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Withdrawn by parent/guardian			1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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