17 December 2015
EMA/CHMP/38474/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revolade

International non-proprietary name: eltrombopag / eltrombopag olamine

Procedure No. EMEA/H/C/001110/II/0023

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
AML	acute myeloid leukaemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
BCRP	breast cancer resistance protein
BCSH	British Committee for Standards in Haematology
CI	Confidence Interval
Cmax	Maximum serum concentration
CSR	Clinical Study Report
CYP	Cytochrome P450
DB	Double Blind
G	Global
Gi/L	Giga/Litre; $x10^9$ per litre
HCV	Hepatitis C virus
HSCT	hematopoietic stem cell transplantation
ICSR	Individual Case Safety Reports
ITP	Immune (idiopathic) thrombocytopenic purpura
ITT	Intent to Treat
IVIg	intravenous immunoglobulin
M	Multi-centre
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg/d	Milligrams/ day
OATP1B1	OATP1B1
OL	Open Label
OR	Odds Ratio
PBO	Placebo
PC	Placebo controlled
PK	Pharmacokinetic
PP	Per protocol
PSUR	Periodic Safety Update Report
PT	Preferred Term
PY	Patient Years
qd	Once daily
R	Randomised
RMP	Risk Management Plan
SAE	Serious adverse event
TEE	Thrombotic/thromboembolic events
TPO	Thrombopoietin
TPO-R	Thrombopoietin receptor
WBC	White blood cell
WHO	World Health Organisation

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 11 March 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to extend the use of Revolade to non-splenectomized patients; as a consequence, section 4.1 of the SmPC is updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0307/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0007/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Greg Markey

Timetable	Actual dates
Submission date	11 March 2015
Start of procedure:	28 March 2015
CHMP Rapporteur Assessment Report	5 June 2015
CHMP Co-Rapporteur Assessment Report	21 May 2015
CHMP members comments	17 June 2015
Updated CHMP Rapporteur Assessment Report	19 June 2015
The CHMP adopted a report on similarity of Revolade with NPlate (see Appendix 1) on	25 June 2015
CHMP 1st Request for supplementary information (RSI)	25 June 2015
MAH's responses submitted to the CHMP on:	21 August 2015
CHMP Rapporteur Assessment Report	28 September 2015
CHMP members comments	15 October 2015
CHMP 2nd Request for supplementary information (RSI)	22 October 2015
MAH's responses submitted to the CHMP on:	17 November 2015
CHMP Rapporteur Assessment Report	3 December 2015
CHMP members comments	7 December 2015
Updated CHMP Rapporteur Assessment Report	11 December 2015
CHMP Opinion	17 December 2015

2. Scientific discussion

2.1. Introduction

Immune (idiopathic) thrombocytopenic purpura (ITP) is an autoimmune disease characterized by platelet destruction caused by antiplatelet autoantibodies. In adults, chronic ITP is more common in women than men (approximately 2:1, respectively) and rarely remits spontaneously. It is classified by duration into newly diagnosed, persistent (3-12 months duration) and chronic (≥ 12 months duration). ITP in adults typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course.

In Europe, adult ITP has an incidence of 1.6 to 3.9 cases per 100,000 per year with increasing incidence with older age and equal for the sexes except in the mid-adult years (30-60 years), when the disease is more prevalent in women. Childhood ITP has an incidence of between 1.9 and 6.4 per 100,000 per year with equal distribution between the sexes.

The diagnosis of ITP can be difficult because of the variety of presentations and lack of specific criteria. The only consistent abnormalities are microangiopathic haemolytic anaemia (with red-cell fragmentation), and thrombocytopenia, features that can also occur in other conditions. Neurologic and renal abnormalities and fever can also occur. The onset of the disease is often insidious because history and

physical examination are normal except for symptoms that accompany platelet disorders (purpura, epistaxis, and gingival bleeding are common). In general, ITP is defined by a low platelet count, normal bone marrow, and the absence of other causes of thrombocytopenia.

According to current guidelines the therapeutic goal is to avoid or defer the risks of more toxic treatments (eg splenectomy or immunosuppression), reduce corticosteroid exposure to minimum levels and for the shortest time and achieve long-lasting responses (EMA/CHMP/153191/2013, 2014).

Splenectomy has been utilized to treat immune thrombocytopenia since the early 1900s and remained the 'first-line, gold standard procedure' until the 1950s, when steroids were introduced. Splenectomy has been the standard second-line treatment for adults with ITP since. It remains the treatment option with the highest overall success rate, with approximately two thirds of patients remaining in clinical remission 5-10 years after splenectomy. A systematic review of 135 case-series published between 1966 and 2004 revealed a complete response rate of 66%, with a median duration of follow-up of 28 months (range, 1-153 months) Kojouri et al, 2004. Also, a > 70% probability of maintaining a response after 5 years was found from follow-up of 402 splenectomized patients (Vianelli, et al, 2005). There are near-term and perioperative complications (general anesthesia, bleeding and thrombosis, as well as postoperative pain, pneumonia and atelectasis, wound/other infection and ileus) and longer-term complications, Risk of Infection, Vascular Complications, Mortality and Relapse.

Even though splenectomy remains an appropriate treatment, the frequency of splenectomy as treatment for ITP in adults seems to be decreasing. Older cohorts described in the literature describe the splenectomy rate at 50 to 60% or higher, and in more recent studies it is around 20 to 25% (Rodeghiero and Ruggeri, 2008). The most recent guidelines of ITP (Provan et al, 2010; Neunert et al, 2011) have both recommended splenectomy as a second-line therapy and agree that splenectomy should be delayed at least 6 to 12 months (Provan et al, 2010; Neunert et al, 2011). However, there is no consensus regarding the best sequence of treatments and therapy should be individualized.

Eltrombopag is an orally bioavailable, 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.

Revolade (eltrombopag) was issued a MA in the EU in March 2010, for the treatment of adult chronic ITP splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins), and as a second line treatment for adult non-splenectomised patients where surgery is contraindicated. During the initial evaluation it was demonstrated that eltrombopag increases platelet count in patients with chronic ITP unresponsive to at least one first line therapy (corticosteroids or immunoglobulins). This effect has been shown to be superior to placebo in both splenectomised and non-splenectomised patients in two well-designed and conducted placebo-controlled clinical trials of short-term (6 weeks) and medium-term (6 months) duration. Efficacy was demonstrated in both splenectomized and non-splenectomized patients, however considering the long term safety uncertainties, its use in non splenectomized patients was restricted to those in whom the surgery was contraindicated. At that time the splenectomy was a definitive curative treatment considered as gold standard within the second line alternatives to patients failed to corticosteroids and immunoglobulins.

Currently, eltrombopag is approved for the treatment of chronic ITP in over 90 countries worldwide including the U.S., Australia, Switzerland and Japan. The MA in the EU has been renewed with unlimited validity.

The MAH on the basis of cumulative evidence proposes to revise the currently approved EU Summary of Product Characteristics (SmPC) indication to remove the phrase "where surgery is contra-indicated".

The proposed therapeutic indication is:

"Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who had an insufficient response to other treatments (e.g. corticosteroids, immunoglobulins or splenectomy).

