

Eltrombopag in Children

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ABSTRACT

Immune (idiopathic) thrombocytopenic purpura (ITP), a disease of low platelet count affects as many as 5 in 100,000 children each year.¹ Being a self-remitting illness patients usually don't need aggressive treatment. However up to 30 percent of children are diagnosed with chronic ITP (cITP) experiencing persistent disease at 1 year from beginning of symptomatology.^{2,3,4} Patients with paediatric cITP are at a high risk of severe bleeding due to low platelet counts. Line of treatment for cITP in children include rituximab, high dose dexamethasone therapy, dapsone, multiple single agents, splenectomy and last but not the least thrombopoietin receptor agonists like eltrombopag which is approved by U.S. FDA for use in children. Eltrombopag being an oral drug compared to other modalities has shown very promising results in paediatric patients with cITP, has attained a consistent platelet response for 6 of 8 weeks compared to placebo (39.7% vs 3.4% respectively, $p < 0.001$).

Keywords: Eltrombopag, Chronic immune thrombocytopenic purpura, Thrombopoietin –receptor agonist

Modalities of Treating Chronic ITP in Children^{5,6,7}

1. Rituximab
2. High dose dexamethasone therapy
3. Dapsone
4. Numerous agents such as azathioprine, danazol, interferon, mycophenolate mofetil, cyclosporine, antiCD52 monoclonal antibody
5. Splenectomy
6. Thrombopoietin receptor agonists

INTRODUCTION

Eltrombopag in Children⁸

Eltrombopag is a non –peptidyl thrombopoietin (TPO) receptor agonist. TPO is the principal cytokine involved in the regulation of megakaryopoiesis and platelet production. Eltrombopag mimics the effect of TPO thereby stimulating platelet production. It is marketed as Promacta in the U.S. and as Revolade (SB-497115) in Europe and other countries across the world.

Eltrombopag has been licensed for paediatric cITP, only in patients whose degree of thrombocytopenia and clinical condition increase the risk of bleeding.

The treatment of adult chronic ITP and chronic hepatitis C virus infection with Eltrombopag is licensed in EU.

Eltrombopag is in phase II clinical trials for chemotherapy induced thrombocytopenia in adults. Recognised common ($\geq 10\%$) adverse effects for ITP includes headache.

least 12 months. In the first trial (n=67), children randomly received either Eltrombopag or placebo daily for a total duration of seven weeks. 62% of the Eltrombopag group between weeks one and six showed an improvement in platelet counts without rescue therapy, compared to 32% in the placebo group. In the second trial (n=92), randomization was done for 13 weeks and in those treated with Eltrombopag, 41% experienced between weeks five to 12, increased platelet counts for at least six out of eight weeks, compared to 3% patients receiving placebo. In both trials, the need for other treatments such as corticosteroids or platelet transfusions was also less in the Eltrombopag treated arm.

All study participants were then treated with eltrombopag in the second phase of the study (through to week 24).

Efficacy and safety data are presented in Table 1.¹³

METHODS

PETIT⁹ (Efficacy and Safety Study of Eltrombopag in Pediatric Patients with Thrombocytopenia from Chronic Idiopathic Thrombocytopenic Purpura (ITP)).

PETIT2 was two double-blind, randomized placebo-controlled and open-label study of 159 participants to investigate the efficacy, safety and tolerability of eltrombopag in paediatric patients with previously treated cITP. The primary objective of the study was to assess the efficacy of eltrombopag, relative to placebo, in achieving platelet counts of ≥ 50 Gi/L among paediatric patients with previously treated cITP for at

