CLINICAL PHARMACOLOGY REVIEW

Submission	**NDA 22291**
Submission Date	**December 19, 2014**
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)	**Tablets; 12.5 mg, 25 mg, 50 mg, 75 mg**
Proposed Indication	(b) (4) (b) (4)
Proposed Dosing Regimen	**Initiate at 50 mg once daily for most pediatric patients 6 years and older with non-East Asian ancestry. 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

1.1. Recommendations

The Office of Clinical Pharmacology Division of Pharmacometrics and Clinical Pharmacology 5 have reviewed the information submitted in the NDA and recommended approval of Promacta® (eltrombopag) for the treatment of [redacted] (b) (4) patients 6 years and older with chronic immune (idiopathic) thrombocytopenia (ITP) to [redacted] (b) (4)
We agree to the starting dosing regimen and titration scheme proposed by the applicant.

Initial Dosing regimen

The recommended initial doses for pediatric patients 6 years and older with chronic immune (idiopathic) thrombocytopenia (ITP) are:

Population	Initial dose
Non-East Asian ancestry	50 mg
East Asian ancestry and/or mild to severe hepatic impairment	25 mg

Dose Adjustment

Each patient's dose needs to be adjusted (b) (4) in order to maintain platelet counts greater than or equal to 50 $\times 10^9$/L.

Labeling

Detailed labeling recommendations are provided in Section 3.

1.2. Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Eltrombopag olamine (in short, eltrombopag) is an orally bioavailable, small molecule, thrombopoietin receptor agonist. Eltrombopag has effects in inducing proliferation and differentiation of (b) (4) from bone marrow progenitor cells.

Eltrombopag is currently approved for the treatment of thrombocytopenia in adults with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The recommended starting doses of eltrombopag are 50 mg and 25 mg once daily for patients with non-East Asian ancestry and East Asian ancestry, respectively. For pediatric 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 $\times$ 10^9/L (50 Gi/L) and the daily cap is 75 mg. The approved dosage forms are 12.5, 25, 50, 75 and 100 mg tablets.

The current submission is for pediatric patients ≥6 years of age with chronic ITP. The efficacy and safety characteristics of eltrombopag in this patient population were evaluated in 2 pediatric trials (PETIT, PETIT2) along with younger pediatric patients 1 to 5 years of age.

Various initial doses were studied during Phase 2 and Phase 3 studies and proposed initial doses were determined based on PKPD modeling and simulation. The studied and proposed initial doses of eltrombopag in pediatric patients with ≥6 years of age are summarized in the table below.

	Study	Ancestry	Body Weight	12-17 years	6 – 11 years
Studied Dose	PETIT	Non East Asian	≥27 kg	37.5 mg	50 mg
			<27 kg		25 mg
		East Asian	≥27 kg	37.5 mg	25 mg
			<27 kg		12.5 mg
	PETIT 2	Non East Asian	≥27 kg	50 mg	50 mg
			<27 kg	37.5 mg	37.5 mg
		East Asian	≥27 kg	25 mg	25 mg
			<27 kg		
Proposed Dose		Non East Asian		50 mg	50 mg
		East Asian		25 mg	25 mg

1.3.1. Pharmacokinetics

Pharmacokinetics of eltrombopag in pediatric patients were characterized in two studies (PETIT and PETIT2) where younger age group of pediatric patients (1-5 years) were also enrolled along with the target age groups. The population PK analyses following eltrombopag dosing 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.

For a typical 70 kg, non-East/Southeast Asian male receiving the eltrombopag tablet formulation, estimated typical (95% CI) PK parameter values were: CL/F 0.612 L/hr, V2/F 2.74 L, Q/F 0.716 L/hr, V3/F 21.5 L, and ka 0.189 /hr.

Plasma eltrombopag CL/F (L/hr), Q (L/hr), V2/F (L), and V3/F (L) increased with increasing body weight. The estimated exponents for weight on clearance and volume parameters were close to allometric values.

Mean plasma eltrombopag CL/F was 30% lower in East/Southeast Asian subjects compared to other races and 20% lower in female subjects. These CL/F differences translate to mean AUC (0-tau) increases of 43% and 25% in Ease Asian and female subjects, respectively.

1.3.2. Pharmacodynamics

Platelet count response following eltrombopag dosing was described by the 7-compartment life-span model (3 PK compartments and 4 PD compartments), where the increase in platelet precursor production rate (KIN) was linearly related to eltrombopag concentration (SLOP). The majority of subjects (96%) were identified as responding to eltrombopag treatment. However, the definition of responders in the PD model is different from the definition of responders for the primary efficacy endpoint where responders were defined as subjects with ≥50 Gi/L and < 200 Gi/L. The typical estimate of SLOP was 0.651 mL/mcg in responders. KOUT (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 for subjects 6 to 17 years of age. No significant covariates were identified on SLOP.

