U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number #:	NDA 022291 / 170
Supplement #:	015
Drug Name:	Promacta® (eltrombopag) tablets
Indication(s):	Treatment of thrombocytopenia in adult and pediatric patients 6 years and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy
Applicant:	GlaxoSmithKline LLC
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Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Chia-Wen Ko, Ph.D.
Concurring Reviewers:	Lei Nie, Ph.D., Team Leader
	Thomas Gwise, Ph.D., Deputy Division Director
Medical Division:	Division of Hematology Products
Clinical Team:	Lori Ehrlich, M.D. Ph.D.
	Virginia Kwitkowski, R.N., M.S.
Project Manager:	Mara Miller

Keywords: pediatric ITP, platelet response, double-blind placebo-controlled randomization

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1 EXECUTIVE SUMMARY

Eltrombopag tablet formulation was approved by the Agency in 2008 for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. This application is seeking to expand the indication of eltrombopag tablet formula to include pediatric patients 6 years and older.

Clinical evidence supporting this application came from Study TRA108062 (the PETIT study) and Study TRA115450 (the PETIT2 study), both were randomized double-blind placebo-controlled trials in pediatric patients aged 1-17 years old with chronic ITP. Both studies had a double-blind randomized period with eltrombopag against placebo, and an open-label eltrombopag only period. The maximum duration of eltrombopag treatment was 24 weeks in either study; however, the duration of randomized period was 7 weeks in the PETIT study versus 13 weeks in the PETIT2 study. The primary efficacy endpoint for the PETIT study was platelet response rate, defined as proportion of patients that had achieved platelet counts ≥50 Giga/Litter (Gi/L) in absence of a rescue treatment during the first 6 weeks of the randomized period. The primary efficacy endpoint for the PETIT2 study was sustained response rate, defined as proportion of patients that had achieved a platelet response (platelet counts ≥50 Gi/L in absence of a rescue treatment) at least 6 out of 8 weeks between Weks 5 to 12 of the randomized period.

Results from the PETIT and PETIT2 studies demonstrated treatment efficacy of eltrombopag in the studied pediatric population. Both studies observed a statistically significant difference between eltrombopag and placebo in their primary endpoint. In either study, the platelet response rate and sustained response rate were at least 30% higher in the eltrombopag group compared to the placebo group. The median duration for a continuous response was longer in the eltrombopag group compared to the placebo group. In addition, both studies reported benefits from eltrombopag treatment in use of rescue treatment and incidence of bleeding without causing additional safety concerns. Results were consistent across subgroups.

One review issue was handling of missing data in analyses. Because the data completion rate was high for the primary endpoint (93% and 92% in the PETIT study and the PETIT2 study, respectively), the issue of missing data did not have a major impact on the reliability and confidence of the primary endpoint results.

Data from the PETIT and PETIT2 studies demonstrated treatment efficacy of eltrombopag as a treatment in pediatric patients with chronic ITP. Approval is recommended to expand the eltrombopag indication from adults only to include pediatric patients.

2 INTRODUCTION

2.1 Overview

Product and Proposed Indication

PROMACTA® (eltrombopag) is a small-molecule Thrombopoietin (TPO)-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells. Eltrombopag tablet formulation was approved by the Agency in 2008 for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Based on clinical data from two studies in children aged 1 to 17 years with chronic ITP, this application is seeking to expand the indication to become the following:
"PROMACTA is indicated for the treatment of thrombocytopenia in adult and pediatric patients 6 years and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy."

Clinical data from children aged 1 to 5 years are also included in this application; however, because those younger children received a (b) (4) rather than the tablet formulation, (b) (4)

Disease Overview

ITP is a disease characterized by an isolated low platelet count and the absence of underlying causes of thrombocytopenia. Approximately 15% to 30% of children with acute ITP become chronic. Disease management in patients with chronic ITP is based primarily on platelet count and severity or risk of bleeding. Currently, there is no single treatment or standard of care that is universally recognized as a treatment of chronic ITP in children.

Clinical Studies

Table 1 summarizes the Applicant's clinical studies in pediatric patients with chronic ITP. Study TRA108062 (the PETIT study) is considered a Phase 2 study, for including a dose-finding phase. Study TRA115450 (the PETIT2 study) is a Phase 3 study, that had a longer randomized period compared to the PETIT study for treatment efficacy evaluation versus placebo. In addition, PETIT2 was different from the PETIT study in the primary efficacy endpoint and the starting dose at randomization.