Table 1

Trial	PETIT2, NCT01520909,115450, 2011-002184-17; eltrombopag vs placebo; Phase III.	PETIT, NCT00908037, 108062; eltombopag vs placebo; phase II.
Sponsor	GlaxoSmithKline.	GlaxoSmithKline.
Status	Complete and published in abstract.	Complete
Source of information	Abstract, trial registry.	Abstract, trial registry, manufacturer.
Location	EU (incl. UK), USA and other countries.	EU (incl UK), USA and Canada.
Design	Randomised; placebo-controlled.	Randomised; placebo-controlled.
Participants	n=92 (planned); aged 1-17 years; ITP; chronic, >12 months duration; refractory or relapsed after ≥ 1 prior ITP therapy; naïve to TPO-RA; platelet count <30Gi/L.	n=67 (planned); aged 1-17 years; ITP; chronic >6 months duration; refractory or relapsed after ≥ 1 prior ITP therapy; naïve to TPO-RA; platelet count <30Gi/L.
Schedule	Randomised to: Part 1, for 13 weeks <ul style="list-style-type: none"> ○ Cohorts 1 (12-17 years) and 2 (6-11 years): eltrombopag, 50 or 37 mg (≥ 27 kg, <27kg respectively; dose adjusted for East Asian (EA) participants who received 25mg) daily, or placebo, both with standard of care; ○ Cohort 3 (1-5 years): eltrombopag, 1.2mg/kg (EA 0.8mg/kg) daily, or placebo, both with standard of care. (dose adjusted based on platelet counts to a maximum of 75mg daily) Part 2, open label for 24 weeks: <ul style="list-style-type: none"> ○ Eltrombopag with standard of care (dose not reported). 	Part 1, open label <ul style="list-style-type: none"> ○ Cohort 1 (12-17 years): eltrombopag, 25mg (EA 12.5mg) for 24 weeks; ○ Cohort 2 (6-11 years): eltrombopag, 25mg (<27kg, EA 12.5mg) or 50mg (≥ 27 kg, EA 25 mg) for 24 weeks; ○ Cohort 3 (1-5 years): eltrombopag, 25mg 0.7mg/kg (EA 0.5mg/kg) for 24 weeks. Part 2 (patients not participating in part 1 randomised 2:1, eltrombopag: placebo, for 7 weeks) <ul style="list-style-type: none"> ○ Cohort 1: randomised to eltrombopag, 37.5mg (EA 25mg); or placebo; both with standard of care. ○ Cohort 2: randomised to eltrombopag, 25mg (<27kg, EA 12.5 mg) or 50 mg (≥27 kg, EA 25 mg); or placebo; both with standard of care. ○ Cohort 3: randomised to eltrombopag, 1.5mg/kg (EA 0.8mg/kg) or placebo; both with standard of care. Part 3, open label up to 24 weeks: <ul style="list-style-type: none"> ○ Eltrombopag (dose not reported)
Follow-up	Active treatment for 37 weeks.	Active treatment for up to 48 weeks.
Primary outcome/s	Consistent platelet counts ≥ 50 Gi/L (x 10 ⁹ cells /L).	Platelet counts ≥ 50 Gi/L (x10 ⁹ cells/L)
Secondary outcome/s	Mean platelet change; maximum time with platelet counts continuously ≥ 50Gi/L; proportion reducing or discontinuing baseline concomitant ITP medications; proportion requiring protocol-defined rescue treatment; ITP symptoms; clinical laboratory assessments; ophthalmic changes; vital signs; pharmacokinetics. No quality of life measures included in trial.	Mean platelet change; plasma concentrations of study drug; safety and tolerability; reduction or discontinuation of ITP medications; use of rescue treatment; KIT ^a ; reduction of bleeding symptoms; ocular examinations.
Key results	Consistent platelet response, eltrombopag 39.7%, placebo 3.4% (p<0.001); clinically significant bleeding present at baseline and end of part 1 respectively, eltrombopag, 28.6%, 4.8%, placebo 13.8%, 6.9%.	For eltrombopag and placebo respectively, consistent platelet response, 62.2%, 31.8% (odds ratio 4.31; 95% CI 1.4, 13.3; p=0.011); reduction in Bleeding ^b , 27%, 59%. At week 24 (part 1), 9/10 patients completing KIT, had higher scores compared to baseline (mean, 19.6-point improvement; range 4.8-37.5).
Adverse effects (AEs)	Most commonly reported AEs included nasopharyngitis, rhinitis, cough, upper respiratory tract infection.	AEs for eltrombopag and placebo respectively (%): headache, 29.5, 42.9; upper respiratory tract infection, 15.9, 9.5; diarrhoea, 15.9, 4.8. Bleeding events, eltrombopag, 15.9%, placebo 38.1%.
Expected reporting date		Not reported

^a Kids' ITP Tools quality of life questionnaire^b World Health Organisation scale, grade 2-4

RESULTS

Of the 92 patients enrolled, 63 patients were assigned to receive eltrombopag and 29 were assigned to receive placebo. Almost 40% of paediatric patients with chronic ITP treated with eltrombopag attained a consistent platelet response for 6 of the last 8 weeks of the double blind trial compared to placebo (39.7% vs 3.4% respectively, $p < 0.001$).