1.3.3. PKPD Simulation for Justification of Initial Dosing Regimens

Since the proposed initial dosing regimen for pediatric patients with body weight <27 kg is different from the dosing regimen evaluated in the clinical trial, simulations were conducted by the applicant to predict platelet counts following various initial dosing regimens. Among those evaluated initial doses, 50 mg for patients with non-East Asian ancestry and 25 mg for patients with East Asian ancestry appear to be reasonable. As shown in Figure 1, the predicted median platelet counts following the proposed initial dosing regimens for 10 weeks without dose adjustment indicate that these dosing regimens could produce the platelet counts close to the target values of ≥50 Gi/L. Furthermore, this initial dosing scheme is also supported by the fact that majority of patients ended up escalating dose to above 50 mg daily dose (Table 7).

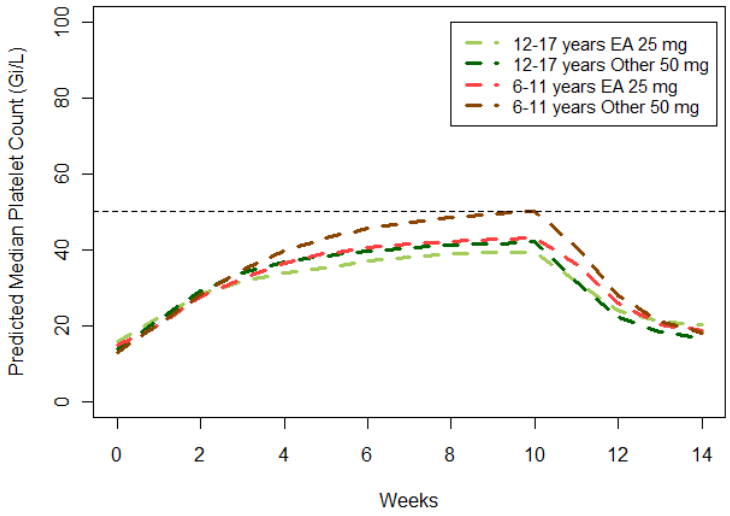


Figure 1. Predicted median platelet counts following the proposed initial dosing regimens for 10 weeks (profiles also show additional 4 weeks off-treatment). EA: Patients with East Asian ancestry; Others: others.
(Source: Reviewer's confirmatory analysis with the sponsor's PKPD model)

Moreover, simulation results with various dose titration schemes support the 2-week dose titration as an adequate titration interval (see Section 4.1.3.).

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, immulglubulins, 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 February 17, 2015, a supplement NDA (sNDA22291/S015) was submitted to extend the indication to adolescents and pediatric patients with 6 years of age or above. To support the proposed indication in the target population, the applicant submitted data from two clinical trials, PETIT and PEIT2, where pediatric patients younger (< 6 years of age) than the target age group were also enrolled as a cohort. The PKPD modeling and simulations were performed with data including this younger age group of patients.

2.1.2. What are the proposed indications?

The proposed indication is the treatment of previously-treated pediatric patients 1 year of age and older with chronic immune (idiopathic) thrombocytopenia (ITP) to increase platelet counts and reduce or prevent bleeding.

2.1.3. What are the proposed dosing regimens?

The proposed initial dose of eltrombopag is 50 mg for most of pediatric patients with 6 year of age and older. The initial dose for patients with East Asian ancestry or mild to severe hepatic impairment is proposed to be 25 mg. These proposed initial doses are the same for adult patients. Since the effect of hepatic impairment was evaluated in adult patients and can be extrapolated, it is not address under the current review.

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.

Subjects ≥6 years of age received tablets, and starting doses ranged from 25 to 50 mg once daily. East Asian subjects initiated eltrombopag at ~ 30 to 50% lower doses. 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).