The indication approved by the CHMP was:

"Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

The posology in non-splenectomised ITP patients is the same as in splenectomised and as currently established in the section 4.2 of the SmPC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

An updated ERA which will address all indications for eltrombopag (tablets and PfOS) is due by April 2016. Reports from the completed aquatic and terrestrial fate and effects studies will be included.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

This variation presents a summary of the clinical efficacy data that were part of the original submission in splenectomised and non-splenectomised adult chronic ITP patients in support of the request to modify the indication statement.

In addition, a supportive summary of relevant clinical efficacy data obtained since the original submission date from the paediatric chronic ITP development program is presented, as these studies were conducted in primarily non-splenectomised patients. Note, a line extension application is ongoing in parallel to this application, in the paediatric ITP population.

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

In support of the Marketing Authorisation Application, 1 dose finding randomised placebo controlled study, 2 phase III randomised placebo controlled studies (one short-term and one long-term) and 2 open label studies were conducted.

All randomised studies included ITP patients with a variable degree of previous exposure to available therapies (failing at least one previous therapy). Both splenectomised and non-splenectomised patients were included in all trials.

Table 1 Revolade ITP Clinical Studies

Study	Phase	Study Design / Primary Objective	Dosing and Administration	Randomised[#] (patients without splenectomy at baseline)
Double-blind Studies				
TRA100773A*	II	G, M, R, DB, PC/ Dose finding	PBO, 30mg, 50mg or 75mg qd for up to 6 weeks; No dose adjustments allowed	PBO: 29 (15) Eltr: 89 (47)
TRA100773B*	III	G, M, R, DB, PC/ Efficacy	PBO or 50mg qd for up to 6 weeks; Dose increase allowed after Day 21	PBO: 38 (24) Eltr: 76 (45)
RAISE* TRA102537	III	G, M, R, DB, PC/ Efficacy	PBO or 50mg qd for up to 6 months; Dose adjustments allowed	2:1 PBO: 62 (41) Eltr: 135 (85)
Open-label Studies (these studies were considered supportive in the original Marketing Authorisation application)				
REPEAT TRA108057	II	G, OL/ Repeat treatment	50mg qd for up to 6 weeks for 3 cycles; Dose increase allowed	Eltr: 66 (46)
EXTEND TRA105325	III	G, OL, Extension study/ Safety	50mg qd; Dose adjustments allowed Subjects that completed TRA100773A, TRA100773B, RAISE or REPEAT and any required follow-up visit were eligible to enrol into the study for long term treatment and observation of safety and tolerability	Eltr: 299 (184) (ongoing) The Clinical Study Report is due in 2015
Paediatric chronic ITP studies (these studies are considered supportive only with regard to the assessment of this application)				
PETIT2 TRA115450	III	First Part: R, DB, PC Second Part: OL Efficacy	PBO or DOSE[¤] for up to 13 weeks; DOSE for 24 weeks	PBO: 29 (29) Eltr: 63 (59)
PETIT TRA108062	III	First Part: R, DB, PC/ dose finding Second part: OL Efficacy	PBO or DOSE[§] for 7 weeks; OL DOSE for up to 24 weeks	PBO: 22 (22) Eltr: 45 (40)
studies collecting data on the safety and utilisation of Revolade				
TRA112940	IV	G, OL/	Longitudinal 2-year bone marrow study in previously-treated adults,	(ongoing)

Study	Phase	Study Design / Primary Objective	Dosing and Administration	Randomised[#] (patients without splenectomy at baseline)
		safety	with chronic (ITP) to assess the levels of bone marrow fibers (reticulin and/or collagen) at baseline and any change from baseline after 1 and 2 years of treatment with eltrombopag in adult subjects with chronic ITP.	The Clinical Study Report is due in 2015
WEUKBRE7133	IV	drug utilisation study	the final study report planned in 2016	(ongoing)

G = global; M=multi-centre R = randomised; DB = double-blind; PC = placebo-controlled; OL = open-label; qd = once daily; Eltr = eltrombopag; PBO=placebo

*randomisation stratified for use or non-use of ITP medications at randomisation, splenectomy status and baseline platelet count (≤15 Gi/L or >15Gi/L)

ᵅSubjects between 6 and 17 years of age with a body weight of ≥27 kg:50 mg qd; <27 kg: 37.5 mg once daily. East Asian subjects, between 6 and 17 years: 25mg qd. Between 1 and 5 years of age: 1.2 mg/kg once daily, or 0.8 mg/kg once daily for East Asian subjects.

[§] 25 mg once daily (12.5 mg if of East Asian ancestry), subjects in Cohort 2 with a body weight of ≥27 kg initiated dosing with eltrombopag at 25 mg and with a body weight of <27 kg at 12.5 mg once daily, subjects in Cohort 3, the starting dose was 0.7 mg/kg once daily, or 0.5 mg/kg once daily for East Asian subjects.

[#] Data Source: GSK Document Number ZM2006/00049/00 TRA100773A CSR, Table 11; GSK Document Number RM2006/00266/01 TRA100773B CSR, Table 11; GSK Document Number UM2008/00026/02 TRA102537 CSR, Table 8

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Adult chronic ITP Studies

TRA100773A

In TRA100773A, a dose-dependent increase in response was observed, and the primary endpoint of the study (shift from baseline platelets <30 Gi/L to platelets ≥50 Gi/L) was achieved by 11% of subjects on placebo, compared to 28%, 70%, and 81% of subjects on eltrombopag 30 mg, 50 mg, and 75 mg, respectively. The odds of treatment response compared to placebo were statistically significant in the 50 mg and 75 mg groups of TRA100773A ($p<0.001$).

Baseline median platelet counts were similar across all 4 treatment groups and a dose dependent increase in the median platelet count was observed at each visit, confirming the dose dependent increase in responders. This response to eltrombopag relative to placebo was observed regardless of splenectomy status and no significant interaction between response and splenectomy status was observed.

Table 3 TRA100773A Response by Splenectomy Status at Baseline

	Placebo	Eltrombopag			
		30mg	50mg	75mg	Total
Splenectomised	N=14	N=14	N=15	N=10	N=39
Responders, n (%)	2 (14)	3 (21)	8 (53)	7 (70)	18 (46)
Non-splenectomised	N=13	N=15	N=12	N=16	N=43
Responders, n (%)	1 (8)	5 (33)	11 (92)	14 (88)	30 (70)

Data Source: eCTD seq. no. 0000, m5.3.5.1, TRA100773A CSR, Source Table 7.16

Paediatric chronic ITP Studies

PETIT (Study TRA108062) was a Phase II, three-part, staggered cohort, open-label and double-blind, randomised, placebo-controlled study to investigate the efficacy, safety, tolerability and pharmacokinetics of eltrombopag in previously treated paediatric patients with chronic ITP. Fifteen subjects, 5 per age cohort, were enrolled in the PETIT Dose Finding Phase. These subjects did not participate in the Randomized Period. Eligibility criteria were similar to PETIT2, except that subjects in PETIT were required to have a confirmed diagnosis of chronic ITP for at least 6 months.

Subjects received 7 weeks of double-blinded study medication, and up to 24 weeks of open-label eltrombopag.