Efficacy results for PETIT 2 were consistent across age cohorts (eltrombopag vs placebo: 39% vs 10% for patients aged 12–17 years, 42% vs 0% for patients aged 6–11 years, and 36% vs 0% for patients aged 1–5 years). The safety profile was consistent with the established profile for eltrombopag and no new safety concerns were observed.

37% of 63 patients receiving Eltrombopag had WHO grades 1–4 bleeding at the end of the double-blind period than did those who received placebo (16 [55%] of 29 patients). Grades 2–4 bleeding were similar in both the groups. Adverse events occurring frequently with eltrombopag included nasopharyngitis 17%, rhinitis 16%, upper respiratory tract infection 11%, and cough 11%. Serious adverse events occurred in 8% patients receiving eltrombopag compared to 14% receiving placebo. No major safety issues, deaths, malignancies, or thromboses occurred during the trial.

Side effects of eltrombopag¹²

Eltrombopag in combination with interferon and ribavirin in patients with hepatitis C may increase the risk of hepatic decompensation.

1. Hepatotoxicity

Measure serum ALT, AST, and bilirubin prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase, and monthly following

establishment of a stable dose as Eltrombopag can cause liver enzyme elevations.

Mechanism: Eltrombopag leads to indirect hyperbilirubinemia by inhibiting UGT1A1 and OATP1B1. If bilirubin is elevated, perform fractionation. Monitor abnormal serum liver tests by repeat testing within 3 to 5 days. Keep monitoring serum liver tests weekly until resolved or stabilized.

Discontinue eltrombopag if ALT levels increase to =3 X upper limit of normal (ULN) in patients with normal liver function or =3 X baseline in patients with pre-treatment elevations in transaminases and are progressively increasing; or persistent for 4 weeks; or accompanied by increased direct bilirubin; or accompanied by clinical symptoms of liver injury or hepatic decompensation.

If the benefits for reinitiating eltrombopag outweighs the risk for hepatotoxicity, then cautiously reintroduce eltrombopag and measure serum liver tests weekly during the dose adjustment phase. Hepatotoxicity may reoccur if eltrombopag is reinitiated. Eltrombopag is permanently discontinued if liver tests abnormalities persist, worsen or recur.

2. Thrombotic/thromboembolic complications

Increase in platelet count with eltrombopag may lead to thrombotic/thromboembolic complication. It includes both venous and arterial events and has been observed at low and also normal platelet counts. Addition caution in administering to patients with known risk factors for thromboembolism. Follow the dose adjustment guidelines to achieve and maintain target platelet counts.

Dosage adjustment recommendations for eltrombopag are presented in Table 2.¹⁴

Table 2: Dosage adjustment recommendations for eltrombopag

Platelet Count	Action
Platelet count $< 50 \times 10^9/L$ (after at least 2 weeks)	Increase daily dose by 25 mg; maximum dose 75 mg/day.
$> 200 \times 10^9/L$ (at any time)	Reduce daily dose by 25 mg; reassess in 2 weeks.
$> 400 \times 10^9/L$	Withhold dose; assess platelet count twice weekly; when platelet count $< 150 \times 10^9/L$ resume with the daily dose reduced by 25 mg.
$> 400 \times 10^9/L$ after 2 weeks of the lowest dose	Permanently discontinue.

3. Cataracts

A baseline ocular examination prior to administration of eltrombopag and, during therapy with eltrombopag, with regularly monitoring for signs and symptoms of cataract is recommended.

In 3 controlled adult clinical trials in chronic ITP, cataracts developed or worsened in 15 (7%) patients who received 50 mg eltrombopag daily and 8 (7%) placebo-group patients. In the extension trial, cataracts developed or worsened in 4% of patients who underwent ocular examination prior to therapy with eltrombopag.

Laboratory monitoring:¹²

In patients with chronic ITP, on eltrombopag, assess complete blood counts (CBCs) with differentials, including platelet counts, weekly until a stable platelet count has been achieved and monthly thereafter. Obtain CBCs with

differentials, including platelet counts, weekly for at least 4 weeks following discontinuation of eltrombopag. On eltrombopag monitor liver function tests.

Drug interactions:¹²

Eltrombopag must not be taken within 4 hours of any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements.