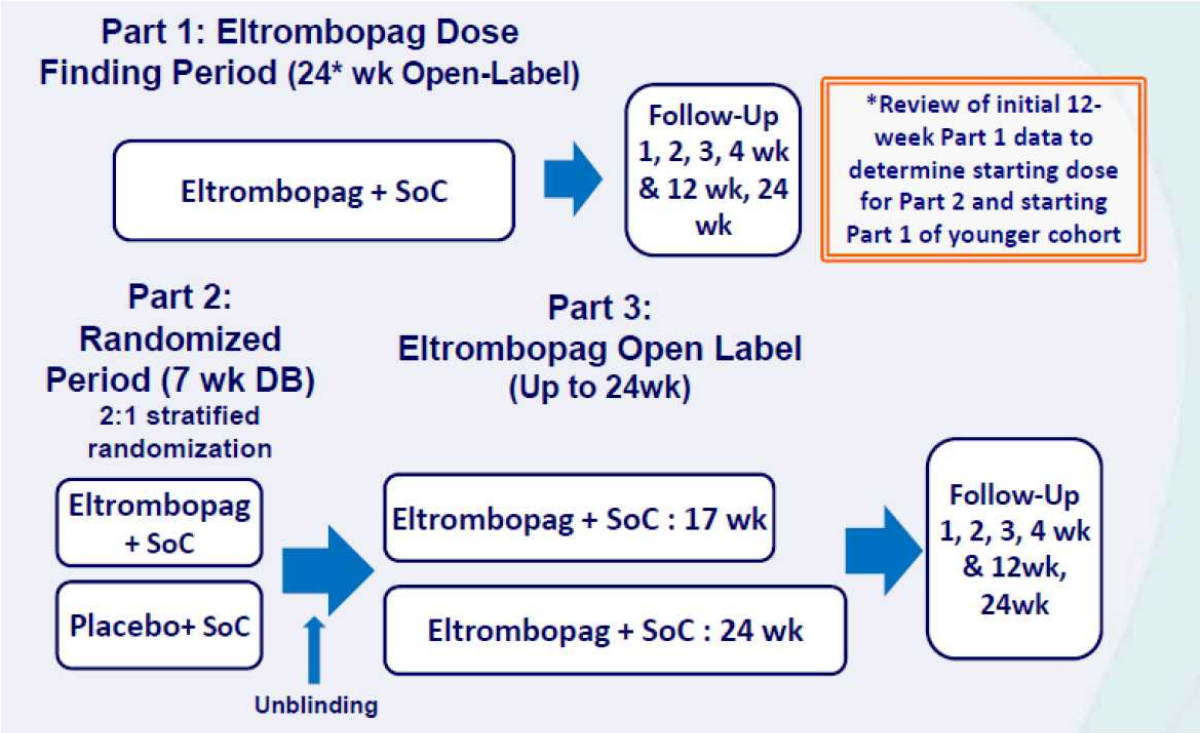


Figure 2. Schematic study design of PETIT
(Source: Sponsor's report, TRA108062, Figure 1, page 48)

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 1 and Table 2. 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 1.

Table 1. 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 2.

Table 2. 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).

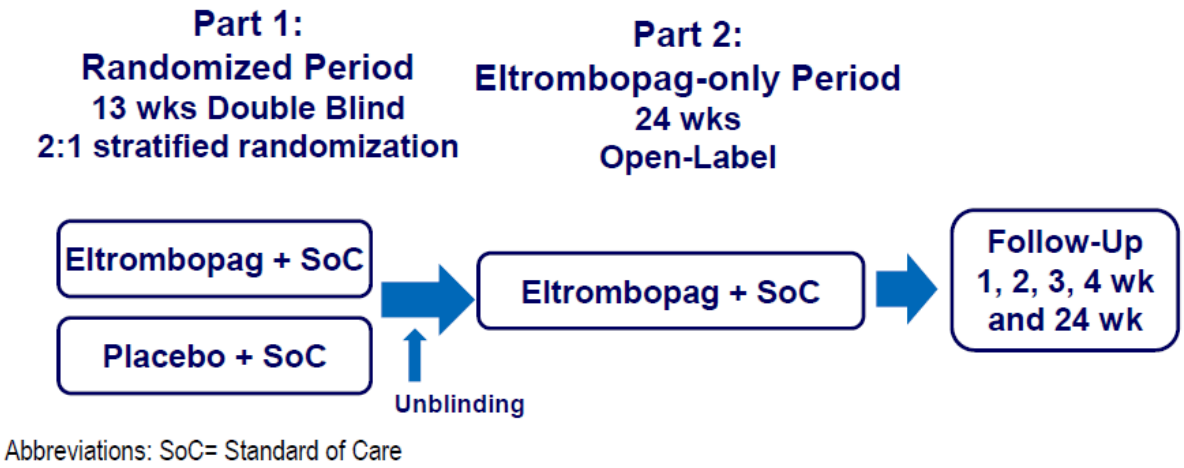


Figure 3. Schematic study design of PETIT2
(Source: Sponsor's report, TRA115450, Figure 1, page 32)

A total of 92 subjects were randomized in the PETIT2 study (72 subjects with 6-17 years of age). Sixty three subjects (49 subjects with 6-17 years of age) received eltrombopag and 29 subjects (23 subjects with 6-17 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 3.

Table 3. 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.

