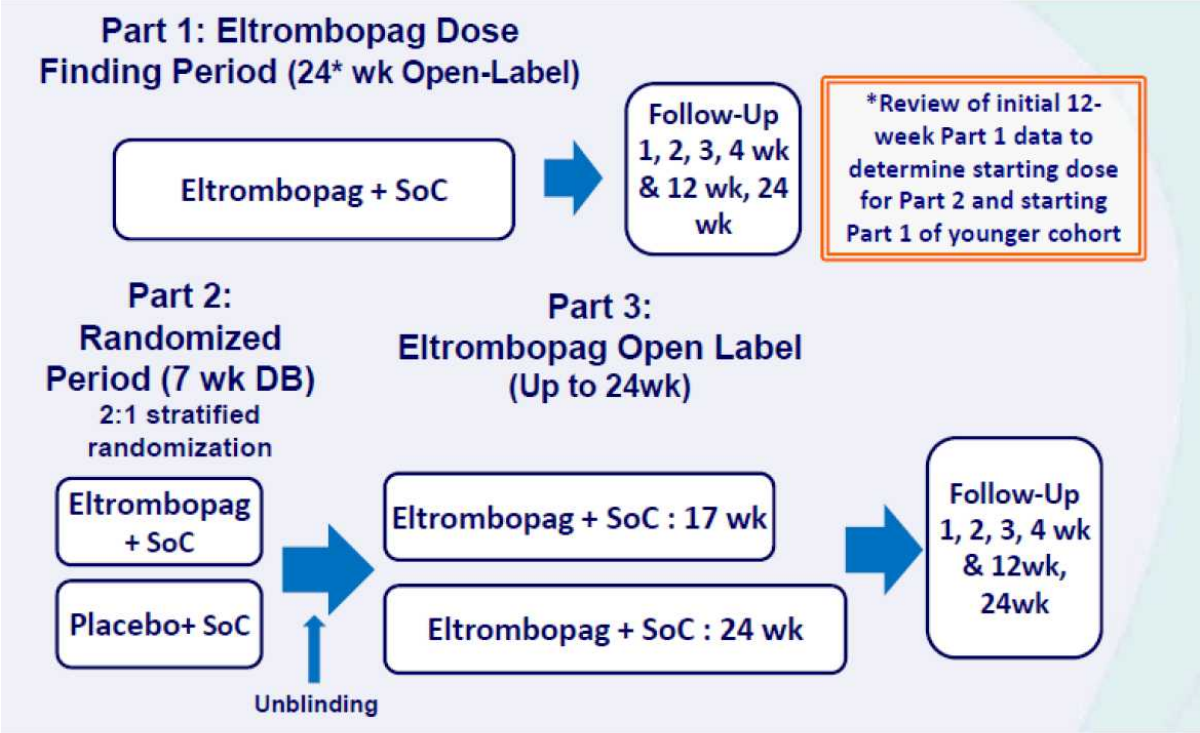


Figure 2. Schematic study design of PETIT
(Source: Sponsor's report, TRA108062, Figure 1, page 48)

Initial Dosing regimens

PETIT starting doses were selected according to age, weight, and race based on adult PK and clinical data and those for Dose Finding Phase and Randomized Period are summarized in Table 2 and Table 3. Adolescents were the first cohort dosed. The safety, PK, and platelet count data were reviewed with the initial 5 subjects in Cohort 1 who had received 12 weeks of treatment, and then the next younger cohort began enrollment and those 5 subjects continued treatment with open-label eltrombopag to complete 24 weeks. The same procedure was followed for the next cohorts during the dose finding phase. The initial doses in the dose finding phase are summarized in Table 2.

Table 2. Initial Dosing Regimens in Dose Finding Phase in PETIT

	Cohort 1 (Age 12-17)	Cohort 2[a] (Age 6-11)		Cohort 3[a] (Age 1-5)
		<27kg	≥27kg	
Non-East Asian	25 mg	12.5 mg	25 mg	0.7 mg/kg
East Asian	12.5 mg			0.5 mg/kg

(Source: Sponsor's report, SCE, Table 6, page 17)

The starting doses were conservative in PETIT study and multiple dose escalations occurred throughout the study. During the 24 week treatment period, 14 of 15 subjects required ≥4 eltrombopag dose increases. At the end of treatment, the majority (70%) of Cohort 1 and Cohort 2 subjects were receiving eltrombopag 75 mg once daily and Cohort 3 subjects were receiving doses 4 times higher than the starting dose (median of 66 mg or 3.0 mg/kg with a range of 34 to 75 mg [2.11 to 4.33 mg/kg]).

The need for multiple escalations to achieve pre-defined response supported increased initial doses in the randomized period. The initial doses in the randomized period are summarized in Table 3.

Table 3. Initial Dosing Regimens in Randomized Period in PETIT

	Cohort 1 (Age 12-17)	Cohort 2 (Age 6-11)		Cohort 3 (Age 1-5)
		<27kg	≥27kg	
Non-East Asian	37.5 mg	25 mg	50 mg	1.5 mg/kg
East Asian	37.5 mg	12.5 mg	25 mg	0.8 mg/kg

(Source: Sponsor's report, SCE, Table 7, page 17)

Subjects who received eltrombopag during the randomized period continued on the same dose in the Eltrombopag-Only Period unless adjustments were warranted according to the dosing guidelines.

Efficacy

The primary efficacy endpoint for PETIT study was 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 majority of subjects (63%) achieved a platelet response during the 24 weeks of dose finding phase and eltrombopag was well tolerated.

Safety

Safety assessment was summarized for all subjects from PETIT and PETIT2 (see *Safety* in Section 2.2.2.).

2.2.2. PETIT2

PETIT2 was a Phase 3, 2-part,double-blind, randomized, placebo-controlled and open-label study to investigate the efficacy, safety, and tolerability of eltrombopag in pediatric subjects with previously treated chronic ITP, with a confirmed diagnosis of chronic ITP for at least 1 year. The 2 parts of the PETIT2 study were: Part 1 (randomized) and Part 2 (eltrombopag only open-label). Randomization was stratified into 3 cohorts based upon age (Figure 3).

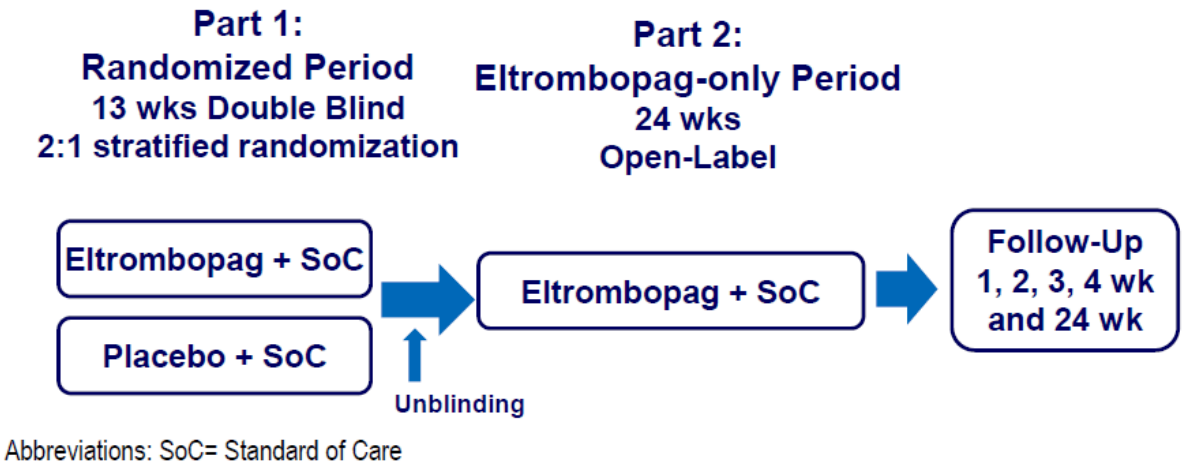


Figure 3. Schematic study design of PETIT2

(Source: Sponsor's report, TRA115450, Figure 1, page 32)

A total of 92 subjects were randomized in the PETIT2 study (20 subjects with 1-5 years of age). Sixty three subjects (14 subjects with 1-5 years of age) received eltrombopag and 29 subjects (6 subjects with 1-5 years of age) received placebo.

Initial Dosing regimens

The initial doses were determined based on the data from the Eltrombopag Dose Finding Phase of the PETIT study and the reduced dose was determined based on the results from adult studies. The initial doses in PETIT2 are summarized in Table 4.