This review will evaluate data from both PETIT and PETIT2 studies. However, because the two studies were different in: duration for the randomized period, main eligibility criteria, starting dose at randomization (as highlighted in the Table 1), the efficacy evaluation in this review will be presented by individual studies and will not be based on any data combination from the studies.

Table 1: Overview of Applicant's Clinical Studies in Pediatric Patients with Chronic ITP

Study	TRA108062 (PETIT)	TRA115450 (PETIT2)
No. of patients	82 (including 15 patients for dose finding only)	92
Study location	22 centers in 6 countries (United States, UK, Canada, Spain, France, Netherlands)	52 centers in 12 countries (United States, European and Asian countries)
Phase of study	II	III
Study population	Pediatric patients with chronic ITP	Pediatric patients with chronic ITP
Study design	• Part 1: dose finding phase • Part 2: double-blind, placebo-controlled, **7-week treatment randomization** • Part 3: open-label eltrombopag only	• Part 1: double-blind, placebo-controlled, **13-week treatment randomization** • Part 2: open-label eltrombopag only
Main eligibility criteria	• 1 to 17 years of age at Day 1 • Confirmed diagnosis of chronic ITP • R/R after ≥1 prior ITP therapy • Platelet count <30 Gi/L on Day 1	• 1 to 17 years of age at Day 1 • Confirmed diagnosis of chronic ITP **for at least 1 year** • R/R after ≥1 prior ITP therapy • Platelet count <30 Gi/L on Day 1
Eltrombopag dose at randomization	Once daily • **Cohort 1 (12-17 years): 37.5 mg** • **Cohort 2 (6-11 years): 25 mg if <27 kg, or 50 mg if ≥27 kg** • **Cohort 3 (1-5 years): 1.5 mg/kg**	Once daily • **Cohort 1 and Cohort 2 (6-17 years): 37.5 mg if <27 kg, or 50 mg if ≥27 kg** • **Cohort 3 (1-5 years): 1.2 mg/kg**
Duration of treatment	Up to 24 weeks	Up to 24 weeks
Randomization	2 : 1 to eltrombopag : placebo Stratified by age cohort	2 : 1 to eltrombopag : placebo Stratified by age cohort
Primary efficacy endpoint	Any platelet response (platelet counts ≥50 Gi/L in absence of rescue) between Weeks 1 and 6 of the Randomized Period	Sustained platelet response (achieving a response at least 6 out of 8 weeks) between Weeks 5 to 12 of the Randomized Period
Secondary endpoints	Sustained platelet response; Continuous response; Rescue treatment; Bleeding events	Any platelet response; Continuous response; Rescue treatment; Reduction in bleeding

ITP = idiopathic thrombocytopenic; R/R = relapsed/refractory; UK = United Kingdom
PETIT = Eltrombopag in PEdiatric patients with Thrombocytopenia from ITP

Regulatory Interactions

Important interactions with the Applicant during protocol development are listed below:

- The PETIT studies were conducted in response to a Written Request for Pediatric studies; PETIT was conducted to satisfy the "*Study 1: PK/PD and Safety study*" and PETIT2 was conducted to satisfy the "*Study 2: Efficacy, PK, and Safety study*" requirements, of the Amended Written Request dated November 2011.
- PETIT2 study primary endpoint was changed from achievement of any platelet response to achievement of a sustained response in Protocol Amendment #1 dated December 2011, following Agency's feedback that sustainability of response may be more clinically meaningful. Achievement of any platelet response then became a secondary endpoint.

2.2 Data Sources

Material reviewed for this application: protocols, statistical analysis plans, study reports, and submitted datasets for the PETIT and PETIT2 studies.

Reviewed data were provided electronically with the standard analysis data formats.

PETIT study datasets are located at:
\\CDSESUB1\evsprod\NDA022291\0170\m5\datasets\tra108062.