The primary efficacy outcomes indicated that that eltrombopag is effective in pediatric patients 6 -17 years with ITP compared to placebo. 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 support the efficacy 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 well-accepted 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 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 6 to 11 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 4. Despite having 50% higher AUC, children ages 6 to 11 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 4. 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] PK parameters were estimated based on a population PK analysis and normalized by 50 mg dose
(Source: Sponsor's analysis, provided in a revised proposed labeling dated May 21, 2015)

Furthermore, the response rates in pediatric patients 6 to 17 years old with ITP were lower than those observed in adults with ITP (Table 5). 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 5. Comparison of Efficacy in Pediatric and Adults Patients with ITP following Eltromobopag

Age Group	**Starting Dose**	**Response Rate in Eltrombopag Arm**	**Response Rate in Placebo Arm**
Adults (TRA100773A)[1]	50 mg	19/27 (70%)	3/27 (11%)
Adults (TRA100773B)[1]	50 mg	43/73 (59%)	6/37 (16%)
12-17 years (PETIT2)[2]	27 kg: 37.5 mg ≥27 kg: 50 mg	10/24 (42%)	1/10 (10%)
6-11 years (PETIT2)[2]	27 kg: 37.5 mg ≥27 kg: 50 mg	11/25 (44%)	0/13 (0%)

[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)
(Source: Sponsor's SCE, Table 1 on page 8 and Table 2 on page 10)

2.3.3. Is the proposed initial dose appropriate?

Yes. The proposed dosing regimens are only for the starting doses and then doses are titrated based on a platelet counts to target ≥50 Gi/L and <200 Gi/L. The predicted concentrations of eltrombopag in pediatric patients with 6 to 17 years of age are comparable following the proposed initial dosing regimens (Table 6). The concentration profiles in patients 6-11 years with non-East Asian ancestry show higher than those in other age groups (Figure 4). The upper bound of 95% CI (10.3 mcg/mL) is considered acceptable range, considering the fact that majority of subjects required increasing doses during the treatment (Table 7) and the majority of the higher than 50 mg as the final doses based on platelet counts. Substantial portion of the observed concentrations were found to be higher than this value.

Table 6. Summary of 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)
	12 – 17 years	51	50 mg QD	93.4 (83.7 – 104)	6.32 (5.78 – 6.91)
	6 – 11 years	53	50 mg QD	137 (122, 154)	9.39 (8.55 – 10.3)
East Asian	Adults	35	25 mg QD	67.2 (57.1 – 79.0)	4.15 (3.57 – 4.83)
	12 – 17 years	11	25 mg QD	79.1 (53.9 – 116)	4.80 (3.49 – 6.59)
	6 – 11 years	15	25 mg QD	111 (92.6 – 132)	7.10 (6.16 – 8.19)

(Source: Sponsor's PKPD report, page 15)

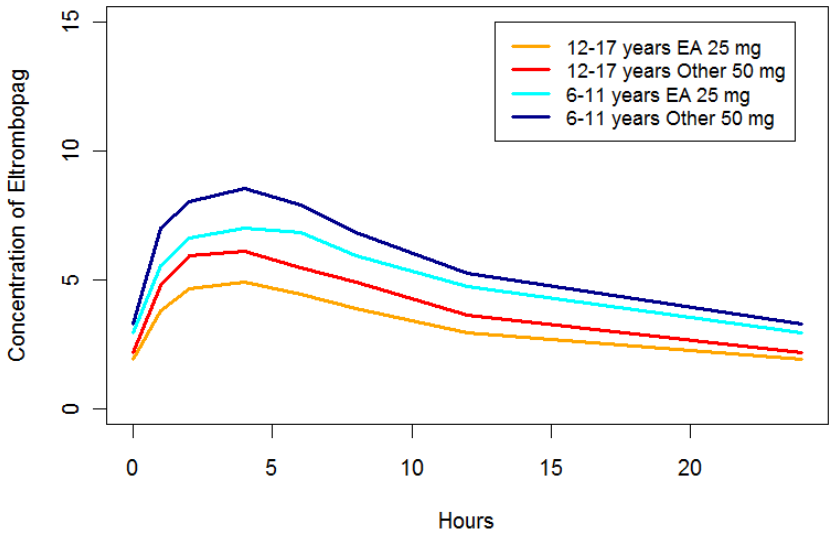


Figure 4. Predicted median eltrombopag concentration vs. time profiles following the proposed initial doses, EA: patients with East Asian ancestry; Others: others.
(Source: Reviewer's confirmatory analysis with sponsor's PKPD model)

Furthermore, the predicted platelet counts following the proposed initial doses for continuous 10 weeks (without dose adjustment) are close to the target platelet count of 50 Gi/L (Figure 4). Other regimens were also evaluated with similar simulation exercises (see Section 4), but the proposed starting doses appear to be adequate to bring platelet counts close to the target platelet count range. Pediatric patients with body weight <27 kg received 37.5 mg dose in PETIT2 study and the predicted platelet counts in pediatric patients <27 kg with non-East Asian ancestry appear to be lower than those in other age-weight-race groups following 25 mg initial dose (see Section 4.1.3). Thus weight-tiered dosing regimen does not appear to be necessary.