A total of 67 subjects were randomized (45 eltrombopag; 22 placebo) and 65 subjects entered the Eltrombopag-Only Period. The majority of subjects received at least 2 prior ITP therapies (84.4% eltrombopag and 86.4% placebo). Baseline disease characteristics were similar between the treatment groups and consistent with a paediatric chronic ITP population. The majority of subjects (77/82, 94%) were not splenectomised at baseline; five subjects had been splenectomised prior to study entry.

In PETIT, analysis of the primary endpoint demonstrated that eltrombopag subjects were more likely to have a platelet response in the absence of rescue treatment at least once over the 6-week Randomised Period compared with placebo subjects (62.2% versus 31.8%; p=0.011).

2.4.2. Main studies

Two Phase III, randomised, double-blind, placebo-controlled studies, RAISE (TRA102537) and TRA100773B, and two open-label studies, REPEAT (TRA108057) and EXTEND (TRA105325), evaluated the safety and efficacy of eltrombopag in adult patients with previously treated chronic ITP as part of the original MAA submission for Revolade. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year (see Table 1).

EXTEND, one of the long-term studies of eltrombopag in patients with chronic ITP, was designed primarily to assess the safety of eltrombopag over long-term dosing and to allow access to eltrombopag for subjects who participated in prior eltrombopag studies (including TRA100773A, TRA100773B, TRA108057/REPEAT and TRA102537/RAISE). EXTEND is continuing and, according to the most recent PSUR for eltrombopag, the final study report is due in 2015.

In addition, there are a number of ongoing studies collecting data on the safety and utilisation of Revolade.

TRA112940 is a longitudinal 2-year bone marrow study of eltrombopag olamine (SB-497115-GR) in previously-treated adults, with chronic idiopathic thrombocytopenic purpura (ITP). The primary objective to assess the levels of bone marrow fibers (reticulin and/or collagen) at baseline and any change from baseline after 1 and 2 years of treatment with eltrombopag in adult subjects with chronic ITP. This is due

by September 2015 as a follow up measure from the original authorisation and is not presented in this application.

WEUKBRE7133, a drug utilisation study, is ongoing with the final study report planned in 2016.

Adult chronic ITP Studies

StudiesTRA100773B and RAISE (TRA102537) were global, multicentre, randomised, double-blind, placebo-controlled clinical trials, and TRA100773A was a randomised, double-blind phase 2 study. In the 3 double-blind studies, eligible subjects had platelet counts at baseline of <30 Gi/L. In TRA100773A and TRA100773B, treatment was administered once daily for up to 6 weeks, whereas in RAISE treatment was administered for up to 6 months. In all 3 studies, randomization was stratified based upon use or non-use of ITP medications at randomization, splenectomy status and baseline platelet count (≤15 Gi/L or >15 Gi/L).

Paediatric chronic ITP Studies

PETIT2 (Study TRA115450) was a Phase III, two-part, double-blind, randomised, placebo-controlled and open-label study to investigate the efficacy, safety, and tolerability of eltrombopag in paediatric patients with previously treated chronic ITP, with a confirmed diagnosis of chronic ITP for at least 1 year. The study enrolled subjects between 1 year and <18 years of age, and a platelet count at baseline of <30 Gi/L.

Subjects were refractory or relapsed after at least one prior ITP therapy, or not eligible, for a medical reason, to continue other ITP treatments. Subjects received 13 weeks of double-blinded study medication, and 24 weeks of open-label eltrombopag.

TRA102537/RAISE

Methods

RAISE was a second, randomised, double-blind, placebo controlled, phase III study to assess the efficacy during 6 month dosing of eltrombobag 50 mg once daily in the treatment of 197 adults with ITP (for detailed assessment please refer to CHMP AR or published EPAR for the original MAA.

Study participants

Inclusion criteria were similar to those used for studies TRA100773A&B and are presented in Table 2. Patients were allowed to receive stable maintenance therapy.

Table 1 Main Inclusion and Exclusion Criteria

	Adult studies ≥18 years
Main inclusion criteria	• Chronic ITP according to the ASH/BCSH guidelines • Platelet count <30 Gi/L within 24 hours prior to dosing on Day 1 • Peripheral blood smear should support the diagnosis of ITP • No suggestion of any disease which may cause thrombocytopenia other than ITP. • Subjects who previously received one or more prior ITP therapies. • Subjects must have had either initially responded (platelet count >100 Gi/L) to a previous ITP therapy or have had a bone marrow examination consistent with ITP within 3 years to rule out myelodysplastic syndromes or other causes of thrombocytopenia.

	Adult studies ≥18 years
Main exclusion criteria	• Any clinically relevant abnormality, other than ITP • Thrombocytopenia secondary to another disease • Concurrent malignant disease and/or history of cancer treatment with cytotoxic chemotherapy and/or radiotherapy • Prior history of arterial or venous thrombosis AND ≥ 2 of the following risk factors: hormone replacement therapy, systemic contraception, smoking, diabetes, hypercholesterolemia, medication for hypertension, cancer, hereditary thrombophilic disorders or any other family history of arterial or venous thrombosis • Pre-existing cardiovascular disease or arrhythmia known to increase the risk of thromboembolic events or subjects with a QTc >450 msec • Nursing or pregnant subjects • Subject treated with drugs that affect platelet function • History of platelet agglutination abnormality that prevents reliable measurement of platelet counts • Secondary immune thrombocytopenia • Subjects planning to have cataract surgery

Treatments

Throughout the 6-month treatment period, the dose of the study medication could be up- (75 mg/d) or down- (25 mg/d) titrated according to platelet count monitoring. Subjects were allowed a dose increase on or after day 22 if the platelet count did not rise above 50 Gi/L for two successive platelet count assessments. The subjects reduced their dose of study drug when the platelet count exceeded 200 Gi/L. When the platelet count reached 400 Gi/L, study medication was interrupted for at least 7 days and until platelet counts fell below 150 Gi/L, at which point subjects were re-commenced at the next lower dose.

After completion of the 6 month dosing period, patients were followed up at weeks 1, 2, and 4 and months 3 and 6.

Outcomes/endpoints

The primary endpoint was the odds of achieving a platelet count $\geq$ 50 and $\leq$ 400 Gi/L for a subject receiving eltrombopag relative to placebo during the 6-month treatment period. Other secondary endpoints proposed in this clinical trial were the overall platelet response, duration of the platelet response, the proportion of patients requiring rescue medication or reducing concomitant ITP medication, and changes in the WHO bleeding and ITP scores.

A subject was classified as a negative response from the time they began taking any form of rescue treatment, for the duration of rescue treatment use, and until the platelet count fell below 50 Gi/L. After this, any subsequent assessments in the appropriate range were counted as a positive response if the platelet count was ≥50 and ≤400Gi/L. Restarting a concomitant medication that had been stopped during the trial was not classified as rescue medication, provided it was at the same or a lower dose. A higher dose counted as rescue medication.