PETIT2 study datasets are located at:
\\CDSESUB1\evsprod\NDA022291\0170\m5\datasets\tra115450.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from the PETIT and PETIT2 studies were provided electronically with standard formats. Documentations on datasets and programming were included with sufficient details for verification of key study results. However, a 16-year patient in the PETIT2 study was mistakenly grouped into the 6-11 years age cohort. *This review will present corrected results with this patient in the 12-17 years age cohort.*

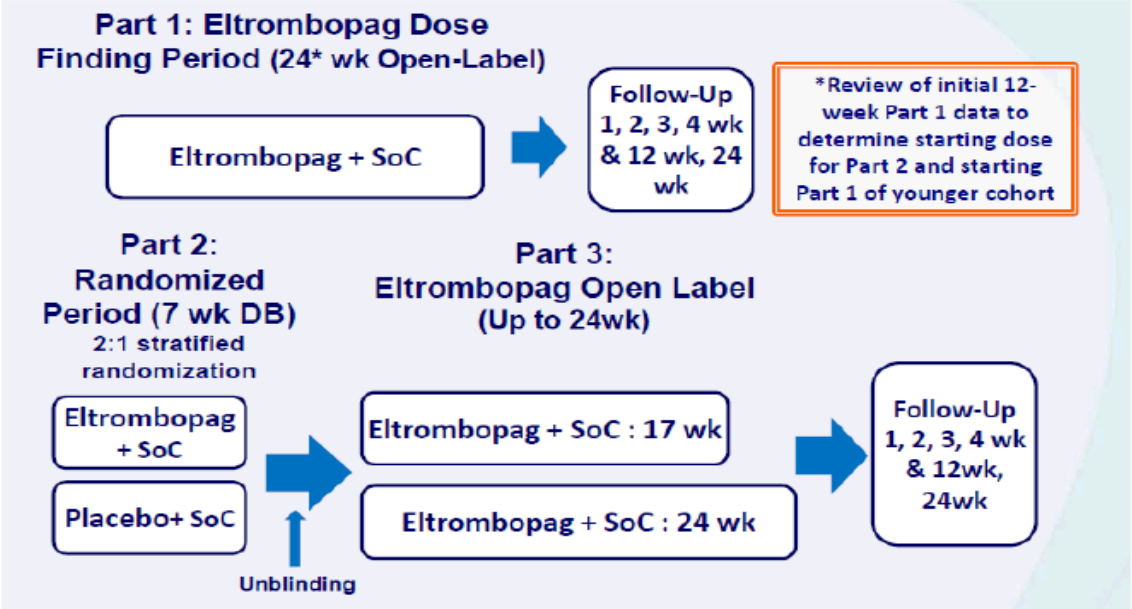
3.2 Evaluation of Efficacy

This session shows the key efficacy results from the PETIT and PETIT2 studies, with Reviewer's comments and evaluations. Due to differences between the studies in duration of randomized treatment period and starting dose, this review will not present pooled data from the 2 studies for efficacy evaluation.

3.2.1 Study Design and Endpoints

This application is supported by the PETIT and PETIT2 studies in pediatric patients with chronic ITP. Figure 1 and Figure 2 show the study design schema for PETIT and PETIT2 studies, respectively. PETIT was a Phase II study with a dose-finding phase; while PETIT2 was a Phase III study. Both studies had a double-blind randomized period with eltrombopag against placebo, an open-label eltrombopag only period, and a follow-up period. The maximum duration of eltrombopag treatment was 24 weeks in either study; however, the duration of randomized period was 13 weeks in the PETIT2 study versus 7 weeks in the PETIT study.