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 7, substantial portion of subjects (83% of patients 12-17 years old, 70% of patients 6-11 years old) enrolled in PETIT2 required 1 or 2 dose modifications, with the majority of the modifications being increases in dose. Furthermore, as shown in Table 8 and Figure 5, substantial portion of patients eventually increased to doses greater than 50 mg. Thus, the 50 mg dose as an initial dose for patients with non-East Asian ancestry and 25 for patients with East Asian ancestry appear to be reasonable.

Table 7. 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)

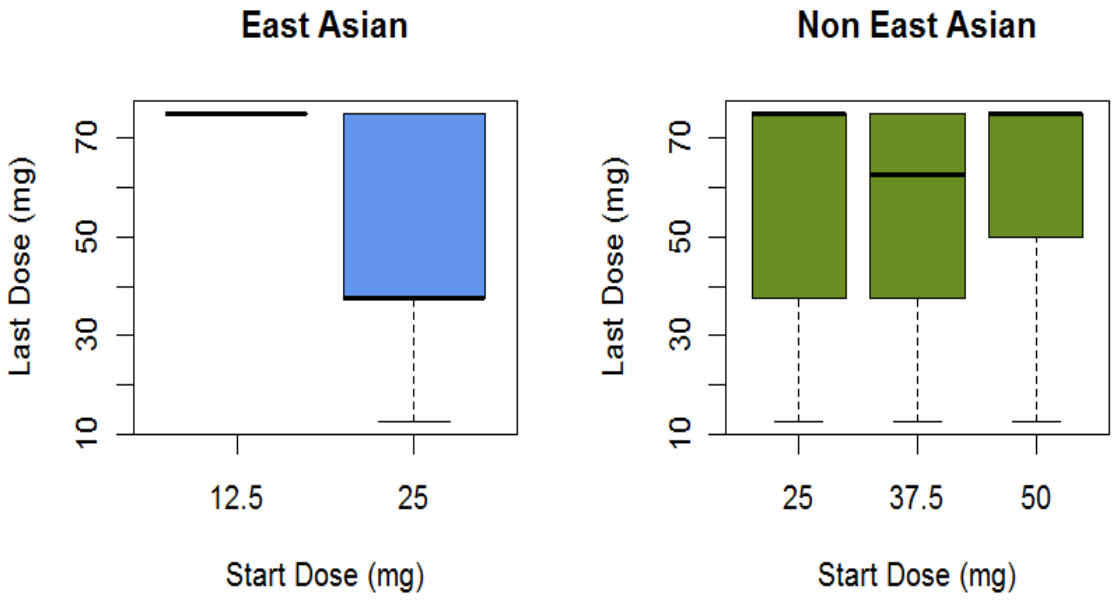


Figure 5. Distribution of Last dose by starting dose
(Source: Reviewer's analysis with PKPD data)

Table 8. Summary of Final Dosage Regimen

Race	Age	N	Baseline Weight (kg, Mean (SD))	Final dose (mg, Mean (SD))	Proportion of subjects on final dose ≥50 mg
Non East Asian	12 – 17 years	51	64.6 (18.5)	60.5 (19.9)	78%
	6 – 11 years	53	37.2 (11.6)	60.6 (18.9)	77%
East Asian	12 – 17 years	11	57.7 (18.8)	58.0 (21.1)	73%
	6 – 11 years	15	31.9 (10.1)	47.5 (23.2)	47%

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

2.4. Biopharmaceutics

2.4.1. Is extrapolation of the food effect with powder formulation for oral suspension (PfOS) to tablet formulation adequate?

No. The food effect evaluated with PfOS cannot be extrapolated to the food effect of tablet formulation which was reviewed in the original submission with adult data. Furthermore, the use of PfOS should be limited to the pediatric patients 1 to 5 years of age since the efficacy of the PfOS formulation was evaluated in these patients in PETIT and PETIT2 studies and the bioequivalence between the table formulation and the PfOS formulation is not established. The detailed information of the food effect of the PfOS and the adequacy of its use in other age groups (b) (4)

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.

Proposed labeling by the applicant and labeling recommendations by this reviewer	**Labeling recommendation rationale**

---------- DOSAGE AND ADMINISTRATION ---------- • Allow a 4 hour interval between (b) (4) PROMACTA and (b) (4) other medications, foods, or supplements containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc). (2.4)	*See Section 2.4.1*
----------DRUG INTERACTIONS ---------- • (b) (4) PROMACTA must not be taken within (b) (4) 4 hours of (b) (4) any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements (7.1)	*See Section 2.4.1*
2.4 Administration Allow at least a 4-hour interval between (b) (4) PROMACTA and (b) (4) other medications (e.g., antacids), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc [*see Drug Interactions (7.1)*]	*See Section 2.4.1*
7.1 Polyvalent Cations (Chelation) (b) (4) PROMACTA must not be taken within (b) (4) 4 hours of (b) (4) any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements to avoid significant reduction in absorption of PROMACTA due to chelation [*see Dosage and Administration (2.4)*]	*See Section 2.4.1*
12.3 Pharmacokinetics (b) (4)	*See Section 2.4.1*
12.3 Pharmacokinetics **Table 9.** Geometric Mean (95% CI) Steady-state Plasma Eltrombopag Pharmacokinetic Parameters in Pediatric Patients and Adults with ITP (50-mg Once-daily Dosing Regimen) **Age** / **C_{max}[b] (mcg/mL)** / **$AUC_{(0-\tau)}$[b] (mcg.h/mL)** 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) Adults / (Applicant add value) / (Applicant add value) [a] PK parameters presented as geometric mean (95% CI). [b] Based on population PK post-hoc estimates.	*Comparison with adults data is recommended*