Adverse reactions:¹²

The most common adverse reactions in 3 placebo-controlled clinical trials in chronic ITP patients (=3% and greater than placebo) for eltrombopag versus placebo were: nausea (9% vs. 3%), diarrhea (9% vs. 7%), vomiting (6% vs. <1%), upper respiratory tract infection (7% vs. 6%), pharyngitis (4% vs. 2%), influenza (3% vs. 2%), increased ALT (5% vs. 3%), increased AST (4% vs. 2%), myalgia (5% vs. 2%), paresthesia (3% vs. 2%), urinary tract infection (5% vs. 3%), oropharyngeal pain (4% vs. 3%), back pain (3% vs. 2%), and rash (3% vs. 2%).

Availability and cost in India

Available as Revolade; a strip of 7 tablets of 25 mg costs Rs. 6700/- in the retail market.

It is available as a tablet taken once-daily or as a powder that is mixed with liquid for children ages one to five to take orally.

CONCLUSION

Eltrombopag seems to be a promising new oral drug for paediatric patients of chronic ITP with no serious adverse events and should be offered to patients who can afford it. U.S. FDA has approved it for use in children with chronic ITP since 24 August 2015. The safety and efficacy of Promacta in pediatric patients younger than one year with ITP, or in pediatric patients with thrombocytopenia associated with chronic hepatitis C and severe aplastic anemia, have not been established.

Take home messages

- Eltrombopag has shown consistent efficacy across all age cohorts with a significant improvement in platelet count of treated children vs placebo (40% vs 3.4% respectively, $p < 0.001$).
- The drug is easy to administer as it is available in oral form.
- The side effects are not severe enough (nasopharyngitis, rhinitis, cough and respiratory tract infection) to warrant concern.

REFERENCES

1. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN, The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports, *Am J Hematol.* 2010 Mar; 85(3):174-80. doi: 10.1002/ajh.21616.

2. El-Bostany E, El-Ghoroury E, and El-Ghafar E. Anti-Beta 2 Glycoprotein I in childhood immune thrombocytopenic purpura, *Blood Coagulation and Fibrinolysis.* 2008; 19(1):26-31.
3. British Committee for Standards in Haematology (BCSH) guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol.* 2003; 120:574-596.
4. Walker R.W, Walker W, Idiopathic thrombocytopenia, initial illness and long term follow up. *Archives of Disease in Childhood,* 1984; 59: 316-322.
5. Cindy Neunert, Wendy Lim, Mark Crowther, Alan Cohen, Lawrence Solberg, Jr and Mark A. Crowther, The American Society of Hematology 2011 evidence based practice guideline for immune thrombocytopenia. *Blood* 2011 117: 4190-4207.
6. Wali YA, Al Lamki Z, Shah W, Zacharia M, Hassan A, pulsed high-dose dexamethasone therapy in children with chronic idiopathic thrombocytopenic purpura, *Pediatr Hematol Oncol* 2002; 19(5): 329-335.
7. Damodar S, Viswabandya A, George B, Mathews V, Chandy M, Srivastava A. Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults: A report on 90 patients, *Eur. J. Haematol* 2005; 75(4): 328-331.
8. Emc.spc. Revolade. Available at <https://www.medicines.org.uk/emc/medicine/22949/SPC/Revolade/INDICATIONS>, Accessed 26 June 2014.
9. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm459430.htm>.
10. GSK Announces Results of Phase 3 PETIT 2 Study of Eltrombopag in Pediatric Patients with Chronic Immune Thrombocytopenia, Ligand Press Release available at [http://investor.ligand.com/Investors/News-and-Events/Press-Releases/Ligand Partner](http://investor.ligand.com/Investors/News-and-Events/Press-Releases/Ligand%20Partner), accessed 26 June 2014.
11. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo- controlled trial. Dr John D Grainger, MD, Franco Locatelli, MD, Thirachit Chotsampancharoen, MD, Elena Donyush, MD et al. Oct 24, 2015 THE LANCET Volume 386 Number 10004 p1599-1706.
12. Rao A, Kelly M, Musselman M, et al, Safety, efficacy and immune reconstitution after rituximab therapy in pediatric patients with chronic or refractory hematologic autoimmune cytopenias, *Pediatr Blood Cancer* 2008; 50(4): 822-825.
13. NIHR Horizon Scanning Centre. NIHR HSC ID: 10027. Eltrombopag (Revolade) for children with chronic immune thrombocytopenic purpura. Available at <http://www.hsc.nihr.ac.uk>, accessed 26 June 2014.
14. Rice L. Treatment of immune thrombocytopenic purpura: Focus on eltrombopag, *Biologics*3, 151-157(2009).