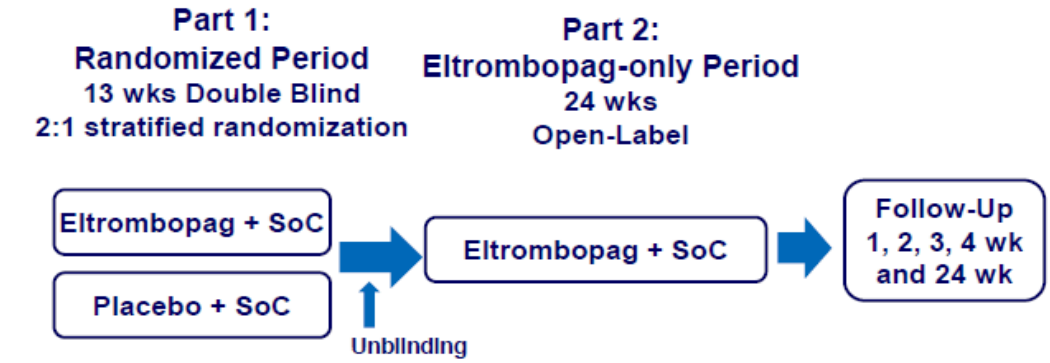
Figure 1: PETIT Study Design Schema



SoC= Standard of Care

Source: PETIT study report Figure 1

Figure 2: PETIT2 Study Design Schema



Abbreviations: SoC= Standard of Care

Source: PETIT2 study report Figure 1

3.2.2 Statistical Methodologies

The determination of treatment efficacy for eltrombopag was based on comparisons between eltrombopag and placebo. For both studies, randomization for the randomized period was conducted at 2:1 ratio to eltrombopag: placebo plus standard of care, and stratified by age cohorts (12-17 years, 6-11 years, and 1-5 years at randomization). All randomized patients, the Double Blind ITT population, were used for assessing efficacy.

The primary efficacy endpoint for the PETIT study was proportion of patients that had at least one platelet response, defined as achieving platelet counts ≥50 Gi/L in absence of a rescue treatment, during the first 6 weeks of the randomized period. The primary efficacy endpoint for the PETIT2 study was proportion of patients that had achieved a platelet response at least 6 out of 8 weeks between Weeks 5 to 12 of the randomized period. For both studies, the secondary endpoints included the maximum duration for a continuous response, the use of rescue treatment, and the reduction in incidence of bleeding.

Both the PETIT and PETIT2 studies had study sample size determined to test efficacy in the primary endpoint with 90% power and at 2-sided 5% level of statistical significance. The PETIT study planned to randomize at least 33 evaluable patients in order to test 70% versus 20% for eltrombopag versus placebo in achieving a platelet response; while the PETIT2 study planned to randomize at least 66 evaluable patients in order to test 50% versus 10% for eltrombopag versus placebo in achieving a sustained response. Taking into account a 30% missing data and dropouts and dose finding evaluations, the PETIT study planned to enroll 70 patients, with 15 patients (5 patients per age cohort) for the dose finding period, and 54 patients for the randomized period. For the PETIT2 study, to allow 10% for the missing data and dropouts, a total sample size of 75 patients (50 on eltrombopag, 25 on placebo) was planned.

The protocol-specified primary analysis method for a comparison between eltrombopag and placebo in a platelet response rate endpoint was a logistic regression model adjusting for age cohorts, with the exception that a Cochran-Mantel-Haenszel (CMH) test adjusting for the age cohorts was used as the primary analysis for the primary endpoint of the PETIT2 study.

For both PETIT and PETIT2 studies, the primary endpoint was tested at 2-sided 5% significance level, with no multiplicity adjustment for the secondary endpoints.

Reviewer Comments:

- *The number of patients in the PETIT studies appears to be reasonable, considering the rarity of the disease in children.*
- *Both PETIT and PETIT2 studies were prospectively designed to detect a clinically meaningful difference between eltrombopag and placebo with respect to study primary efficacy endpoint. Therefore, results from both studies may be used for labeling.*
- *CMH test was recommended by the Agency for analyzing a sparse binary outcome such as achievement of a sustained response within age cohorts in the PETIT2 study.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The PETIT study was completed on 03-Feb-2014. Fifteen subjects were enrolled in the Dose Finding Period, 5 subjects per age cohort. Those subjects did not participate in the Randomized Period, and therefore will not be part of the efficacy evaluation in this review.

Table 2 and Table 3 summarize the subject disposition and baseline characteristics, respectively, for Double Blind ITT population in the PETIT study. The study randomized 67 subjects; 63

subjects (94%) completed the randomized treatment, and 57 subjects (85%) completed the 24 weeks of total eltrombopag treatment plus additional 24 weeks of follow-up. Demographic and baseline factors were similar between the eltrombopag and placebo treatment groups.