Table 4. Initial Dosing Regimens in PETIT2

	Cohort 1 (Age 12-17)		Cohort 2 (Age 6-11)		Cohort 3 (Age 1-5)
	<27 kg	≥27 kg	<27 kg	≥27 kg	
Non-East Asian	37.5 mg	50 mg	37.5 mg	50 mg	1.2 mg/kg
East Asian	25 mg		25 mg		0.8 mg/kg

(Source: Sponsor's report, SCE, Table 5, page 16)

Doses were titrated based on target platelet count range of ≥50 Gi/L and <200 Gi/L. For dose escalation, the next higher level of available dosage strength was chosen and if an intermediate dose was required, the frequency was reduced. The maximums daily dose was 75 mg.

Efficacy

The primary efficacy endpoint for PETIT2 study was the proportion of subjects on eltrombopag, compared to placebo, achieving platelet counts ≥50 Gi/L for at least 6 of 8 weeks, between Weeks 5 to 12 of randomized period.

For patients enrolled in the eltrombopag and placebo arms, response rates were 41 and 4% (p-value=0.0108), respectively, indicating that eltrombopag increases platelet count in patients with ITP.

Safety

Overall, the number of subjects in the Safety Population (including pediatric patients 1-5 years old) who reported an adverse event (AE) was similar between eltrombopag groups (81.3%) and placebo groups (82.0%). The most common AEs in the eltrombopag groups (≥10% of subjects) were headache, upper respiratory tract infection, and nasopharyngitis. Grade 3 or 4 AEs were reported in 7/50 (14.0%) of subjects in the placebo group and 13/107 (12.1%) of subjects in the eltrombopag group.

The most common AEs reported in the placebo group (≥10% of subjects) were headache, epistaxis, vomiting, nausea, and upper abdominal pain. Upper respiratory tract infection was more frequently observed in patients with eltrombopag treatment compared to those with placebo: 18/107 (16.8%) with eltrombopag vs. 3/41 (6.0%) with placebo. Nasopharyngitis was also observed more frequently in patients with eltrombopag treatment compared to those with placebo: 13/107 (12.1%) with eltrombopag vs. 2/41 (4.0%) with placebo.

The safety profile in pediatric patients with ITP was consistent with the known safety profile of eltrombopag in chronic ITP in adults.

2.3. Exposure-Response

2.3.1. Is there exposure-response relationship to provide supportive evidence of effectiveness of PfOS of eltrombopag in pediatric patients with ITP?

Yes. The PKPD modeling indicates that the platelet counts are positively correlated with eltrombopag concentrations. The PKPD model incorporates the production and the maturation of platelet precursors and it is a model for thrombopoietin receptor agonists. In the PKPD model, a parameter SLOP was used to describe the linear relationship between the platelet precursor production rate (KIN) and eltrombopag concentration. The typical estimate of SLOP was 0.651 mL/mcg in responders indicating increase in eltrombopag concentrations leads to increase in the platelet precursor production rate.

2.3.2. Are the exposure and response in pediatric patients 1 to 5 years of age comparable with those in adults?

No. The pediatric patients received various starting doses and the estimated PK parameters normalized to a 50 mg dose show comparable exposure between adolescents and adults. However, the exposures in pediatric patients 1 to 5 years old are higher than those in adults. The geometric mean (95% CI) of steady-state plasma eltrombopag pharmacokinetic parameters in pediatric patients and adult patients with ITP are summarized in Table 5. Despite having 62% higher AUC, children ages 1 to 5 have lower response rate than adults (Table 5). In addition, since the rate of Grade 3 or 4 AEs were similar in the placebo and eltrombopag arms of the PETIT2 trial (Section 2.2.2), the increased AUC in children ages 6 to 11 years old is not expected cause increased rates of adverse events.

Table 5. Summary of Eltrombopag PK Parameters in Pediatrics and Adults

Age	C_{max}[1] (GLSM [95% CI], mcg/mL)	$AUC_{(0-\tau)}$[1] (GLSM [95% CI], mcg*h/mL)
Adults (n = 108)	7.03 (6.44, 7.68)	101 (91.4, 113)
12 to 17 years (n = 62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n = 68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n = 38)	11.6 (10.4, 12.9)	162 (139, 187)

[1] PK parameters were estimated based on a population PK analysis and normalized by 50 mg dose
(Source: Sponsor's PKPD report, Table 13 page 44)

Furthermore, the response rates in pediatric patients 6 to 17 years old with ITP were lower than those observed in adults with ITP (Table 6). Since some of pediatric patients started with lower initial dose (37.5 mg for pediatric patients with <27 kg), the proposed initial doses were determined by simulations with a PKPD model (see Section 4.1.3).

Table 6. Comparison of Efficacy in Pediatric and Adults Patients with ITP Following Eltrombopag

Age Group	Response Rate in Eltrombopag Arm	Response Rate in Placebo Arm
Adults (TRA100773A)[1]	19/27 (70%)	3/27 (11%)
Adults (TRA100773B)[1]	43/73 (59%)	6/37 (16%)
12-17 years (PETIT and PETIT2)[2]	25/39 (64.1%)	2/18 (11.1%)
6-11 years (PETIT and PETIT2)[2]	29/25 (44%)	6/223 (27.3%)
1-5 years (PETIT and PETIT2)[2]	13/24 (54.2%)	4/11 (36.4%)

[1] Platelet count response (≥50 Gi/L and <400 Gi/L) for 6 out of the last 8 weeks in adults (p-value<0.001 for Promacta vs. placebo)
[2] Platelet count response (≥50 Gi/L without rescue) for 6 out of 8 weeks (p-value=0.0011 for Promacta vs. placebo for all age cohorts for PETIT2)
(Source: Sponsor's SCE, Table 1 on page 8 and Table 37 on page 56)

2.3.3. Is the proposed initial dose for pediatric patients 1 to 5 years old appropriate?

The 25 mg QD for non-East Asians is adequate but we do not agree with the [redacted] for East Asian patients.

- The proposed dosing regimens are only for the starting doses and then doses are to be titrated based on platelet counts to target ≥50 Gi/L and <200 Gi/L. The predicted concentrations of eltrombopag in pediatric patients 1 to 5 years of age with non-East Asian ancestry are comparable with those in adults following the proposed initial dosing regimens (Table 7). The predicted concentrations in patients 1-5 years of age with East Asian ancestry show wider range reflecting the characteristics [redacted]

- The predicted platelet counts following [redacted] without dose titration could reach [redacted] Gi/L, [redacted] The high peak to trough ratio with fluctuation of eltrombopag concentrations following [redacted] is also of concern for steady delivery of drug for desirable efficacy.

- The number of dose modifications and higher final doses in patients with different staring doses give another perspective for the initial dose justification. As shown in Table 8, substantial portion of subjects (79% of patients 1 to 5 years old) enrolled in PETIT and PETIT2 required more than 3 dose modifications, with the majority of the modifications being increases in dose. Furthermore, as shown in Table 9, substantial portion of patients eventually escalated dose to >50 mg. Thus, 25 mg QD as an initial dose does not generate safety concern for pediatric patients 1 to 5 years old with either East Asian or non-East Asian ancestry.

- The predicted platelet counts with 25 mg QD without dose titration could reach close to 40 Gi/L for both East Asian and non-East Asian (Figure 1). Furthermore, [redacted] (b) (4) is also a concern. Therefore, 25 mg QD appears to be reasonable initial dose for pediatric patients 1 to 5 years old regardless of race.

- The absence of 12.5 mg strength with oral suspension for titration would be a concern. We recommend the applicant 12.5 mg [redacted] (b) (4) available so that adequate titration would be possible for patients 1 to 5 years.

Table 7. Summary of Predicted Plasma Eltrombopag PK for Doses Based on Age and Race

Race	Age	N	Dose (mg)	AUC (0 – τ, mcg*hr/mL))	Cmax (mcg/mL)
Non-East Asian	Adults	70	50 mg QD	87.1 (77.0 – 98.5)	6.42 (5.78 –7.13)
	1 – 5 years	**31**	**25 mg QD**	**77.2 (66.8, 89.3)**	**5.51 (4.97, 6.09)**
East Asian	Adults	35	25 mg QD	67.2 (57.1 – 79.0)	4.15 (3.57 – 4.83)
	1 – 5 years	[redacted] (b) (4)			

[redacted] (b) (4)

Table 8. Summary of Subjects Requiring an Increase in Dose and/or Frequency of Eltrombopag in PETIT2

	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)	
	Placebo (N=10) n (%)	Eltrombopag (N=23) n (%)	Placebo (N=13) n (%)	Eltrombopag (N=26) n (%)	Placebo (N=6) n (%)	Eltrombopag (N=14) n (%)
Any Increase in Dose and/or Frequency	**10 (100.0)**	**23 (100.0)**	**13 (100.0)**	**23 (88.5)**	**6 (100.0)**	**13 (92.9)**
0 increase	0	0	0	3 (11.5)	0	1 (7.1)
1 increase	7 (70.0)	15 (65.2)	4 (30.8)	12 (46.2)	0	1 (7.1)
2 increases	3 (30.0)	6 (26.1)	8 (61.5)	9 (34.6)	1 (16.7)	2 (14.3)
3 increases	0	2 (8.7)	0	2 (7.7)	3 (50.0)	5 (35.7)
4 increases	0	0	1 (7.7)	0	0	1 (7.1)
≥5 increases	0	0	0	0	2 (33.3)	4 (28.6)