Sample size

The primary analysis was to compare the odds of achieving a platelet count ≥50 and ≤400,000/µL during the treatment period in the eltrombopag group relative to the placebo group. Assuming 60% and 25% positive response rates in the eltrombopag and placebo groups, respectively, 120 evaluable subjects were needed to provide ≥90% power at the 1% (two-sided) level of significance. To ensure sufficient power for both the primary and main secondary endpoints, a 30% increase in subjects was pre-specified to compensate for potential missing data and drop-outs during the full 6 month study duration for a total of 189 subjects (63 placebo subjects; 126 eltrombopag subjects).

Randomisation

Patients were randomised on a 2:1 ratio to receive eltrombopag 50 mg/d (135 subjects) or placebo (62 subjects). The randomisation scheme was stratified by splenectomy (yes/no), use of ITP medication at randomization (yes/no), and baseline platelet count ≤15 Gi/L (yes/no).

Blinding (masking)

The study was double-blinded. Treatments were blinded to the research subjects and all study and sponsor personnel. Treatment blind was maintained by use of matching placebo medication.

Statistical methods

Response profiles were compared using a repeated measures model for binary data adjusted for the randomization stratification variables. Generalized estimating equations (GEE) methodology was used to estimate the regression model parameters with the correlation of an individual subject's responder status between visits being modelled as exchangeable (i.e. assuming the correlation between any 2 measures for a subject is the same). Significance testing was two-sided at the 1% level of significance for the primary endpoint, and unless stated otherwise, significance testing was two-sided at the 5% level of significance for all other comparisons. Unless otherwise stated, 95% confidence intervals (CI) around the odds ratios or treatment differences, as appropriate, were presented. There were no requirements for multiplicity adjustments in this study. The overall Type I error rate was 0.01 (two-sided) for the primary efficacy analysis and, unless otherwise indicated, 0.05 (two-sided) for all secondary and exploratory analyses.

Populations for the main analysis were the intent-to-treat (ITT) population (all randomized subjects), the per-protocol (PP) population (ITT excluding major protocol violators), and the safety population was comprised of all randomized subjects who had received at least one dose of the study treatment.

Results

One hundred and ninety-seven subjects were randomized to receive either placebo (n=62) or eltrombopag 50 mg (n=135) for up to 6 months. Subjects in the placebo and eltrombopag groups had a median age of 52.5 and 47 years, respectively, and 69% of subjects in both groups were female. All subjects in both treatment groups had at least 1 prior ITP therapy (including splenectomy).
Most patients (placebo 42 [68%]; eltrombopag 95 [70%]) were of white/Caucasian /European heritage.

All subjects in both treatment groups had ≥1 prior ITP therapy (including splenectomy). Eighty-one percent of placebo-treated subjects and 78% of eltrombopag-treated subjects had received at least 2 prior therapies, and more than 30% of subjects in each group had received ≥4 prior therapies.

Table 1 Summary of Baseline Characteristics in Adult Chronic ITP Studies

	TRA100773A				TRA100773B		RAISE	
	PBO N=29	30mg N=30	50mg N=30	75mg N=28	PBO N=38	Eltrombopag N=76	PBO N=62	Eltrombopag N=135
Actual Splenectomy Status, n (%)								
Yes	14 (48)	15 (50)	15 (50)	11 (39)	14 (37)	31 (41)	21 (34)	50 (37)
No	15 (52)	15 (50)	15 (50)	17 (61)	24 (63)	45 (59)	41 (66)	85 (63)
Actual Baseline ITP Medication Use, n (%)								
Yes	6 (21)	10 (33)	12 (40)	10 (36)	17 (45)	32 (42)	31 (50)	63 (47)
No	23 (79)	20 (67)	18 (60)	18 (64)	21 (55)	44 (58)	31 (50)	72 (53)
Actual Baseline Platelet Count, n (%)								
≤15Gi/L	14 (48)	15 (50)	12 (40)	15 (54)	17 (45)	38 (50)	30 (48)	67 (50)
>15Gi/L	15 (52)	15 (50)	17 (57)	13 (46)	21 (55)	38 (50)	31 (50)	68 (50)
Missing	0	0	1 (3)	0	0	0	1 (2)	0

Data Source: GSK Document Number ZM2006/00049/00 TRA100773A CSR, Table 11; GSK Document Number RM2006/00266/01 TRA100773B CSR, Table 11; GSK Document Number UM2008/00026/02 TRA102537 CSR, Table 8

The primary endpoint of the study was achieved, demonstrating the effectiveness of eltrombopag in comparison to placebo for the treatment of chronic ITP. The odds of achieving a platelet response between 50 Gi/L and 400 Gi/L were 8 times greater in eltrombopag-treated subjects throughout the 6-month treatment period compared to placebo-treated subjects, providing strong evidence of the long-term efficacy of eltrombopag compared to placebo (Odds Ratio [99% confidence interval] = 8.2 [3.59, 18.73], p<0.0001). This response to eltrombopag relative to placebo was observed regardless of splenectomy status, baseline platelet count, and use of baseline ITP medications.

Median platelet counts for eltrombopag-treated subjects began to rise after 1 week of treatment and remained above 50 Gi/L throughout the 6 month treatment period. In contrast, median platelet counts for subjects treated with placebo did not rise above 30 Gi/L throughout the study. Two weeks after discontinuation of eltrombopag, median platelet counts had returned to near baseline levels.

Significantly more subjects in the eltrombopag group (33%) maintained platelet counts between 50 and 400 Gi/L for ≥75% of on-treatment assessments compared to the placebo group (3%). No significant interaction between response to eltrombopag and splenectomy status was observed.Eltrombopag treatment allowed significantly more subjects to reduce or discontinue baseline ITP therapies (predominantly corticosteroids) compared to placebo treatment (59% vs. 32%; p=0.02).

Additionally, significantly fewer eltrombopag-treated subjects required protocol-defined rescue treatment (new ITP medication, increased dose of a baseline ITP medication, platelet transfusion, and/or splenectomy) compared to placebo-treated subjects (18% vs. 40%, p=0.001). No significant interaction between requirement for rescue treatment and splenectomy status was observed the need for rescue treatment was not influenced by splenectomy status.

TRA100773B

TRA100773B confirmed the predictability of response to eltrombopag observed in TRA100773A, with 16% of subjects on placebo compared to 59% of subjects on eltrombopag achieving platelet counts ≥50 Gi/L (p<0.001). This effect of eltrombopag relative to placebo was significant across all subgroups regardless of baseline platelet count, use of concomitant ITP medication, or splenectomy status.