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 9.

Table 9. 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 6). 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).

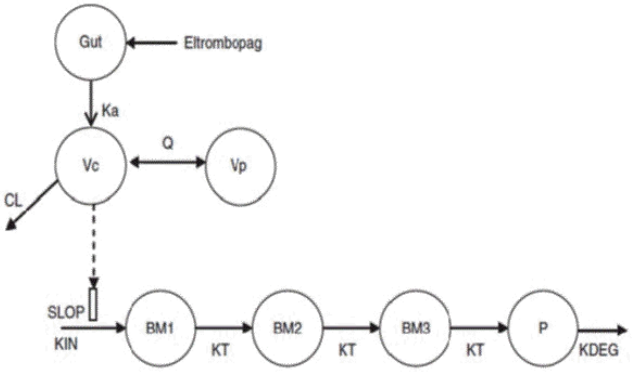


Figure 6. Schematic of the final eltrombopag PKPD model for patients with chronic ITP
CL: clearance; Ka: first-order absorption rate constant; Vc: Volume of central compartment; Q: intercompartmental clearance; Vp: Volume of peripheral compartment; KIN: zero-order production rate of platelet precursors; 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 (1.43 Gi/L/hr/14 Gi/L). Based on this KDEG, the median half-life was estimated to be approximately 7 hours.

The estimated PK parameters are summarized in Table 10 and the estimated PD parameters are summarized in Table 11.

Table 10. 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%)**		
$\omega^2_{IOV\text{-}CL/F}$	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 11. 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

Adolescents 12 to 17 years of age had similar plasma eltrombopag AUC(0-tau) and Cmax values as adults for the same dose of 50 mg. When normalized by a 50 mg dose, pediatric patients 1 to 11 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 7 and Figure 8, respectively.

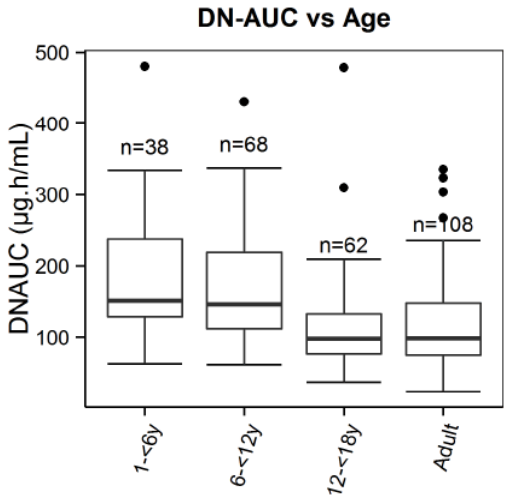


Figure 7. Plasma eltrombopag dose-normalized to 50 mg AUC(0-tau) by age
(Source: Sponsor's PKPD report, Figure 2, page 45)

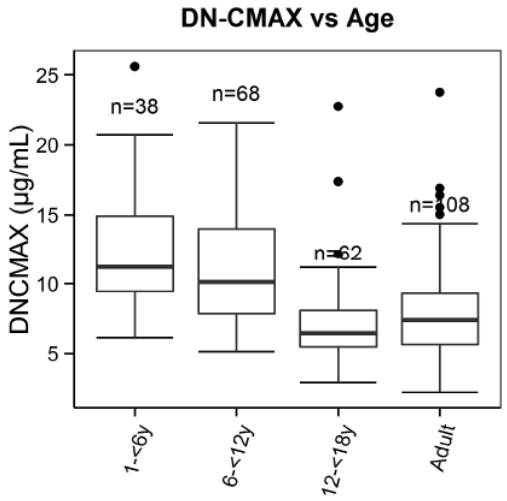


Figure 8. Plasma eltrombopag dose-normalized to 50 mg AUC(0-tau) by age
(Source: Sponsor's PKPD report, Figure 3, page 46)

The majority of subjects aged 6 to 17 years of age received eltrombopag doses ≥50 mg as their final dose. Geometric mean plasma eltrombopag AUC(0-tau) values at the final doses ranged from 104 to 188 mcg*hr/mL.