Table 2: Disposition of Randomized Patients in the PETIT Study

Total number of subjects	**Eltrombopag N = 45**	**Placebo N = 22**	**Total N = 67**
Completed randomized treatment	**42**	**21**	**63**
Did not receive allocated treatment[1]	2	1	3
Did not complete treatment	1	0	1
Continued to the Eltrombopag Only Period	**42**	**22**	**64**
Completed treatment			**57**
Discontinued eltrombopag			7
Adverse event			2
Lack of efficacy			2
Withdrawn by parent/guardian			1
Lost to follow up			2
Completed the Follow-up Period			**57**

[1] Two subjects in the eltrombopag group did not receive any study medication, and one subject in the placebo group received eltrombopag instead

Table 3: Demographics and Other Baseline Factors for Randomized Patients in the PETIT Study

Factor	**Eltrombopag N = 45**	**Placebo N = 22**	**Total N = 67**
Age (years)			
1-5 / 6-11 / 12-17	10 / 19 / 16 (22 / 42 / 36 %)	5 / 9 / 8 (23 / 41 / 36 %)	15 / 28 / 24 (22 / 42 / 36 %)
mean (SD), median, min-max	9.1 (4.3), 9, 1─17	9.6 (4.7), 10, 2─17	9.3 (4.4), 10, 1─17
Sex			
Female / Male	27 / 18 (60 / 40 %)	13 / 9 (59 / 41 %)	40 / 27 (60 / 40 %)
Race			
White / South-East Asian / Other	40 / 2 / 3 (89 / 4 / 7 %)	20 / 2 / 0 (91 / 9 / 0 %)	60 / 4 / 3 (90 / 6 / 4 %)
Region			
Europe / United States / Canada	16 / 24 / 5 (36 / 53 / 11 %)	7 / 14 / 1 (32 / 64 / 5 %)	23 / 38 / 6 (34 / 57 / 9 %)
ITP medication use			
Yes / No	5 / 40 (11 / 89 %)	2 / 20 (9 / 91 %)	7 / 60 (10 / 90 %)
Platelet count per litter			
≤15Gi / >15Gi / Missing	23 / 20 / 2 (51 / 44 / 4 %)	11 / 10 / 1 (50 / 45 / 5 %)	34 / 30 / 3 (51 / 45 / 4 %)
Splenectomy status			
Yes / No	5 / 40 (11 / 89 %)	0 / 22 (0 / 100 %)	5 / 62 (7 / 93 %)
Time since ITP diagnosis			
<12 months / ≥12 months	8 / 37 (18 / 82 %)	2 / 20 (9 / 91 %)	10 / 57 (15 / 85 %)

ITP = Idiopathic thrombocytopenia

The PETIT2 study was completed on 02-Jan-2014. Table 4 and Table 5 summarize the subject disposition and baseline characteristics, respectively, for ITT population in the PETIT2 study. The study randomized 92 subjects; 89 (97%) completed the randomized treatment, 80 (87%) completed the 24 weeks of total eltrombopag treatment, and 77 (84%) completed additional 24 weeks of follow-up. Demographic and baseline factors were similar between the eltrombopag and placebo treatment groups, except that the ITP medication was used at baseline in 21% of subjects in the eltrombopag group versus 3% of subjects in the placebo group.

Table 4: Disposition of Randomized Patients in the PETIT2 Study

Total number of subjects	**Eltrombopag N = 63**	**Placebo N = 29**	**Total N = 92**
Completed randomized treatment	**61**	**28**	**89**
Did not receive allocated treatment	0	0	0
Did not complete randomized treatment	2	1	3
Continued to the Eltrombopag Only Period	**59**	**28**	**87**
Completed eltrombopag treatment			**80**
Discontinued eltrombopag			7
Adverse event			4
Lack of efficacy			2
Withdrawn by parent/guardian			1
Lost to follow up			0
Completed the Follow-up Period			**77**

[1] Two subjects in the eltrombopag group did not receive any study medication, and one subject in the placebo group received eltrombopag instead

Table 5: Demographics and Other Baseline Factors for Randomized Patients in the PETIT2 Study