Table 2 Response by Splenectomy Status at Baseline

	TRA100773B		RAISE
	Placebo	Eltrombopag	
Splenectomised	N=13	N=29	NA
Responders, n (%)	2 (15)	18 (62)	
Odds ratio (95% CI)	9.63 (1.72, 53.76)		6.02 (1.89, 19.62)
p value	0.01		0.0024
Non-splenectomised	N=24	N=44	NA
Responders, n (%)	4 (17)	25 (57)	
Odds ratio (95% CI)	12.00 (2.80, 51.46)		9.41 (4.51, 19.62)
p value	<0.001		<0.001

Data Source: TRA100773B, Table 7.164; TRA102537, Table 7.238

EXTEND Study

The baseline demographics and disease characteristics for the splenectomised and nonsplenectomised subjects are presented in the following tables

Table 2-1 Baseline Splenectomy Status

Splenectomy Status, n (%)	Eltrombopag N=302
Yes	115 (38%)
No	187 (62%)

Data Source: Table 6.11

Table 2-2 Demographics

Demographic	Not Splenectomised N=187	Splenectomised N=115
Age (yrs), median (min, max)	51 (18, 86)	48 (22, 82)
Male, n (%)	61 (33)	40 (35)
Female, n (%)	126 (67)	75 (65)
African American/ American Heritage	2 (1)	2 (2)
American Indian or Alaskan Native	7 (4)	6 (5)
East Asian, South East Asian or Japanese Heritage	28 (15)	13 (11)
Central/South Asian Heritage	4 (2)	0
White	146 (78)	94 (82)

Data Source: Table 6.901, 6.903

Table 2-3 Baseline Characteristics

Baseline Characteristic	Not Splenectomised N=187	Splenectomised N=115
Platelet Count <=15 Gi/L, n (%)	75 (40)	56 (49)
Platelet Count >15 - <30 Gi/L, n (%)	48 (26)	32 (29)
Platelet Count >=30 - <=50 Gi/L, n (%)	38 (20)	14 (12)
Platelet Count >50 Gi/L, n (%)	26 (14)	13 (11)
ITP medication use at baseline, n (%)	47 (25)	54 (47)
No ITP medication use at baseline, n (%)	140 (75)	61 (53)

Data Source: Table 6.902

The efficacy of eltrombopag in the EXTEND study, as of the clinical cut-off date of 06 April 2015, is described below for splenectomised and non-splenectomised subjects.
A similar proportion of subjects in each subgroup achieved platelet counts ≥ 50 Gi/L at any time post-baseline and in the absence of rescue medication (Table 2-5). More nonsplenectomised subjects maintained a response for >50% and >75% of assessments than the splenectomised subjects (Table 2-6).

Table 2-5 **Summary of Subjects Achieving Maximum Platelet Count Levels >=50 GI/L While Not Receiving Rescue Therapy By Baseline Splenectomy Status**

Platelet Count Level	Not Splenectomised N=187	Spenectomised N=115
≥ 50 Gi/L at baseline, n (%)	26 (14)	13 (11)
≥ 50 Gi/L at any time post-baseline, n (%)	166 (89)	92 (80)

Data Source: Table 7.832

Table 2-6 **Summary of Percentage of On-Treatment Assessments with Platelet Counts >=50 GI/L While Not Receiving Rescue Therapy by Baseline Splenectomy Status**

Platelet Count Level	Not Splenectomised N=187	Spenectomised N=115
≥ 50 Gi/L for >50% of assessments, n (%)	126 (67)	59 (51)
≥ 50 Gi/L for >75% of assessments, n (%)	90 (48)	36 (31)

Data Source: Table 7.838

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

- **Paediatric Chronic ITP**

TRA115450/PETIT2

A total of 92 subjects were randomized in the PETIT2 study (63 to eltrombopag and 29 to placebo). The majority of subjects (78%) were treated with 2 or more prior therapies. Baseline characteristics of each treatment group are presented in Table 4. The majority of subjects (88/92, 96%) were not splenectomised at baseline, and all 4 previously splenectomised subjects in PETIT2 were randomized to the eltrombopag group. The median baseline platelet count for the eltrombopag group was 13.65 Gi/L and for the placebo group was 11.0 Gi/L.

Table 4 **Summary of Baseline Characteristics in Paediatric Studies (Safety Population)**

	PETIT		PETIT2		Overall		
	Placebo N=22	Eltrombopag N=45	Placebo N=29	Eltrombopag N=63	Placebo N=51	Eltrombopag N=108	Total N=159
Actual Splenectomy Status, n (%)							
Yes	0	5 (11)	0	4 (6)	0	9 (8)	9 (6)
No	22 (100)	40 (89)	29 (100)	59 (94)	51 (100)	99 (92)	150 (94)
Actual Baseline ITP Medication Use, n (%)							
Yes	2 (9)	5 (11)	1 (3)	13 (21)	3 (6)	18 (17)	21 (13)
No	20 (91)	40 (89)	28 (97)	50 (79)	48 (94)	90 (83)	138 (87)
Actual Baseline Platelet Count, n (%)							
≤15Gi/L	11 (50)	23 (51)	19 (66)	38 (60)	30 (59)	61 (56)	91 (57)
>15Gi/L	10 (45)	20 (44)	10 (34)	24 (38)	20 (39)	44 (41)	64 (40)
Missing	1 (5)	2 (4)	0	1 (2)	1 (2)	3 (3)	4 (3)

Data Source: eCTD seq. no. 0083, m5.3.5.1 TRA108062/ PETIT CSR, Table 13; m5.3.5.1 TRA115450/PETIT2 CSR, Table 12; m2.7.4 Table 13

Eltrombopag produced a clinically meaningful sustained platelet response in the paediatric population. A greater proportion of eltrombopag subjects achieved a response for at least 6 of 8 weeks (between Weeks 5 through 12 of the Randomised Period) in the absence of rescue treatment in comparison to placebo subjects (39.7% versus 3.4%; p<0.001). Sustained platelet response by splenectomy status is presented in Table 5.

A repeated measures analysis of platelet response over 12 weeks of therapy during the Randomized Period was performed to understand the effect of treatment over time. This analysis accounts for between

and within subject variability in response. Results of this analysis indicated that for eltrombopag subjects, the odds of continuing to maintain a (better) response profile over time is higher than for placebo subjects (odds ratio: 25.33; 95% CI: 8.15, 78.73; p<0.001)

Table 5 Response by Splenectomy Status at Baseline

	PETIT2	
	Placebo	Eltrombopag
Splenectomised	N=0	N=4
Responders, n (%)	N/A	2 (50)
Non-splenectomised	N=29	N=59
Responders, n (%)	1 (3)	23 (39)

Data Source: eCTD seq. no. 0083, m5.3.5.1 TRA115450/PETIT2 CSR Figure 4

TRA108062/PETIT + PETIT 2 (Pooled Paediatric Data)

Pooled data from the 2 paediatric studies showed that a significantly higher proportion of eltrombopag subjects achieved platelet counts ≥50 Gi/L at least once during the Randomised Period from Day 8 to 43 (Weeks 1 to 6) compared with placebo subjects (62.0% versus 23.5%; p<0.001). Response during Weeks 1 to 6 was analyzed by splenectomy status and is presented in Table 6.

Table 6 Primary Efficacy Response by Splenectomy Status at Baseline

	Pooled Paediatric Data	
	Placebo	Eltrombopag
Splenectomised	N=0	N=9
Responders, n (%)	N/A	7 (78)
Non-splenectomised	N=51	N=99
Responders, n (%)	12 (24)	60 (61)

Data Source: eCTD seq. no. 0083, m2.7.3 Section 3.3.2

2.4.3. Discussion on clinical efficacy

The MAH proposes to modify the indication statement for ITP patients who had an insufficient response to other treatments (e.g. corticosteroids, immunoglobulins or splenectomy) to allow physicians the opportunity to make individualized treatment decisions, including the use of eltrombopag in non-splenectomised patients, if based upon their medical judgment that would be the most suitable option for their patient.