(Source: Sponsor's report, TRA115450, Table 20, page 73)

Table 9. Summary of Final Dosage Regimen in Pediatric Patients 1 to 5 Years Old

Race	N	Final dose (mg, mean (SD))	Proportion of subjects on final dose ≥50 mg
Non-East Asian	31	48.8 (21.2)	48%
East Asian	7	53.0 (23.3)	57%

(Source: Sponsor's PKPD report, page 17)

Table 10. Comparison of Subject Distribution on Starting Dose and Final Dose above 25 mg

Study	Race	N	Subjects on starting dose >=25mg (N (%))	Subjects on final dose >=25mg (N (%))
Pooled Data	**Non-East Asian**	31	10 (32.2)	27 (87.1)
	East Asian	7	0	6 (85.7)
PETIT	**Non-East Asian**	18	7 (38.9)	16 (88.9)
	East Asian	1	0	0
PETIT2	**Non-East Asian**	13	3 (23.1)	11 (84.6)
	East Asian	6	0	6 (100)

(Source: Reviewer's analysis)

2.4. Biopharmaceutics

2.4.1. What is relative bioavailability of powder formulation for oral suspension (PfOS) compared to tablets?

The PfOS formulation had 22% higher geometric mean of AUC(0-∞) and 31% higher geometric mean of Cmax compared to tablet formulation. The applicant suggested [redacted] (b) (4) when a patient switches between the two formulations. The proposed labeling also indicates that the sponsor may intend to use PfOS formulation for patients ≥6 years of age. However, whether allowing switching between these two formulations for patients ≥6 years of age would be a regulatory issue since the bioequivalence between these two formulations are not established.

2.4.2. What is food effect with powder formulation for oral suspension (PfOS) and how is it different from that with tablet formulation?

Significant chelation interactions with polyvalent metal cation-containing antacids and high-calcium meals were observed with table formulation, which resulted in 60-70% reductions in eltrombopag exposure and recommendation of administration of eltrombopag at least 4 hours apart from these products. As shown in Table 11, eltrombopag exposure was markedly decreased by administration of PfOS with or 2 hours after a high-calcium meal. Administration of PfOS 2 hours before a high-calcium meal reduced the exposure by 20% for AUC and 14% for Cmax. Therefore the sponsor proposes the administration of eltrombopag 2 hours before the meal as an alternative to the administration of eltrombopag at least 4 hours apart from taking this type of meal. However, the effect of a high-calcium meal 2 hour prior to the administration of eltrombopag was evaluated with PfOS and cannot be extrapolated to tablet formulation.

Table 11. Assessment of Impact of Administration of PfOS with and Two Hours Apart from a High-Calcium Meal

	Treatment Comparison		
PK Parameter for Comparison	C vs. B	D vs. B	E vs. B
AUC(0-∞)	0.254 (0.224, 0.287)	0.804 (0.711, 0.908)	0.531 (0.470, 0.601)
Cmax	0.211 (0.184, 0.243)	0.859 (0.750, 0.984)	0.524 (0.457, 0.601)
Tmax	1.00 (0.50, 1.50)	-0.5 (-0.5, 0)	0 (-0.5, 0)
$T_{1/2}$	0.902 (0.858, 0.948)	0.995 (0.947, 1.05)	0.958 (0.912, 1.01)

B: eltrombopag 25 mg PfOS fasted
C: eltrombopag 25 mg PfOS administered with high calcium meal
D: eltrombopag 25 mg PfOS administered 2 hours before high calcium meal
E: eltrombopag 25 mg PfOS administered 2 hours after high calcium meal
(Source: Sponsor's report for TRA111718, Table 15 on page 35)

2.5. Bioanalytical methods

2.5.1. What bioanalytical methods were used to determine eltrombopag concentrations in plasma? Briefly describe the performance of the assay.

HPLC and MS/MS methods were used to analyze eltrombopag (SB-497115) in human biological fluids (plasma) for samples from all clinical trials. The lower limit of quantitation (LLOQ) for the assay was 100 ng/mL and the linear calibration range is 100 to 50,000 ng/mL for 50 µL human plasma aliquot, containing dipotassium EDTA. Samples were stored in polypropylene tubes and kept frozen at ~ 20 °C prior to analysis, and no apparent abnormalities were observed from freeze/thaw stability test. The assay

was selective and specific for eltrombopag in human plasma. There was no significant interference observed from endogenous components in the control human biological fluids. The accuracy of the intra-assay of quality control (QC) samples did not deviate by more than 10% of the nominal concentrations. The precision (coefficient of variation, CV %) of the intra-assay of QC samples was less than 10% at each concentration.

3. LABELING RECOMMENDATIONS

Detailed labeling revisions are summarized as below. The sections in red are the labeling changes proposed by the Applicant. The ~~double-strikethrough in red~~ text indicates recommended deletion by the reviewer. The texts in blue are recommended labeling changes by the reviewer. The *italic texts* provide the labeling recommendations rational based on this clinical pharmacology review.

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

4. PHARMACOMETRICS REVIEW

4.1. Results of Sponsor's Analysis

4.1.1. Sponsor's Population PK and PKPD Modeling

The Pop PK and PKPD analyses included concentration-time and platelet count-time data following eltrombopag dosing in pediatric ITP patients 1 to 17 years of age enrolled in Studies PETIT and PETIT2. Subjects were randomized 2:1 to eltrombopag: placebo for the first 7 weeks of PETIT and for the first 13 weeks of PETIT2. Subjects randomized to placebo switched to eltrombopag dosing after the randomized period. All subjects received eltrombopag for at least 24 weeks. Subjects 1 to 5 years of age received the eltrombopag PfOS formulation and subjects 6 to 17 years of age received tablets.

Subjects underwent weekly visits until platelet counts were stable and then underwent monthly visits thereafter. Doses were increased at 2-week intervals if platelet counts were <50 Gi/L and the maximum eltrombopag dose was 75 mg daily. Doses were decreased at any time platelet counts were >200 Gi/L and dosing was interrupted when platelet counts were >400 Gi/L. Serial PK samples were collected at Week 6 in PETIT and a single PK sample was collected at all visits in both studies. Platelet counts were collected at all visits.

The initial pop PK analysis was done with data from PETIT and the final model developed with data from PETIT. The data from PETIT2 were used as an external validation and then the final pop PK model parameters were estimated using pooled data from both PETIT and PETIT2. The platelet count data were fitted alone using the individual post-hoc PK parameter estimates obtained from the final pop PK model to predict plasma eltrombopag concentrations. Simulations of plasma eltrombopag exposure and platelet response were completed for various initial eltrombopag dosage regimens and dose titration schedules.

The summary of demographics and baseline characteristics are summarized in Table 12.

Table 12. Summary of Demographics and Baseline Characteristics of Patients Included in the Pop PK and PKPD Analyses

Variable	N=168
Number (%) of Subjects per age Cohort	
Cohort 1: 12-17 years	62 (37)
Cohort 2: 6-11 years	68 (40)
Cohort 3: 1-5 years	38 (23)
Age (y)	9.5 (4.3) [1.0-17.0]
Body weight (kg)	42.1 (22.3) [11.0-135]
Gender	
Female	86 (51)
Male	82 (49)
Race	
East/Southeast Asian	33 (20)
Other	135 (80)
Splenectomy	
No	158 (94)
Yes	10 (6)
Baseline bleeding severity score	
Grade 0 (No Bleeding)	42 (25)
Grade 1 (Petechiae)	87 (52)
Grade 2 (Mild blood loss)	38 (23)
Grade 3 (Gross blood loss)	1 (1)
Prior use of ITP medication	
No	4 (2)
Yes	164 (98)
Concurrent use of ITP medication (based on number of events)	
No	3487 (83)
Yes	695 (17)
Baseline platelet count (Gi/L)	14 (8) [1-38]
Number of Subjects with Serial PK Samples	52 (31)
Number of PK samples	2607
Number of platelet counts	4182
Final Dose (mg)	56.8 (20.8) [7.0-75.0]

Final dose based on last on-treatment visit recorded in the pop PKPD dataset, with median (minimum, maximum) time from first eltrombopag dose = 29 weeks (10 to 69 weeks).
(Source: Sponsor's PKPD report, page 10)

Plasma eltrombopag PK were described by a 2-compartment model, with first-order absorption and elimination. IIV was included on CL/F, V2/F, and Q/F. Lower plasma CL/F was observed for pediatric ITP patients of East/Southeast Asian ancestry (30% lower CL/F) and female sex (20% lower CL/F). Plasma eltrombopag CL/F, Q, V2/F and V3/F were increased as body weight increased. The estimated exponents for weight on CL/F, V2/F, and V3/F were close to allometric values.