Factor	**Eltrombopag N = 63**	**Placebo N = 29**	**Total N = 92**
Age (years)			
1-5 / 6-11 / 12-17	14 / 26 / 23 (22 / 41 / 37 %)	6 / 13 / 10 (21 / 45 / 34 %)	20 / 39 / 33 (22 / 42 / 36 %)
mean (SD), median, min-max	9.4 (4.4), 9, 1─17	9.8 (4.0), 9, 4─17	9.5 (4.3), 9, 1─17
Sex			
Female / Male	30 / 33 (48 / 52 %)	14 / 15 (48 / 52 %)	44 / 48 (48 / 52 %)
Race			
White / South-East Asian / Other	41 / 20 / 2 (65 / 32 / 3 %)	19 / 10 / 0 (66 / 34 / 0 %)	60 / 30 / 2 (65 / 33 / 2 %)
Region			
Europe / Asia / US / Argentina	31 / 26 / 3 / 3 (49 / 41 / 5 / 5 %)	16 / 11 / 1 / 1 (55 / 38 / 3 / 3 %)	47 / 37 / 4 / 4 (51 / 40 / 4 / 4 %)
ITP medication use			
Yes / No	13 / 50 (21 / 79 %)	1 / 28 (3 / 97 %)	14 / 78 (15 / 85 %)
Platelet count per litter			
≤15Gi / >15Gi / Missing	38 / 24 / 1 (60 / 38 / 2 %)	19 / 10 / 0 (66 / 34 / 0 %)	57 / 34 / 1 (62 / 37 / 1 %)
Splenectomy status			
Yes / No	4 / 59 (6 / 94 %)	0 / 29 (0 / 100 %)	4 / 88 (4 / 96 %)

ITP = Idiopathic thrombocytopenia

3.2.4 Efficacy Results

3.2.4.1 Platelet Count Endpoints

Table 6 shows the results on platelet count endpoints from the randomized period. The numbers highlighted are the primary endpoint results. Both the PETIT and the PETIT2 studies demonstrated a statistically significant difference between eltrombopag and placebo in the primary endpoint. In either study, the platelet response rate and sustained response rate were at least 30% higher in the eltrombopag group compared to the placebo group. The median duration for a continuous response was longer in the eltrombopag group compared to the placebo group.

Table 6: Results of the Randomized-Period Platelet Count Endpoints

Endpoint	PETIT study		PETIT2 study	
	Eltrombopag n = 45	Placebo n = 22	Eltrombopag n = 63	Placebo n = 29
Sustained response	16 (35.6%)	0 (0.0%)	**25 (39.7%)**	**1 (3.4%)**
	Δ = 35.6%		**Δ = 36.3%**	
	p-value* = 0.0020		**p-value < 0.001**	
Any response	**28 (62.2%)**	**7 (31.8%)**	47 (74.6%)	6 (20.7%)
	Δ = 30.4%		Δ = 53.9%	
	p-value = 0.011		p-value* < 0.001	
Median (range) maximum continuous response duration	1 (0-6) week	0 (0-2) week	3 (0-12) weeks	0 (0-8) week

Sustained response in PETIT study = having ≥ 60% of positive response assessments between Weeks 2 to 6
Sustained response in PETIT2 study = having ≥ 75% of positive response assessments between Weeks 5 to 12
* Nominal p-value, without adjusting for multiplicity

Table 7 and Table 8 give the results on platelet count endpoints from the randomized period by age cohort for the PETIT study and the PETIT2 study, respectively. These results by age cohorts were consistent with the overall results. The only exception was in the PETIT study cohort 3, which had a 60% response rate in the eltrombopag group, but 80% in the placebo group. However, the actual number of patients achieved a response was comparable between the two groups, and some of those responders on the eltrombopag group had a long duration for a continuous response.

Table 7: Results of Platelet Count Endpoints by Age Cohorts – PETIT Study

Endpoint	Cohort 1 (12-17 years)		Cohort 2 (6-11 years)		Cohort 3 (1-5 years)	
	Eltrombopag n = 16	Placebo n = 8	Eltrombopag n = 19	Placebo n = 9	Eltrombopag n = 10	Placebo n = 5
Sustained response	6 (37.5%)	0 (0.0%)	7 (36.8%)	0 (0.0%)	3 (30.0%)	0 (0.0%)
Any response	10 (62.5%)	0 (0.0%)	12 (63.2%)	3 (33.3%)	6 (60.0%)	4 (80.0%)
Median (range) maximum continuous response duration	1 (0-5) week	0 (0-0) week	2 (0-6) weeks	0 (0-2) week	1 (0-6) week	1 (0-2) Week

Table 8: Results of Platelet Count Endpoints by Age Cohorts – PETIT2 Study

Endpoint	Cohort 1 (12-17 years)		Cohort 2 (6-11 years)		Cohort 3 (1-5 years)	
	Eltrombopag n = 24	Placebo n = 10	Eltrombopag n = 25	Placebo n = 13	Eltrombopag n = 14	Placebo n = 6
Sustained response	10 (41.7%)	1 (10.0%)	10 (40.0%)	0 (0.0%)	5 (35.7%)	0 (0.0%)
Any response	19 (79.2%)	3 (30.0%)	18 (72.0%)	3 (23.1%)	10 (71.4%)	0 (0.0%)
Median (range) maximum continuous response duration	2.5 (0-10) Week	0 (0-8) week	3 (0-11) weeks	0 (0-1) week	1.5 (0-12) weeks	0 (0-0) Week