Design and conduct of clinical studies

In support of this variation, the MAH has submitted data from the studies presented to support the initial MAA in the adult population (Studies TRA100773A [dose-finding], TRA100773B, and RAISE) together with a summary of the studies conducted in the paediatric population; however, these are being assessed in a parallel procedure (EMEA/H/C/1110/X/22/G) and could not be considered supportive to the claimed extension of the indication.

The interim analysis of the EXTEND study was submitted as supportive. This is an open label study to evaluate the safety and efficacy of eltrombopag in subjects with cITP who have previously been enrolled in any of the following studies: TRA100773, TRA102537/RAISE, or TRA108057/REPEAT. Baseline characteristics were balanced between groups based on splenectomy status except that more patients had received ITP medication in the splenectomized arm than in the non-splenectomized subset (47% vs 25%) and the history of clinically significant bleeding was higher in splenectomised than non-splenectomised patients (23% vs 13%), which denotes the more advanced disease status of splenectomized patients. The cumulative exposure to eltrombopag was ≥6 months for the majority of the patients (86% in non-splenectomised and 82% in splenectomised) and more than half were exposed for ≥24 months in both arms.

A total of 302 patients had been enrolled by the cut-off date of 6th April 2015. Of these, 62% (187) were non-splenectomised and the majority were white females with a median age of 51 years in the non-splenectomized and 48 years in the splenectomized groups. Baseline characteristics were balanced between groups except that more patients had received ITP medication in the splenectomized subset than in the non-splenectomized subset (47% vs 25%) and that patients' history of clinically significant bleeding was higher in splenectomised than non-splenectomised patients (23% vs 13%). These data denote the more advanced disease status of splenectomized patients. The cumulative exposure to eltrombopag was $\geq$6 months for the majority of the patients (86% in non-splenectomised and 82% in splenectomised) and more than half were exposed for $\geq$24 months in both arms.

Efficacy data and additional analyses

The main evidence comes from the two phase III studies, where 311 patients were studied; 114 enrolled in the TRA100773B study and 197 in the RAISE study. Of these, 116 were splenectomised (35 in placebo and 81 eltrombopag treated arm) and 195 were non-splenectomized (65 placebo-treated and 130 eltrombopag-treated). The longest protocol-specified time of follow up was 6 months in the RAISE trial. The results from these studies show the superiority of eltrombopag compared to placebo to increase platelet count $\geq$50 x 10^9 /L and achieve a odds (95%CI) of response statistically superior either in splenectomised (6.02 (1.89, 19.62) in the RAISE study and 9.63 (1.72, 53.76) in the TRA100773B study) or non-splenectomised patients (9.41 (4.51, 19.62) in the RAISE study and 12.00 (2.80, 51.46) in the TRA100773B study), with a higher magnitude of the short-term effect occurring in non-splenectomized patients.

The evidence initially presented was limited to efficacy results in the short term (24-week at best in the RAISE Study). Studies, including TRA111433 and TRA113765, have investigated and confirmed the effectiveness of eltrombopag in cITP patients in addition to the long-term safety from the TRA105325/EXTEND study.

In the EXTEND study, more non-splenectomised subjects maintained a response for >50% and >75% of assessments than splenectomised subjects (67% vs 51% and 48% vs 31%). With regard to WHO bleeding events, it is difficult to see a clear effect, although in both arms the number of events seems to decrease. It is noted that this endpoint was not systematically collected and the number of subjects at each time point varied throughout the study duration. With regard to subjects permanently stopping all ITP medications without receiving rescue, better results were seen for non-splenectomized than splenectomized patients (38% [18/47] of the non-splenectomized patients who were taking ITP medication at baseline, 20%]11/54] of the splenectomised patients). The results of the proportion of patients that permanently interrupted treatment with eltrombopag show similar results in non-splenectomized (4% [8/187]) and splenectomized patients (6% [7/115]). These 15 subjects maintained platelet counts ≥50 Gi/L for a range of 5 months to 2.5 years after interrupting eltrombopag and any other ITP medications. Seven subjects (4%) in EXTEND underwent splenectomy despite treatment with eltrombopag.

Overall, these results support the positive effect of eltrombopag in non-splenectomized patients, which is very much in line with that observed in splenectomised patients.

Splenectomy remains the standard treatment after failure of corticosteroids or IVIg, and offers a curative treatment option in about two thirds of patients. It is associated with few complications due to the use of current laparoscopic procedures.

In the context of available options, Revolade is deemed as a supportive treatment which induces a sustained effect on platelet counts. However, it is recognised that the benefits and risks of splenectomy are well established and, for the time being, it offers the highest rates of cure with durable responses over existing second-line treatment options, even though surgery may not be a suitable and immediate

treatment option in all cases. Thus, the availability of other pharmacological interventions is welcomed. Patients should be clinically evaluated periodically, and continuation of treatment should be decided on an individual basis by the treating physician. In non-splenectomised patients, this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section 4.2 and 4.4 of the SmPC).

Assessment of paediatric data on clinical efficacy

The submitted data obtained in the paediatric population are of little value as supportive evidence of the claimed indication given the different roles of splenectomy in children and adults with cITP.

2.4.4. Conclusions on the clinical efficacy

Eltrombopag has demonstrated efficacy in both splenectomized and non-splenectomized patients in the clinical trials conducted and submitted within the original submission and, as expected, is reconfirmed by the current assessment.

2.5. Clinical safety

Introduction

The safety profile of eltrombopag in the original MAA submission has been evaluated based on data from 26 completed or ongoing clinical studies in 1616 eltrombopag-treated and 247 placebo-treated healthy volunteers and patients with ITP, hepatitis C, or chemotherapy-induced thrombocytopenia. Adverse reactions observed during eltrombopag treatment included headache (13%); nausea, alanine aminotransferase increased and aspartate aminotransferase increased (4%); diarrhoea and fatigue (3%); paraesthesia, constipation, rash, pruritus, blood bilirubin increased, cataract, arthralgia, myalgia and hyperbilirubinaemia (2%), abdominal pain upper, alopecia, dry eye, oedema peripheral, muscle spasm, bone pain, hepatic function abnormal and insomnia (1%). Safety concerns included hepatobiliary laboratory abnormalities, thromboembolic events, post-therapy recurrence of thrombocytopenia, bone marrow reticulin formation and risk of bone marrow fibrosis, haematological malignancies, cataracts, and loss of response to eltrombopag.

Patient exposure

As of 01 February 2010, across the adult ITP clinical development program, 446 subjects were exposed to eltrombopag, of which approximately 60% (273 subjects) were not splenectomised at baseline. The total observation period for the splenectomised group was 216.77 patient-years (PYs) compared to 367.64 PYs for the non-splenectomised group.

In the 6 month pivotal RAISE study, 197 subjects were randomized to receive either placebo (n=62) or eltrombopag 50 mg (n=135). The extent of exposure was summarized by the number of days on treatment and average daily dose. The median number of days on treatment was 183 days for both the placebo and eltrombopag groups, and was similar regardless of splenectomy status at baseline. The median average daily dose for the eltrombopag group was 58.0 mg (range 16, 72); the subjects with prior splenectomy (n=50) had a somewhat higher median average daily dose (64.0 mg, range 16.3, 72.4) than subjects without prior splenectomy (n=85, 52.9 mg, range 21.3, 72.3).