The final PKPD model was a 7-compartment life-span model, including 3 PK compartments (Figure 4). The 4 PD compartments represented 3 bone marrow compartments (1 for platelet precursor production

and 2 for maturation compartments) and one blood platelet compartment in which the increase in the rate of platelet precursor production (KIN) was linearly related to plasma eltrombopag concentrations (SLOP).

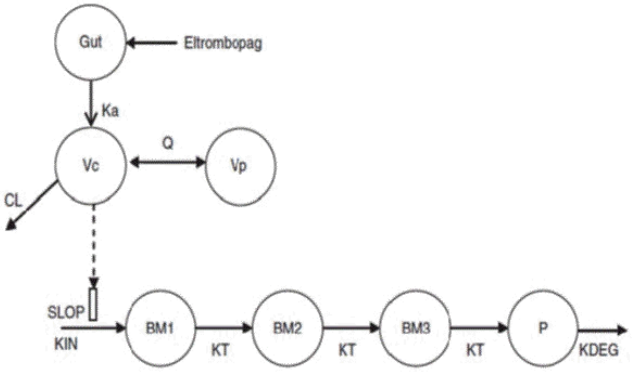


Figure 4. Schematic of the final eltrombopag PKPD model for patients with chronic ITP
CL: clearance; Ka: first-order absorption rate constant; Vc: Volume of central compartment; Q: intercompartmental clearance; Vp: Volume of peripheral compartment; KIN: zero-order production rate of platelet precursors; KT: first-order maturation rate of platelet precursors; KDEG: first-order platelet degradation rate; SLOP: linear coefficient of drug effect; BM: bone marrow compartments for precursors; P: proportion of responders
(Source: Sponsor's PKPD report, Figure 1, page 21)

SLOP, KOUT (platelet maturation rate) and P1 (the proportion of subjects identified as responders) were estimated, and KIN was fixed to adult value. IIV was included on SLOP and KOUT. The majority of subjects (96%) were identified as responding to eltrombopag treatment. The typical estimate of SLOP was 0.651 mL/μg in responders, while it was 0 for non-responders. KOUT increased with increasing age. No significant covariates were identified on SLOP. The first-order platelet degradation rate constant (KDEG) was calculated as KIN divided by BASL (baseline value), and the population value of KDEG was 0.102/hr. Based on this KDEG, the median half-life was estimated to be approximately 7 hours.

The estimated PK parameters are summarized in Table 13 and the estimated PD parameters are summarized in Table 14.

Table 13. PK Parameter Estimates in Pediatric Patients with ITP

Parameter (units)	Notation	Population Estimate	%RSE	Bootstrap Median (95% CI)
CL/F (L/hr) =Θ1*(BWT/70)**Θ6 *Θ8**FEM *Θ9**RACE	Θ1	0.612	5.54	0.610 (0.554, 0.674)
V2/F (L) =Θ2*(BWT/70)**Θ7	Θ2	2.74	19.9	2.83 (1.05, 9.34)
Q/F (L) =Θ3*(BWT/70)**Θ6	Θ3	0.716	9.76	0.688 (0.369, 1.06)
V3/F (L/hr) =Θ4*(BWT/70)**Θ7	Θ4	21.5	7.81	20.8 (14.7, 27.2)
Ka (1/hr)	Θ5	0.189	9.74	0.201 (0.101, 0.624)
BWT~CL/F,Q/F	Θ6	0.691	11.3	0.685 (0.552, 0.824)
BWT~V2/F,V3/F	Θ7	0.791	12.5	0.830 (0.423, 1.10)
FEM~CL/F	Θ8	0.796	6.54	0.792 (0.708, 0.884)
RACE~CL/F	Θ9	0.696	8.22	0.693 (0.600, 0.796)
PfOS~F1	Θ10	0.707	9.68	0.717 (0.622, 0.834)
Inter-individual variability (IIV)		**Population Estimate (CV%)**		
$\omega^2_{CL/F}$	Ω 1	0.0920 (30.3)	17.5	0.0892 (0.0621, 0.1162)
$\omega^2_{V2/F}$	Ω2	0.521 (72.2)	40.1	0.411 (0.0852, 0.945)
$\omega^2_{Q/F}$	Ω3	0.316 (56.2)	31.1	0.381 (0.131, 1.288)
Inter—occasion variability (IOV)		**Population Estimate (CV%)**		
$\omega^2_{IOV-CL/F}$	Ω4,5,6	0.0584 (24.2)	14.1	0.0560 (0.0374, 0.0758)
Residual Variability		**Population Estimate (CV% or SD)**		
σ^2_{prop}	σ1	0.103 (32.1)	2.18	0.0993 (0.0822, 0.1157)
σ^2_{add}	σ2	0.0097 (0.099)	80.1	0.0097 (0.0007, 0.2418)

(Source: Sponsor's PKPD report, page 12)

Table 14. PD Parameter Estimated for Eltrombopag in Pediatric Patients with ITP

Parameter (units)	Notation	Population Estimate	%RSE
SLOP (mL/μg)	Θ1	0.651	9.88
KIN (Gi/L/hr)	Θ2	1.43 Fixed	-
KOUT (1/hr)	Θ3	0.0126	12.7
P(1)	Θ4	0.957	2.04
BAGE~KOUT	Θ7	0.611	30.0
Inter-individual variability (IIV)		**Population Estimate (CV%)**	
ω^2_{SLOP}	Ω1	1.22 (110)	13.4
ω^2_{KOUT}	Ω3	1.09 (104)	17.0
Residual Variability		**SD**	
σ_{add}	Θ6	0.892	0.372

(Source: Sponsor's PKPD report, page 13)

4.1.2. Summary of Plasma Eltrombopag PK

When normalized by a 50 mg dose, pediatric patients 1 to 5 years of age, females, and East/Southeast Asian subjects had higher plasma eltrombopag dose-normalized AUC (DN-AUC(0-tau)) and DN-Cmax values. Geometric mean plasma eltrombopag half-life ranged from 46.9 to 51.9 hours across age cohorts, which was similar to that in adults (44 hours). The DN-AUC(0-tau) and DN-Cmax in each age cohort in comparison with adults are shown in Figure 5 and Figure 6, respectively.

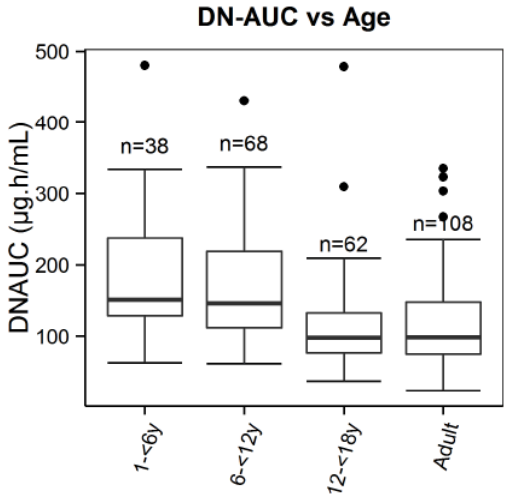


Figure 5. Plasma eltrombopag dose-normalized to 50 mg AUC(0-tau) by age

(Source: Sponsor's PKPD report, Figure 2, page 45)

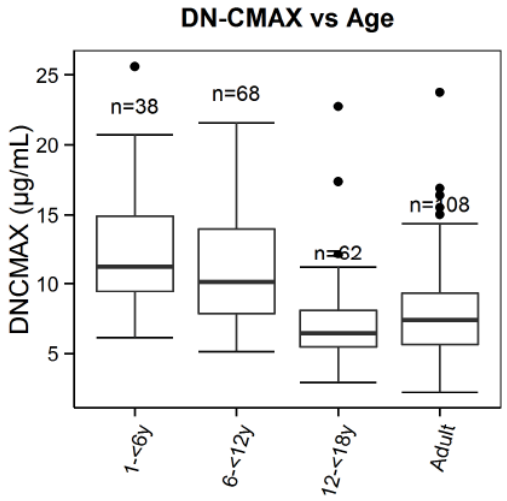


Figure 6. Plasma eltrombopag dose-normalized to 50 mg AUC(0-tau) by age

(Source: Sponsor's PKPD report, Figure 3, page 46)

The majority of subjects aged 1 to 5 years of age received eltrombopag doses close to50 mg as their final dose. Geometric mean plasma eltrombopag AUC(0-tau) values at the final doses ranged from 133 to 188 mcg*hr/mL.