3.2.4.2 Rescue Treatment

Per protocol, rescue treatment during the randomized-period included any new ITP medication, increased dose pf a concomitant ITP medication, platelet transfusion, and/or splenectomy. Both studies reported a lower percentage of patients in the eltrombopag group had to initiate a rescue treatment in comparison with the placebo group. For the PETIT study, the percentage for eltrombopag versus placebo was 13% versus 50% in the Double-Blind ITT population, 12% versus 75% in the 12-17 years age cohort, 16% versus 44% in the 6-11 years age cohort, and 10% versus 20% in the 1-5 years age cohort. For the PETIT2 study, the percentage for eltrombopag versus placebo was 19% versus 24% in the Double-Blind ITT population, 13% versus 20% in the 12-17 years age cohort, 23% versus 23% in the 6-11 years age cohort, and 21% versus 33% in the 1-5 years age cohort.

Reviewer Comment:

- *The PETIT studies did not have multiplicity adjustment for secondary endpoints. No labeling claims should be made for any secondary endpoints from the studies.*

3.2.4.3 Incidence of Bleeding

For the impact of eltrombopag on bleeding, both studies reported that the eltrombopag had a greater reduction since baseline in the proportion of patients that had a clinically significant bleeding (WHO Bleeding Scale Grades 2-4). The PETIT study reported the incidence of clinically significant bleeding decreased from 20% to 2% in the eltrombopag group versus from 27% to 18% in the placebo group. The PETIT2 study reported the incidence of clinically significant bleeding decreased from 25% to 5% in the eltrombopag group versus from 21% to 7% in the placebo group.

Reviewer Comment:

- *The PETIT studies did not have multiplicity adjustment for secondary endpoints. No labeling claims should be made for any secondary endpoints from the studies.*

3.2.4.4 Primary Efficacy Endpoint by Subgroups

Table 9 and Table 10 display the primary endpoint result by subgroups for the PETIT and the PETIT2 study, respectively. These subgroup results were supportive of the overall results. The only exception was in the PETIT study age 1-5 years old cohort, which had a 60% response rate in the eltrombopag group, but 80% in the placebo group. However, the actual number of patients achieved a response was comparable between the eltrombopag and placebo groups, and some of those responders on the eltrombopag group had the maximum 6 weeks for a continuous response (Table 7), suggesting treatment benefit from eltrombopag was also present for this subgroup.

Table 9 : Primary Endpoint by Subgroups – PETIT Study

Factor	Subgroup	Any platelet Response			
		Eltrombopag		Placebo	
		No. responders/total	%	No. responders/total	%
Age (years)	12 to 17	10/16	62.5	0/8	0.0
	6 to 11	12/19	63.2	3/9	33.3
	1 to 5	6/10	60.0	4/5	80.0
Sex	Female	17/27	63.0	4/13	30.8
	Male	11/18	61.1	3/9	33.3
Race	White	25/40	62.5	7/20	35.0
	Other	3/5	60.0	0/2	0.0
Region	US/Canada	16/29	55.2	5/15	33.3
	Europe	12/16	75.0	2/7	28.6
Baseline ITP medication	Yes	5/5	100.0	2/2	100.0
	No	23/40	57.5	5/20	25.0
Baseline platelet count	≤ 15 Gi/L	13/23	56.5	2/11	18.2
	> 15 Gi/L	15/20	75.0	5/10	50.0
Baseline splenectomy	Yes	4/5	80.0	0/0	-
	No	24/40	60.0	7/22	31.8

Any platelet response = having at least one positive response assessment during the 6-week randomized period; ITP = immune idiopathic thrombocytopenia; CI = confidence interval; Gi/L = giga per litter; US = United States