Table 12. Summary of Plasma Eltrombopag PK Parameters for Final Doses by Age and Race

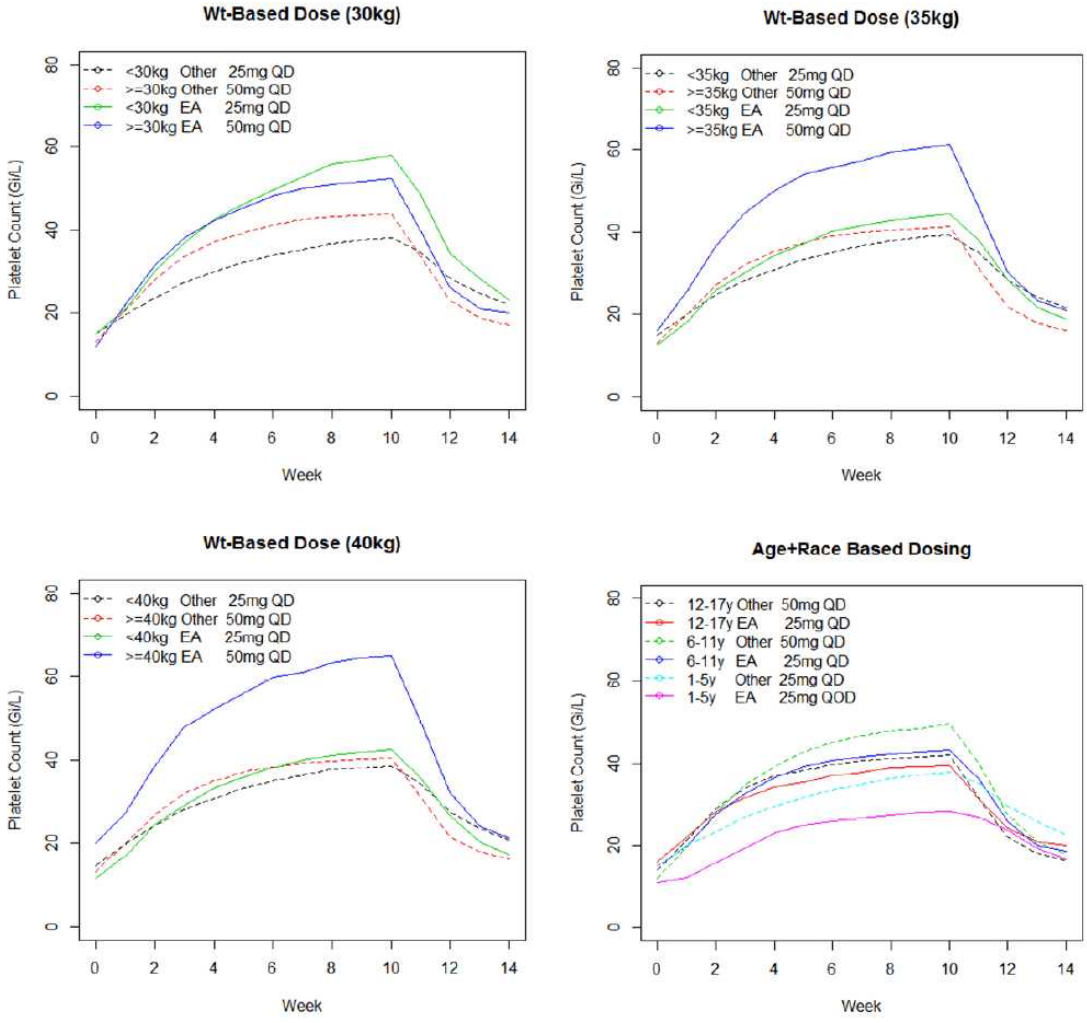
Covariate	N	Actual Age Enrolled (y)	Baseline Weight (kg)	Final Dose[a] (mg)	Proportion of Subjects on Final Dose >=50mg (%)	AUC(0-τ)[b] (µg.h/mL)	Cmax[b] (µg/mL)
Age + Race							
12-17 Years, EA	11	13.7 (1.6) [12.0-17.0]	57.7 (18.8) [30.0-82.1]	58.0 (21.1) [12.5-75.0]	73%	166 (93.9, 292)	10.0 (5.95, 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

Weight-based dosing

The sponsor performed simulations with different dosing regimens with various weight cutoffs: 30 kg, 35 kg, and 40 kg. As shown in Figure 9, 25 mg dose for the patients with non-East Asian ancestry below any weight cutoffs does not appear to produce adequately close platelet counts to the target values.



EA=East/Southeast Asian
In simulations, subjects received eltrombopag for 10 weeks. Platelet counts were predicted for an additional 4 weeks off-treatment

Figure 9. Predicted median platelet counts vs time for various starting doses
(Source: Sponsor's PKPD report, Figure 5, page 51)

Dose titration

Simulations support dose titration every two weeks because the proportion of subjects predicted to be at each dose level following dose titration is similar for dose titration at 2-, 3-, and 4-week intervals. The comparisons of dose titration on 2-, 3-, or 4-week intervals are shown in Table 13.