Table 15. Summary of Plasma Eltrombopag PK Parameters for Final Doses by Age and Race

Covariate	N	Actual Age Enrolled (y)	Baseline Weight (kg)	Final Dose[a] (mg)	Proportion of Subjects on Final Dose >=50mg (%)	AUC(0-τ)[b] (µg.h/mL)	Cmax[b] (µg/mL)
Age + Race							
12-17 Years, EA	11	13.7 (1.6) [12.0-17.0]	57.7 (18.8) [30.0-82.1]	58.0 (21.1) [12.5-75.0]	73%	166 (93.9, 292)	10.0 (5.95, 17.0)
12-17 Years, Non-EA	51	14.2 (1.7) [12.0-17.0]	64.6 (18.5) [37.2-135]	60.5 (19.9) [12.5-75.0]	78%	104 (87.8, 122)	7.00 (6.02, 8.14)
6-11 Years, EA	15	8.6 (1.7) [6.0-11.0]	31.9 (10.1) [18.6-58.3]	47.5 (23.2) [12.5-75.0]	47%	181 (123, 266)	11.6 (7.97, 16.9)
6-11 Years, Non-EA	53	8.4 (1.8) [6.0-11.0]	37.2 (11.6) [19.0-64.0]	60.6 (18.9) [12.5-75.0]	77%	155 (137, 176)	10.6 (9.49, 11.9)
1-5 Years, EA	7	3.4 (1.5) [1.0-5.0]	15.1 (3.4) [11.0-19.5]	53.0 (23.3) [18.0-75.0]	57%	188 (96.4, 366)	13.8 (8.47, 22.5)
1-5 Years, Non-EA	31	3.7 (1.2) [1.0-5.0]	18.8 (3.9) [11.9-25.7]	48.8 (21.2) [7.0-75.0]	48%	133 (107, 164)	9.45 (7.68, 11.6)

(Source: Sponsor's PKPD report, Table 14, page 47)

4.1.3. Simulation

PK Simulation

The applicant performed simulations with various dosing regimens using the final population PK and PKPD model developed from 168 pediatric patients 1 to 17 years of age and based on the individual covariate records from 38 children 1 to 5 years of age. Of these 38 children aged 1 to 5 years, 7 were East Asian and 31 Non-East Asian. Figure 7 shows PK profiles of eltrombopag following 25 mg daily in non-EA pediatric patients 1 to 5 years and 12.5 mg daily, 0.8 mg/kg daily, or 25 mg every other day in EA pediatric patients 1 to 5 years. The 95% prediction intervals for Cmin, Cavg, and Cmax are summarized in Table 16. The applicant interprets the results that Cmin and Cavg are comparable across all three regimens for patients with EA ancestry, while Cmax was slightly higher with 25 mg every other day dosing.

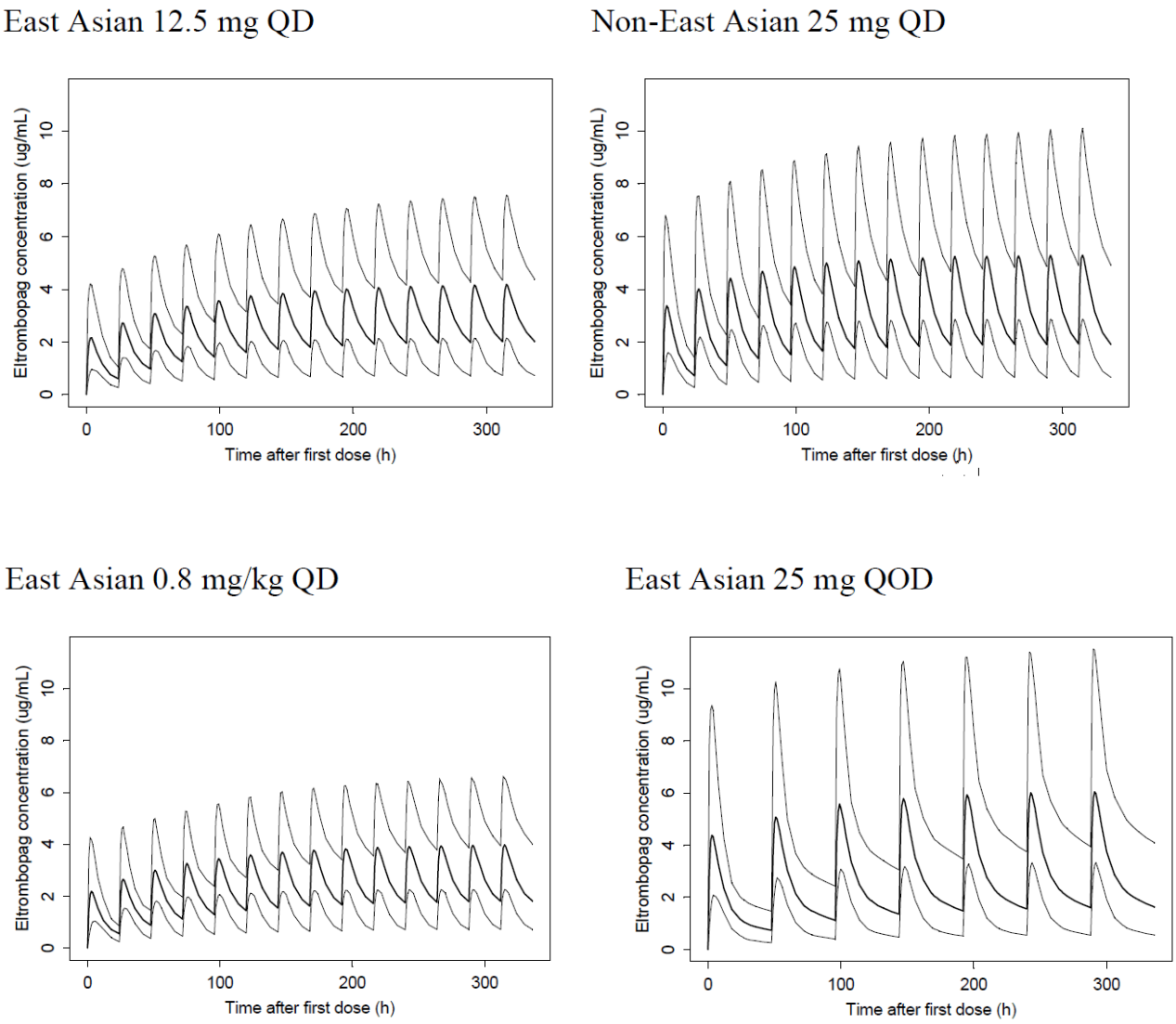


Figure 7. Simulated PK profiles of eltrombopag following various dosing regimens

(Source: Response to Information Request dated June 16, 2015)

Table 16. Simulated PK measures following various dosing regimens

		Cmin			Cavg			Cmax		
Race	Dose	2.5th %tile	50th %tile	97.5th %tile	2.5th %tile	50th %tile	97.5th %tile	2.5th %tile	50t h %tile	97.5th %tile
EA	0.8 mg/kg QD	0.71	1.79	3.86	1.53	2.81	5.49	2.34	4.06	6.81
Non-EA	1.5 mg/kg QD	0.75	2.14	5.12	1.96	3.75	7.01	3.50	6.07	10.16
EA	12.5 mg QD	0.71	1.98	4.28	1.41	3.04	5.88	2.17	4.29	7.58
Non-EA	25 mg QD	0.65	1.91	4.86	1.69	3.39	7.18	3.00	5.45	10.23
EA	25 mg QOD	0.55	1.60	3.94	1.50	3.00	6.12	3.44	6.25	11.91

(Source: Response to Information Request dated June 16, 2015)

PD Simulation

Figure 8 further show the profiles of platelet counts following 0.5 mg/kg daily, 12.5 mg daily, 25 mg every other day dose in children 1 to 5 years of age with EA ancestry and those following 1.5 mg/kg daily and 25 mg daily for those with non-EA ancestry.

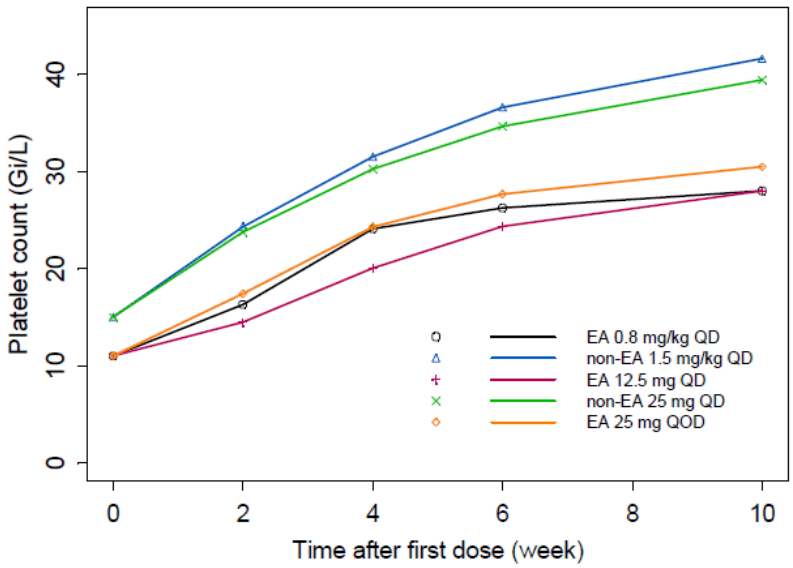


Figure 8. Predicted median platelet counts vs time for various starting doses

(Source: Sponsor's response to Clinical Pharmacology IR dated June 10, 2015, Figure 2, page 4)

Reviewer's comments

The population PK model and the PKPD model described the observed data reasonably well. Even though body weight was identified as a significant covariate on clearance and two volume of distribution parameters, its effect on platelet counts does not appear to be significant. Mean relative bioavailability of the PfOS formulation was estimated to be 29% lower compared to the tablet formulation. This

formulation effect was confounded by age 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. Moreover, the bioavailability of PfOS was evaluated in adult healthy subjects in a relative BA study. However, the observed bioavailability from the study was not reflected in the population PK analysis.