Long-term safety of eltrombopag has been evaluated in the ongoing, long-term extension study, TRA105325/EXTEND. As of 01 February 2010, 299 subjects had been enrolled in EXTEND. The majority of

subjects had baseline platelet counts <30 Gi/L (208 subjects, 70%), were not taking any concomitant ITP medications at baseline (199 subjects, 67%), and were not splenectomised at baseline (184 subjects, 62%). The majority of subjects (210 subjects; 70%) have been exposed to eltrombopag in EXTEND for at least 1 year, and 138 subjects (46%) have been exposed to eltrombopag for at least 2 years (Table 9).

Table 9 Cumulative Exposure to Eltrombopag in EXTEND (Safety Population)

Duration of Exposure, n (%)[a]	Eltrombopag N=299
Missing	1 (<1)[b]
< 6 months	49 (16)
≥ 6 months	249 (83)
≥ 12 months	210 (70)
≥ 18 months	188 (63)
≥ 24 months	138 (46)
≥ 36 months	24 (8)

Data Source: 2010 TRA105325 Table 6.40

a. A window of ± 3 days was applied.
b. One subject (594) had one exposure record with a start date and unknown end date, which excludes them from these calculations. The subject was subsequently withdrawn for non-compliance.

The Applicant provided clarification of the pooled database of all cITP patients in the clinical program. For short-term exposure, the population included patients who had a duration of therapy up to 6 months. Studies TRA100773A (N=118), TRA100773B (N=114), RAISE (N=197), and TRA113765 (N=155) were used for the assessment of the short term safety profile of eltrombopag. These 4 studies are randomized, double-blind, parallel group, and placebo-controlled studies in adult subjects with chronic ITP.

For the medium-term exposure, the population was restricted to patients who had a duration of therapy between 6 months and 2 years. The assessment of the medium-term safety profile of eltrombopag was performed using studies TRA112940 (N=162) and TRA105325/EXTEND (N=299), which were non-randomized, open-label studies with a length of exposure of up to 2 years in the first and more than 2 years for the second study.

The long-term exploration of safety was limited to patients who had more than 2 years of eltrombopag exposure. The long-term analysis of safety was conducted using the EXTEND study, as only the EXTEND study meets the criterion for long term exposure of >2 years.

Adverse events

The overall incidence of on-therapy AEs, SAEs, treatment-related AEs, and AEs leading to withdrawal in pooled data from TRA100773A, TRA100773B and RAISE was similar when comparing the placebo and eltrombopag groups (Table 7). The incidence of events was similar between splenectomised and non-splenectomised subjects.

Table 7 Overall Summary of Subjects with Adverse Events Started On Therapy (Pooled Safety Population)

	Overall		Splenectomised		Non-splenectomised	
	Placebo (N=128)	Eltrombopag (N=299)	Placebo (N=48)	Eltrombopag (N=96)	Placebo (N=80)	Eltrombopag (N=145)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with an AE	88 (69)	209 (70)	36 (75)	94 (77)	52 (65)	115 (65)
Subjects with a SAE	16 (13)	20 (7)	7 (15)	7 (6)	9 (11)	13 (7)
Subjects with a drug-related AE	32 (25)	95 (32)	12 (25)	45 (37)	20 (25)	50 (28)
Subjects with an AE leading to withdrawal	9 (7)	18 (6)	3 (6)	5 (4)	6 (8)	13 (7)

Data Source: TRA_SUBM Table 8.947 and Table 8.948

Common Adverse Events

The AE profile was similar between the non-splenectomised and splenectomised eltrombopag groups. The incidence of each common AE in the non-splenectomised eltrombopag group was the same or less than the splenectomised group receiving eltrombopag, with the exception of urinary tract infection. Urinary tract infection was more common in non-splenectomised subjects than splenectomised subjects in both treatment groups.

Table 8 On-therapy AEs reported by 5% or More of Subjects in Either Treatment Group (Pooled Safety Population)

Preferred Term	Overall		Splenectomised		Non-splenectomised	
	Placebo N=128	Eltrombopag N=299	Placebo N=48	Eltrombopag N=122	Placebo N=80	Eltrombopag N=177
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with Any AE	**88 (69)**	**209 (70)**	**36 (75)**	**94 (77)**	**52 (65)**	**115 (65)**
Headache	30 (23)	60 (20)	14 (29)	31 (25)	16 (20)	29 (16)
Diarrhoea	9 (7)	22 (7)	6 (13)	12 (10)	3 (4)	10 (6)
Nausea	4 (3)	22 (7)	2 (4)	10 (8)	2 (3)	12 (7)
Nasopharyngitis	11 (9)	21 (7)	5 (10)	12 (10)	6 (8)	9 (5)
Fatigue	13 (10)	19 (6)	8 (17)	9 (7)	5 (6)	10 (6)
Upper respiratory tract infection	8 (6)	17 (6)	4 (8)	8 (7)	4 (5)	9 (5)
Vomiting	1 (<1)	14 (5)	0	6 (5)	1 (1)	8 (5)
ALT increased	4 (3)	14 (5)	0	6 (5)	4 (5)	8 (5)
Arthralgia	7 (5)	12 (4)	4 (8)	6 (5)	3 (4)	6 (3)
Epistaxis	7 (5)	12 (4)	6 (13)	8 (7)	1 (1)	4 (2)
Pain in extremity	8 (6)	11 (4)	3 (6)	7 (6)	5 (6)	4 (2)
Constipation	7 (5)	11 (4)	2 (4)	7 (6)	5 (6)	4 (2)
Abdominal pain upper	7 (5)	8 (3)	3 (6)	4 (3)	4 (5)	4 (2)
Dizziness	8 (6)	7 (2)	3 (6)	5 (4)	5 (6)	2 (1)
Pruritus	7 (5)	6 (2)	2 (4)	2 (2)	5 (6)	4 (2)
Oedema peripheral	8 (6)	4 (1)	4 (8)	2 (2)	4 (5)	2 (1)
Abdominal distension	6 (5)	3 (1)	4 (8)	2 (2)	2 (3)	1 (<1)

Data Source: TRA_SUBM Table 8.942 and Table 8.946
ALT= Alanine aminotransferase

Serious adverse events / deaths / other significant events

The incidence rate of AEs per 100 subject years across adult ITP studies (TRA100773A, TRA100773B, REPEAT, RAISE, EXTEND, and TRA112940) for splenectomised and nonsplenectomised patients is presented in the table below.

Table 2-10 Incidence Rates per 100 Subject Years for Adverse Events across Adult ITP Studies for Subjects with and without Splenectomy.