Table 10 : Primary Endpoint by Subgroups – PETIT2 Study

Factor	Subgroup	Sustained platelet Response			
		Eltrombopag		Placebo	
		No. responders/total	%	No. responders/total	%
Age (years)	12 to 17	10/24	41.7	1/10	10.0
	6 to 11	11/25	44.0	0/13	0.0
	1 to 5	5/14	35.7	0/6	0.0
Sex	Female	15/30	50.0	0/14	0.0
	Male	11/33	33.3	1/15	6.7
Race	White	18/41	43.9	1/19	5.3
	Other	8/22	36.4	0/10	0.0
Region	Americas	3/6	50.0	0/2	0.0
	Europe	13/31	41.9	1/16	6.3
	Asia	10/26	38.5	0/11	0.0
Baseline ITP medication	Yes	6/13	46.2	0/1	0.0
	No	20/50	40.0	1/28	3.6

Factor	Subgroup	Sustained platelet Response			
		Eltrombopag		Placebo	
		No. responders/total	%	No. responders/total	%
Baseline platelet count	≤ 15 Gi/L	11/38	29.0	0/19	0.0
	> 15 Gi/L	14/24	58.3	1/10	10.0
Baseline splenectomy	Yes	2/4	50.0	0/0	-
	No	24/59	40.7	1/29	3.5

Sustained response = having at least 6 positive response assessments during Weeks 5 to 12 of randomized period; ITP = immune idiopathic thrombocytopenia; CI = confidence interval; Gi/L = giga per litter

3.2.5 Evaluation of Review Issues

The only major review issue was about handling of missing data in analyses. This issue was communicated to the Applicant during the protocol development. The agreed primary analysis was to treat missing data as a negative response in the computation of the primary endpoint.

Fortunately, the data completion rate for the primary endpoint was pretty high in both studies. In the PETIT study, 93% (62 out of 67) randomized patients had platelet counts available for weeks 1 to 6. In the PETIT2 study, 92% (85 out of 92) randomized patients had platelet counts available for weeks 5 to 12. The protocol pre-specified sensitivity analysis using multiple imputations produced a similar result to the primary analysis.

Reviewer Comment:

- *The protocol-specified sensitivity analysis is to impute missing platelet data assuming missing at random and assuming logarithm transformed platelet values to be multivariate normally distributed. Treatment group and age cohort were used as classifying variables and baseline value was used as a covariate in the multiple imputations. With the high data completion rate in each of the PETIT and the PETIT2 studies, results from imputed data were similar to the results from the original data.*

3.3 Evaluation of Safety

The safety database consists of 171 patients that received at least one dose of eltrombopag anytime in the PETIT and PETIT studies. Overall, there were 128 (75%) patients who received at least 24 weeks of treatment with eltrombopag, and the percentage of patients reported an adverse event was similar between treatment groups (82.0% placebo; 81.3% eltrombopag).

Please refer to the clinical review for detailed safety evaluation and clinical interpretation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Please refer to Table 9 and Table 10 for primary endpoint results by gender, race, age, and geographic region.

4.2 Other Special/Subgroup Populations

Please refer to Table 9 and Table 10 for primary endpoint results by other baseline factors.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This application is seeking to expand the indication of eltrombopag tablet formula to include pediatric patients 6 years and older. Clinical evidence supporting this application came from the PETIT and the PETIT2 studies, both were randomized double-blind placebo-controlled trials in pediatric patients with chronic immune thrombocytopenia.

Results from the PETIT and PETIT2 studies demonstrated treatment efficacy of eltrombopag in the studied pediatric population. Both studies observed a statistically significant difference between eltrombopag and placebo in their primary endpoint (Table 6). In either study, the platelet response rate and sustained response rate were at least 30% higher in the eltrombopag group compared to the placebo group. The median duration for a continuous response was longer in the eltrombopag group compared to the placebo group. In addition, both studies reported benefits from eltrombopag treatment in use of rescue treatment and incidence of bleeding without causing additional safety concerns. Results were consistent across subgroups.

The issue of missing data did not have a major impact on the reliability and confidence of the primary endpoint results, because the data completion rate was high at 93% and 92% for the primary endpoint in the PETIT study and the PETIT2 study, respectively.

5.2 Conclusions and Recommendations

Clinical data from the PETIT and PETIT2 studies demonstrated treatment efficacy of eltrombopag as a treatment in pediatric patients with chronic ITP. Approval is recommended to expand the eltrombopag indication from adults only to include pediatric patients.

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CHIA-WEN KO
05/26/2015

LEI NIE
05/26/2015

THOMAS E GWISE
05/27/2015