4.2. Reviewer's Analysis

4.2.1. Introduction

The sponsor conducted population PK and PKPD analyses and performed simulations to predict eltrombopag PK and platelet counts with different dosing scenario. Most of the sponsor's analyses appear to be reasonable for justification of the starting doses. The reviewer reanalyzed the data and performed simulations to confirm the sponsor's analyses and simulations.

4.2.2. Objectives

The analysis objective is to confirm the sponsor's analyses and simulations for justification of the proposed initial doses.

4.2.3. Data

Datasets used in the analysis are summarized in Table 17.

Table 17. Analysis Data Sets

Study Number	Name	Link to EDR
POP PK Modeling	nonmem4.xpt	\\CDSESUB1\evsprod\NDA022291\0170\m5\datasets\pop-pkpd-ped-itp\analysis\legacy\datasets
PKPD Modeling	nonmem6.xpt	\\CDSESUB1\evsprod\NDA022291\0170\m5\datasets\pop-pkpd-ped-itp\analysis\legacy\datasets
POP PK Simulation	pksim1.xpt pksim2.xpt, pksim3.xpt, pksim4.xpt, pksim5.xpt, pksim6.xpt, pksim7.xpt, pksim8.xpt, pksim9.xpt, pdsim1.xpt, pdsim2.xpt, pdsim3.xpt	\\CDSESUB1\evsprod\NDA022291\0170\m5\datasets\pop-pkpd-ped-itp\analysis\legacy\datasets
PKPD Simulation	pdsim4.xpt, pdsim5.xpt, pdsim5.xpt, pdsim6.xpt, pdsim7.xpt, pdsim8.xpt, pdsim9.xpt, pdsim10.xpt, pdsim11.xpt	\\CDSESUB1\evsprod\NDA022291\0170\m5\datasets\pop-pkpd-ped-itp\analysis\legacy\datasets

4.2.4. Software

Population PKPD modeling and simulation were performed with NONMEM (version 7.3) and graphical, statistical analysis were performed with R (version 2.13.2).

4.2.5. Results

Predicted median concentrations of eltrombopag following various dosing regimen in age/race groups are shown in Figure 9. The predicted PK profiles of eltrombopag following 1.5 mg/kg appear to be similar for patients with either East Asian ancestry or non-East Asian ancestry. The predicted PK profile of eltrombopag following 25 mg in non-East Asian ancestry appears to be lower than those following 25 mg in East Asian ancestry or those following 1.5 mg/kg in either non-East Asian or East Asian ancestry but still similar to those following 25 mg in patients 12 to 17 years old with East Asian ancestry. Predicted median platelet counts following 15 mg, 25 mg, or 50 mg of eltrombopag for all age groups for 14 weeks regardless of race are shown in Figure 10. Both 25 mg and 15 mg doses do not achieve the target platelet counts for all populations including pediatric patients 1 to 5 years old. As age becomes small the effect of race on the eltrombopag PK appears to be smaller.

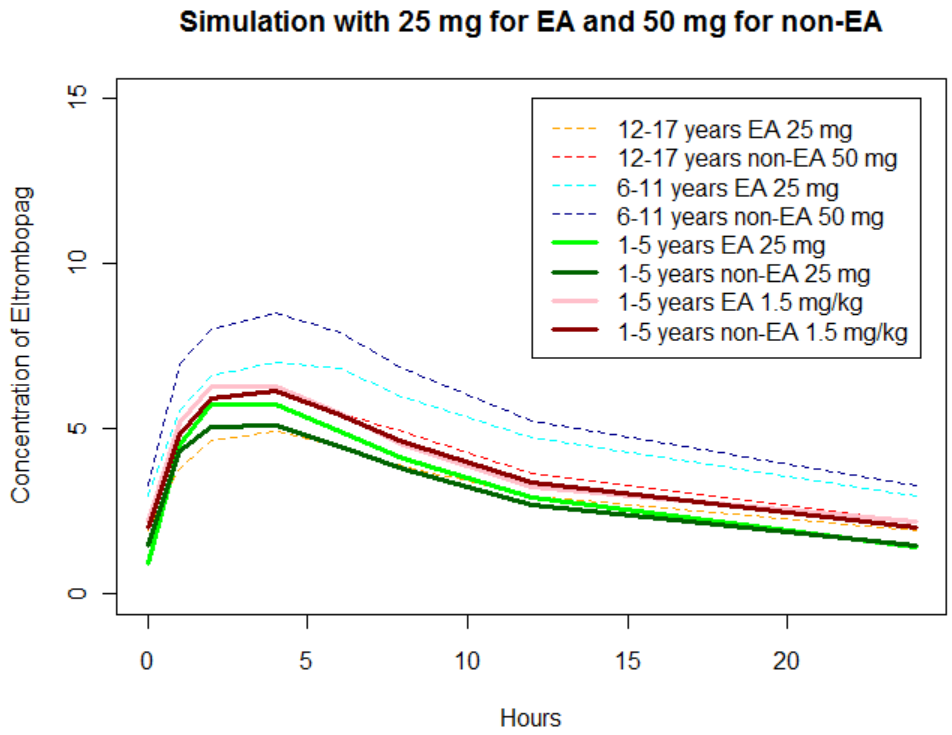


Figure 9. Simulated PK profiles of Eltrombopag with single dose of various regimens

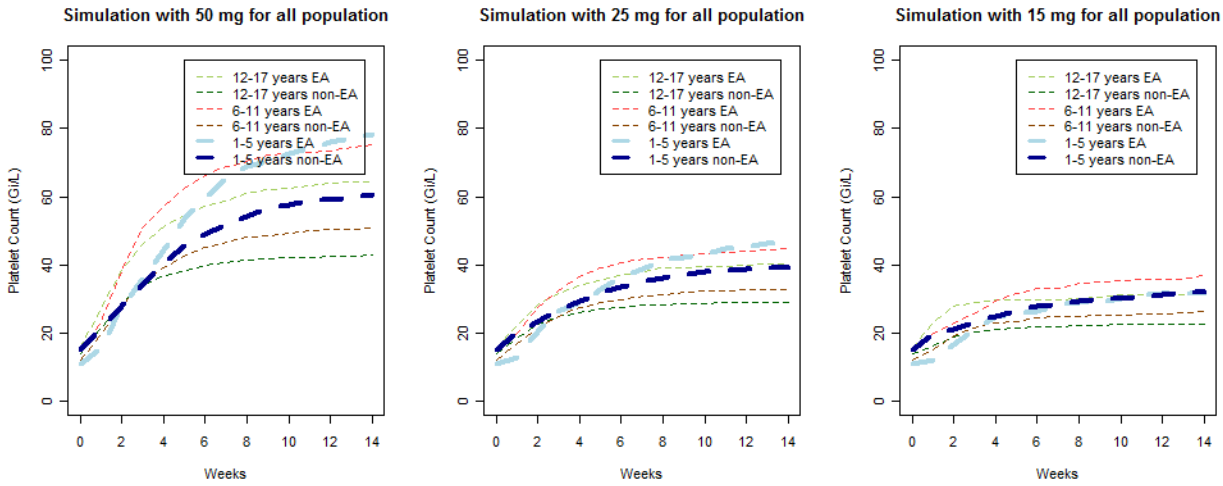


Figure 10. Predicted median platelet counts following 50 mg, 25 mg, and 15 mg for all subjects for 14 weeks

Although starting daily dose of eltrombopag was lower than 25 mg in majority of pediatric patients 1 to 5 years old, dose was escalated targeting platelet counts 50 Gi/L – 200 Gi/L (Figure 11, Table 9). Consequently, majority of patients (48% of non-East Asian and 57% of East Asian) escalated dose to >50 mg. This is supportive evidence that 25 mg QD is adequate starting dose for pediatric patients 1 to 5 years of age regardless of race.