Table 13. Proportion of Subjects Predicted to Achieve Platelet Count Thresholds with Various Dose Titration on 2-, 3-, or 4-week intervals

Dose Titration Schedule	Age (yrs)/Race	Final Dose (mg)	Proportion of Subjects on Final Dose (%)	Proportion of Subjects Predicted to Achieve Platelet Count Threshold (%)			
				<50	50-200	>200	>400
50-25-12.5 mg 50-75 mg Q2W	6-17/Others	12.5	9	67	3	30	8
		25	10	81	6	13	<1
		50	15	81	11	8	<1
		75	66	34	65	1	<1
		Overall		49	46	6	1
50-25-12.5 mg 50-75 mg Q3W	6-17/Others	12.5	9	72	3	26	6
		25	11	83	7	10	1
		50	15	81	12	6	<1
		75	65	35	64	<1	<1
		Overall		50	45	5	1
50-25-12.5 mg 50-75 mg Q4W	6-17/Others	12.5	8	74	8	18	4
		25	11	81	10	10	1
		50	16	81	11	7	1
		75	65	35	64	1	0
		Overall		51	45	4	1

(Source: Sponsor's PKPD report, Table 18, page 53)

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 seem to be great enough to justify half dose of the approved adult dose. 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. This issue is currently under review for another submission (NDA2507027 for PfOS formulation in pediatrics patients with 1-5 years of age).

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 14.

Table 14. 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 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 but 50 mg dose in patients with East Asian ancestry seem to achieve above the target platelet counts while 50 mg dose in patients with non-East Asian ancestry seem to achieve close the target platelet counts. As shown in Figure 1, 25 mg dose in patients with East Asian ancestry seem to achieve similar platelet counts to those achieved by 50 mg dose in patients with non-East Asian ancestry.

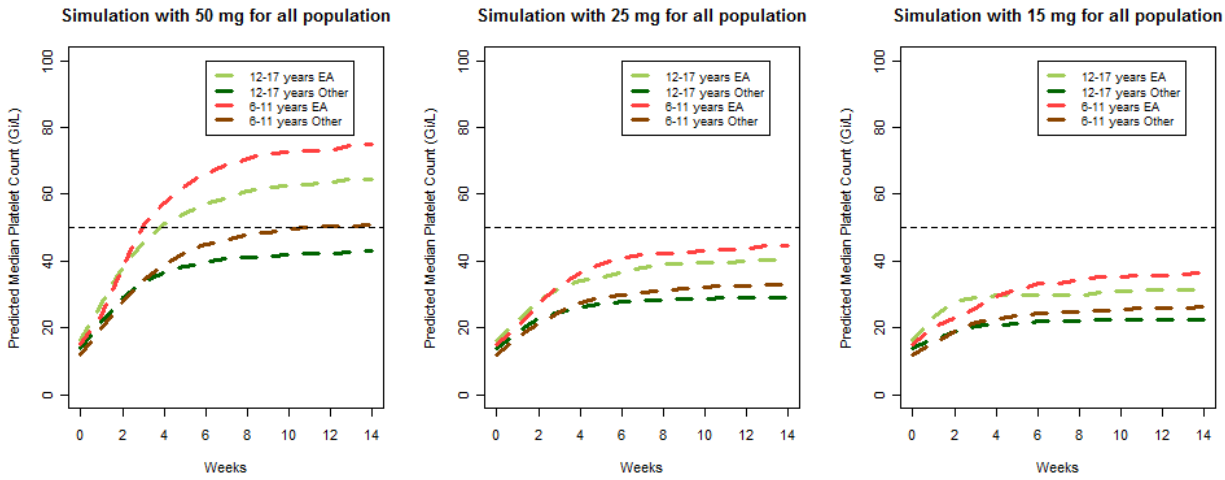


Figure 10. Predicted median platelet counts following 50 mg, 25 mg, and 15 mg for all subjects for 14 weeks

Furthermore, a lower dose of 25 mg for patients with non-East Asian ancestry who are weighing below body weight cutoffs of 30 kg, 35 kg, or 40 kg did not achieve platelet counts close to the target value as the sponsor's analysis showed in Figure 9. Thus the proposed initial dosing regimens appear to be reasonable with the condition of dose adjustment based on a platelet count.

5. LISTING OF ANALYSIS CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
NDA22291PKPD.R	PKPD modeling for efficacy	Reviews\Ongoing PM Reviews\Promacta_NDA22291_JEL

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

/s/

JEE E LEE
05/26/2015

BAHRU A HABTEMARIAM
05/26/2015

NITIN MEHROTRA
05/26/2015