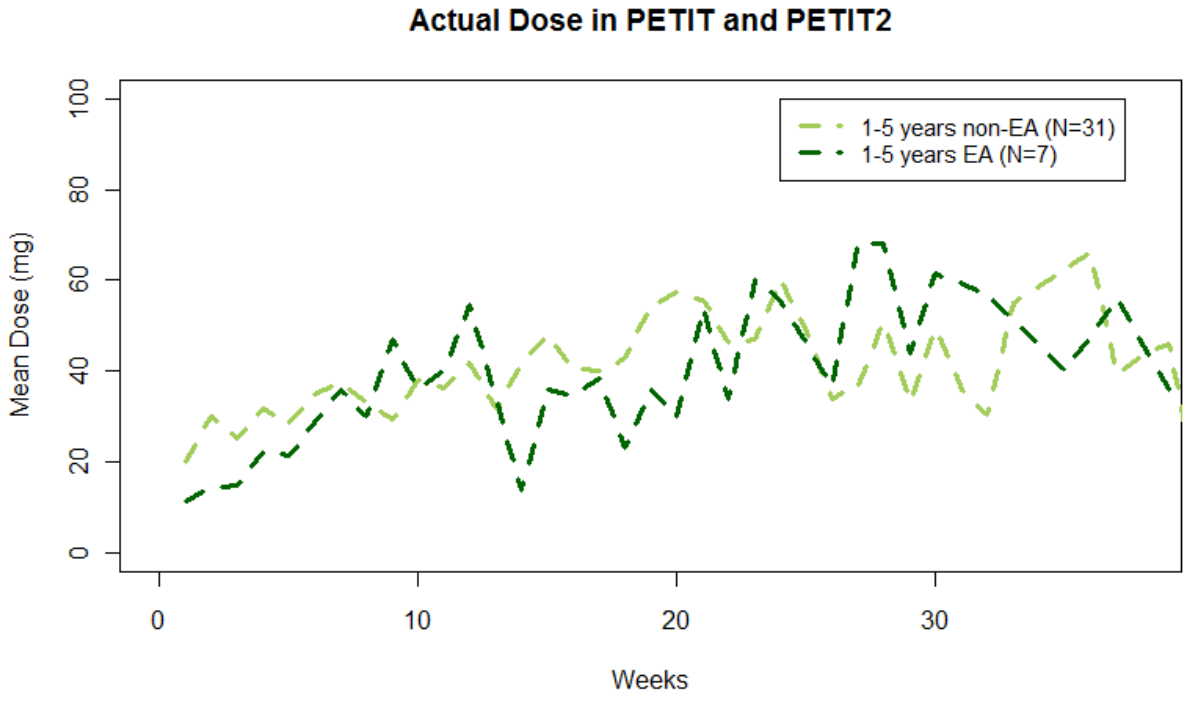


Figure 11. Mean dose for pediatric patients 1 to 5 years old in PETIT and PETIT2 (N=38)

5. LISTING OF ANALYSIS CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
NDA207027_PKPD.R	PKPD modeling for efficacy	Reviews\Ongoing PM Reviews\Promacta_NDA207027_JEL

Appendix: Individual Study Reports

BE/BA Study: TRA111718

Title: A randomized, open-label, five-period, balanced crossover study to evaluate the relative bioavailability of an eltrombopag Powder for Oral Suspension (PfOS) formulation relative to the commercial 25 mg tablet formulation and to evaluate administration of the PfOS formulation with and separated 2 hours from a high calcium meal in healthy adult subjects

A total of 35 of the 40 randomized subjects complete all five periods of the study. The most frequently reported adverse events were headache (11 subjects, 27%) and pre-syncope (3 subjects, 7.5%). Eight of the reported events were considered related to study drug; all were headaches. No deaths or serious adverse events were reported. Two subjects discontinued early for adverse events and neither event was considered related to study drug. Clinically significant changes in clinical laboratory values, vital signs and ECGs were not observed.

The eltrombopag PfOS formulation delivered an average of 22% higher 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. Eltrombopag PK was similar between subjects of African American/African and White-White/Caucasian/European heritage.

Objectives: To evaluate the bioavailability of a PfOS formulation relative to the commercial eltrombopag 25 mg tablet formulation in healthy adult subjects.

To evaluate the effect of high calcium, moderate fat and calorie meal on the PK of a single oral 25 mg dose of eltrombopag PfOS in healthy adult subjects when eltrombopag is administered concurrently, two hours before, or two hours after the meal.

- Primary endpoints: AUC(0-∞) and Cmax
- Secondary endpoints: AUC(0-t), %AUCex, tlag, tmax, t1/2, and CL/F

This study was conducted prior to PETIT study where patients < 6 years old would receive PfOS formulation. Previously the sponsor found that plasma eltrombopag AUC and Cmax were decreased by 60-70% when administered with polyvalent metal cation-containing products such as antacids and a high calcium meal. Therefore, the approved labeling which recommends separate the administration of eltrombopag and polyvalent metal cations by at least 4 hours. However, the 4-hour separation between eltrombopag and dairy products may be difficult for pediatric subjects to incorporate into their daily routines; therefore, the shorter time interval (2 hour) between drug administration and the meal was evaluated.

Table 18. Study Design for TRA111718

Treatment Code	Treatment Description
A	25 mg tablet single dose fasted
B	25 mg PfOS single dose fasted
C	25 mg PfOS single dose administered with a meal
D	25 mg PfOS single dose administered 2 hours prior to meal
E	25 mg PfOS single dose administered 2 hours after meal

Sequence	N	Period 1[1]	Period 2[1]	Period 3[1]	Period 4[1]	Period 5[1]
1	4	A	E	B	D	C
2	4	B	A	C	E	D
3	4	C	B	D	A	E
4	4	D	C	E	B	A
5	4	E	D	A	C	B
6	4	C	D	B	E	A
7	4	D	E	C	A	B
8	4	E	A	D	B	C
9	4	A	B	E	C	D
10	4	B	C	A	D	E

(Source: Sponsor's report TRA111718 Table 1 on page 11 and Table 2 on page 14)

Subjects abstained from taking drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or five half-lives prior to the first dose of study medication until the completion of the follow-up visit. Administration of eltrombopag with a polyvalent cation-containing antacid decreases plasma eltrombopag by 70% and a similar reduction was observed when eltrombopag was administered with a high-calcium meal. Therefore, use of polyvalent cation-containing antacids (such as aluminum hydroxide and magnesium carbonate, e.g., Maalox, TUMS™, or GAVISCON™) were not permitted during the study. Dairy products were allowed.

The description of the high calcium mean used in the study is shown in Table 19.

Table 19. High Calcium Meal Used in TRA111718

Food	Kilocalories	Calcium (mg)	Fat (gm)
1 cup Cheerios	111	100	1.8
½ cup (4 oz) 2% milk	61	150	2.3
1 slice toast	69	20	1.2
2 teaspoon jam	37	2.7	0
1 teaspoon butter	34	1	3.8
½ cup (4 oz) calcium fortified orange juice	60	175	0
TOTALS	**372**	**448**	**9.1**

(Source: Sponsor's report, Table 3 on page 15)

A total of 60 PK samples were collected from subjects completing all fie periods of the study. The data analysis was performed to compare treatments for relative bioavailability and food effect as described in Table.

Table 20. Treatment Comparisons in Study TRA111718

Comparison	Test Treatment	Reference Treatment
Relative Bioavailability	B	A
Food Effect	C	B
	D	B
	E	B

A: eltrombopag 25 mg tablet fasted
B: eltrombopag 25 mg PfOS fasted
C; eltrombopag 25 mg PfOS administered with high calcium meal
D: eltrombopag 25 mg PfOS administered two hours before high calcium meal
E: eltrombopag 25 mg PfOS administered two hours after high calcium meal

(Source: Sponsor's report, Table 6 on page 20)

The analysis results for PK parameters are summarized in Table 21 and the treatment comparisons are summarized in Table 22 and Table 11.

Table 21. Summary of Selected Plasma Eltrombopag PK Parameters

	Treatment				
PK Parameter	A (N=38)	B (N=38)	C (N=37)	D (N=40)	E (N=39)
AUC(0-∞) (mcg*hr/mL)	34.2 (29.9, 39.1)	41.1 (35.2, 48.0)	10.6 (8.89, 12.6)	33.9 (29.6, 38.8)	22.1 (18.9, 25.8)
Cmax (mcg/mL)	2.55 (2.27, 2.87)	3.30 (2.88, 3.78)	0.70 (0.586, 0.835)	2.87 (2.53, 3.26)	1.74 (1.53, 1.98)
Tmax (hr)	3.0 (2.0, 6.0)	3.0 (2.0, 6.0)	4.0 (2.0, 6.0)	2.0 (1.0, 4.0)	3.0 (2.0, 6.0)
$T_{1/2}$ (hr)	20.5 (19.3, 21.9)	20.6 (19.1, 22.1)	18.9 (17.4, 20.6)	20.7 (19.4, 22.2)	19.9 (18.5, 21.3)

A: eltrombopag 25 mg tablet fasted

B: eltrombopag 25 mg PfOS fasted
C: eltrombopag 25 mg PfOS administered with high calcium meal
D: eltrombopag 25 mg PfOS administered 2 hours before high calcium meal
E: eltrombopag 25 mg PfOS administered 2 hours after high calcium meal
(Source: Sponsor's report, Table 12 on page 33)

Table 22. Assessment of Relative Bioavailability of PfOS Compared to Tablet

PK Parameter	Treatment Comparison B vs. A
AUC(0-∞)	1.22 (1.08, 1.38)
Cmax	1.31 (1.14, 1.50)
Tmax	-0.5 (-1.0, 0)
$T_{1/2}$	1.01 (0.959, 1.06)

A: eltrombopag 25 mg tablet fasted
B: eltrombopag 25 mg PfOS fasted
(Source: Sponsor's report, Table 14 on page 34)

Reviewer's comments:

The PfOS formulation had 22% higher geometric mean of AUC(0-∞) and 31% higher geometric mean of Cmax compared to tablet formulation. The applicant suggested [redacted] (b) (4) when a patient switches between the two formulations. The proposed labeling also indicates that the sponsor may intend to use PfOS formulation for patients ≥6 years of age. However, whether allowing switching between these two formulations for patients ≥6 years of age would be a regulatory issue since the bioequivalence between these two formulations are not established.

Significant chelation interactions with polyvalent metal cation-containing antacids and high-calcium meals were observed with table formulation, which resulted in 60-70% reductions in eltrombopag exposure and recommendation of administration of eltrombopag at least 4 hours apart from these products. As shown in Table 11, eltrombopag exposure was markedly decreased by administration of PfOS with or 2 hours after a high-calcium meal. Administration of PfOS 2 hours before a high-calcium meal reduced the exposure by 20% for AUC and 14% for Cmax. [redacted] (b) (4)

Study 2011N117417

Title: Quantitation of SB-497115 in Human Plasma via HPLC with MS/MS Detection

Method: The quantitation of SB-497115 within a nominal range of 100 to 50000 ng/mL and requires a 50-uL human plasma aliquot containing dipotassium EDTA. Sample were stored in polypropylene tubes and kept frozen at ~ -20 °C prior to analysis. A 50-uL matrix aliquot was fortified with 500 uL of 400 ng/mL internal standard working solution. Analytes were isolated through protein precipitation using 90:10 acetonitrile/10 mM ammonium formate, pH .0. Samples were then purified through an Ostro lipid removal 96-well plate. The final extract was analyzed via HPLC and MS/MS detection using negative ion electrospray.

Precision and accuracy: precision and accuracy were evaluated by analyzing quality control pools prepared at 100, 250, 600, 2250, 8000, and 37500 ng/mL. Precision was expressed as the percent coefficient of variation (%CV) of each pool. Accuracy was measured as the percent difference from theoretical value. Run acceptance quality controls: Quality controls (QC) at the LLOQ, low-, mid low -, medium-, mid high-, and high-levels were analyzed in duplicate in each validation run to determine run acceptance.

Intra-assay precision and accuracy were evaluated for each quality control pool by multiple analyses (N=6) of the pool during validation runs. Inter-assay precision and accuracy were calculated from the intra-assay samples.

Study 2012N151375

(GSK Study TRA115450)

Title: Quantitation of SB-497115 in Human Plasma via HPLC with MS/MS Detection

One thousand two hundred seventy-two (1272) original and two duplicate human plasma samples, containing dipotassium EDTA, were received frozen at -70 °C up to 90 days and then stored at -20 °C. Long-term storage stability in human plasma containing dipotassium EDTA at -70 °C has been demonstrated for up to 336 days.

Method validated by JCX2. Calibration standard concentrations were 100, 200, 350, 1200, 4000, 15000, 40000, and 50000 ng/mL. QC concentrations were 250, 600, 2250, 8000, 375000, and 100000 ng/mL.

The accuracy of the intra-assay of quality control (QC) samples did not deviate by more than 10% of the nominal concentrations. The precision (coefficient of variation, CV%) of the intra-assay of QC samples was less than 13% at each concentration.

Study 2013N179766

Title: Method validation report addendum 1, LCMS 562, Quantitation of SB-497115 in Human Plasma via HPLC with MS/MS Detection

This report corrected the incorrect purity information for the reference standard provided in the previous report (JCX3, JCX4, YQX)

Study 2013N184022

Title: Within-Study Analytical Performance Data for the Determination of SB-497115 in Human Plasma

(For Study TRA108062: A three part, double blind and open-label, randomized, placebo controlled, staggered cohort study to investigate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of eltrombopag, a thrombopoietin receptor agonist, in previously treated pediatric patients with chronic idiopathic thrombocytopenic purpura (ITP))

HPLC MS/MS method was utilized. QC samples were prepared for SB-497115 in human plasma at three concentrations (300, 4000, and 40000 ng/mL) which spanned the calibration range of the method. A total of 241 incurred SB-497115 human plasma samples from Study TRA108062 (15.4% of total equivalence study samples) were reanalyzed after approval of the original assay result. 66.7% or more of the incurred sample results were within the limits of +/-20% of the mean of the reanalysis results and its corresponding original result.

The accuracy of the intra-assay of quality control (QC) samples did not deviate by more than 10% of the nominal concentrations. The precision (coefficient of variation, CV%) of the intra-assay of QC samples was less than 10% at each concentration.

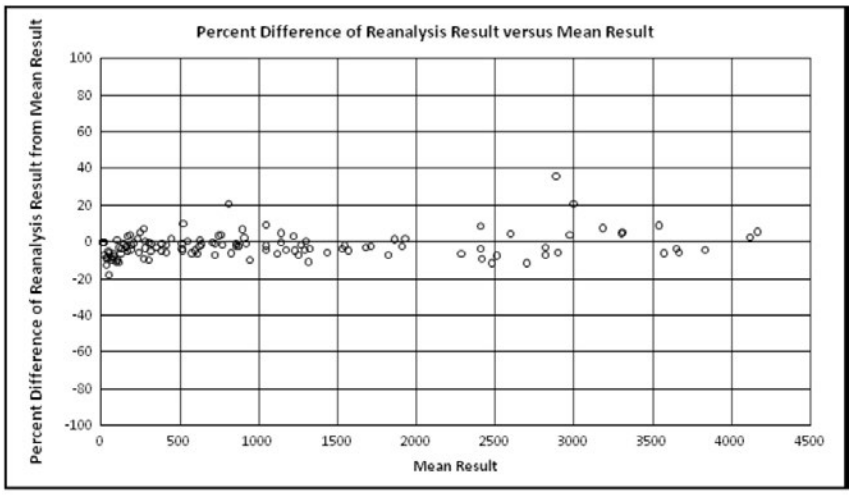
Study 2013N185090

Title: Within-Study Analytical Performance Data for the Determination of SB-497115

(For Study TRA111718 "A randomized four-period-crossover study to evaluate the relative bioavailability of single oral doses of eltrombopag commercial 25 mg tablets compared to 25 mg suspension and the effect of diary 2 hours pre and post suspension dose in healthy volunteers")

Samples were analyzed by HPLC-MS/MS using a TurboIonspray interface with negative ion multiple reaction monitoring. This method was validated over the range 10 – 2500 ng/mL and the lower limit of quantification (LLQ) was 10 ng/mL for a 50 µL aliquot of human plasma.

One hundred thirty (130) incurred SB-497115 human plasma samples from Study TRA111718 (5.2% of total equivalent study samples) were reanalyzed and 66.7% or more of the incurred sample results were within the limits of 20% of the mean of the reanalysis results and its corresponding original result.



% Difference = ((Reanalysis Result - Original Result) / Mean Result) x 100

Mean Result = (Reanalysis Result + Original Result) / 2

Figure 12. Incurred sample reproducibility results from Study TRA111718

The accuracy of the intra-assay of quality control (QC) samples did not deviate by more than 10% of the nominal concentrations. The precision (coefficient of variation, CV%) of the intra-assay of QC samples was less than 10% at each concentration.

Study 2014N195886

Title: Supplemental Validation Data to "Method for the Determination of SB-497115 in Human Plasma (range 100 to 50000 ng/mL) using HPLC-MS/MS"

This report describes supplemental validation including but not limited followings:

- Stability of SB-497115 in human plasma at -20 °C for 547 days
- Stability of SB-497115 in human whole blood at -37 °C, on wet ice and at ambient temperature

The results showed that the SB-497115 samples were stable at stored temperature of -20 °C for 547 days.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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07/31/2015

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