Events included	Splenectomised Patients			Non- Splenectomised Patients		
	No. of subjects with first event (N=209)	Total person days exposure	Incidence rate (95% CI) per 100 person years	No. of subjects with first event (N=400)	Total person days exposure	Incidence rate (95% CI) per 100 person years
Drug-Related AEs	106	79, 226	48.87 (40.01, 59.1)	164	197, 132	30.39 (25.91, 35.41)
Serious AEs	71	100, 435	25.87 (19.97, 32.25)	109	262, 944	15.14 (12.43, 18.26)
Drug-Related serious AEs	18	134, 043	4.9 (2.91, 7.75)	33	298, 004	4.04 (2.78, 5.68)
AEs leading to withdrawal	29	133, 377	7.94 (5.32, 11.41)	56	305, 124	6.70 (5.06, 8.71)
Fatal AEs	6	135, 717	1.61 (0.59, 3.51)	6	308, 725	0.71 (0.26, 1.55)

Data Source: Table 8.610; Table 8.611

Table 2-11 Deaths Across Adult ITP Studies

Study	Subject ID	Time of Death	Primary Cause of Death
Non-Splenectomised			
TRA100773A	144	26 days	Cardiopulmonary failure
REPEAT	711	6 and one-half months post-therapy	Pancreatic carcinoma
EXTEND	1272	42 days post-therapy	multi-organ failure secondary to sepsis of pulmonary origin
TRA112940	351	8 days post therapy	Road traffic accident
TRA112940	383	267 days	Cerebral haemorrhage
TRA112940	385	31 days	Cerebral haemorrhage
Splenectomised			
EXTEND	122	86 days	Road traffic accident
EXTEND	127	540 days	Sudden death (definitive cause of death unknown)
EXTEND	1051	55 days post-therapy	Anemia and Hypovolemic shock
EXTEND	1064	107 days post-therapy	Intraventricular haemorrhage
EXTEND	1168	306 days	Adenocarcinoma
TRA112940	403	467 days	Acute respiratory distress syndrome

Other significant events

Long-Term Safety in Adult Chronic ITP

Long-term safety of eltrombopag has been evaluated in the ongoing, long-term extension study, TRA105325/EXTEND. As of 01 February 2010, 299 subjects had been enrolled in EXTEND.

Bone Marrow Reticulin Formation and Fibrosis

The risk of bone marrow reticulin formation and fibrosis was assessed in the TRA105325/EXTEND study as a postmarketing requirement in the US and a risk management plan commitment in the EU. The following is a summary of the findings in bone marrow biopsy reports received as of 23 March 2010.

The table 10 shows the summary of the maximum reticulin grade at different on-treatment time intervals, based on each subject's first exposure to eltrombopag in any study. As of 23 March 2010, 223 on-treatment bone marrow biopsy results were available from 171 subjects; 204 biopsies from 159 subjects were stained for reticulin and graded using the European (EU) Consensus scale (MF) and constitute the basis for the analysis herein presented.

Table 10 Maximum MF[a] Grade at Each On-treatment Time Interval (Safety Population[b])

On Treatment Assessment interval	Pre-12 month (<10 months) n=13	12 month (10 - <22 months) n=144	24 month (22 - <34 months) n=38	36 month (34 - <46 months) n=7
MF Grade 0, n (%)	10 (77)	92 (64)	31 (81)	6 (86)
MF Grade 1, n (%)	3(23)	40 (28)	6 (16)	1 (14)
Collagen reported, n		1		
MF Grade 2, n (%)	0	12[c] (8)	1[c] (3)	0
Collagen reported, n	0	3	0	0
MF Grade 3, n (%)	0	0	0	0

Data Source: 2010 TRA105325 Table 8.149

a. European Consensus Scale, MF. MF-0: Scattered linear reticulin with no intersections corresponding to normal bone marrow; MF-1: Loose network of reticulin with many intersections, especially in perivascular areas; MF-2: Diffuse and dense increase in reticulin with extensive intersections, occasionally only focal bundles of collagen and/or focal osteosclerosis; MF-3: Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

b. A subject may have had more than 1 biopsy during a time-interval, only the maximum MF grade is included. A subject will be counted in more than 1 time interval when a bone marrow biopsy was done during each interval.

c. The findings for 2 subjects (Subjects 508 and 509) were considered staining artifacts by the central pathologist, who after re-processing the biopsies graded the samples as MF-0.

Shifts in Reticulin Grade from First Assessment

In an additional analysis, shifts in MF grade between the first on-treatment bone marrow biopsy in EXTEND and the second on-treatment biopsy were evaluated for the 42 subjects with 2 biopsies performed.

Less than 10 months between first and second bone marrow assessments (n=3):

- 1 subject had MF-0 on both assessments.

- 1 subject shifted from MF-0 to MF-1

- 1 subject shifted from MF-1 to MF-0

10 to <22 months between first and second bone marrow assessments (n=38 [1 missing sample]):

- 24 subjects had MF-0 on both assessments.

- 3 subjects shifted from MF-0 to MF-1

- 3 subjects had MF-1 on both assessments.

- 6 subjects shifted from MF-1 to MF-0

- 1 subject shifted from MF-2 to MF-0

22 to <34 months between first and second bone marrow assessments (n=2):

- 1 subject shifted from MF-0 to MF-2

- 1 subject shifted from MF-1 to MF-0

A total of 5 subjects had a shift to a higher MF score over the observation period and a total of 9 subjects had a shift to a lower MF score over the observation period. Overall, no pattern of increased reticulin deposition after a longer treatment period was apparent in these subjects.

Three subjects interrupted treatment with eltrombopag due to bone marrow findings. One subject had collagen fibers reported and the investigator withdrew him pre-emptively.

The second subject had a report of moderate increase in collagen and a loss of response concomitant to starting a calcium supplement; she experienced a gastrointestinal haemorrhage due to a duodenal arteriovenous fistula and the investigator decided to withdraw her from the trial. Both of these subjects had reticulin documented in bone marrow biopsies taken before exposure to eltrombopag. The third subject was found to have an MF-1 in the routine bone marrow biopsy after a year of treatment, and the investigator chose to withdraw her pre-emptively.

Hepatobiliary Events

Many medications have the potential to induce liver injury, which can range from a transient, self-limited increase in aminotransferases to a severe liver injury and liver failure. Hepatotoxicity was assessed because of evidence of liver toxicity in non-clinical studies. There were no direct hepatobiliary-related deaths and no lasting clinical sequelae. The majority of events resolved prior to the clinical cut-off date in most cases despite continuation of treatment. Indirect bilirubin increases were found in several patients, most likely due to inhibition of the OATP1B1 transporter. These elevations of indirect bilirubin are considered of little clinical significance.

Table 11 Summary of Subjects with Hepatobiliary Laboratory Abnormalities in EXTEND (Safety Population)

Parameters	Eltrombopag N=299 n (%)
≥3x ULN AT and >1.5x ULN Total Bilirubin	5 (2)
≥20x ULN ALT	0
≥10x ULN ALT	1 (<1)
≥5x ULN ALT	5 (2)
≥3x ULN ALT	11 (4)
>2x ULN Total Bilirubin	5 (2)
>1.5x ULN Total Bilirubin	16 (5)

Data Source: 2010 TRA105325 Table 8.80

ULN = upper limit of normal; AT = aminotransferase (alanine and/or aspartate aminotransferase); ALT = alanine aminotransferase

Thromboembolic Events

As of 01 February 2010, a total of 16 subjects in EXTEND and 20 subjects out of 446 (4.5%) exposed to eltrombopag across the ITP program have experienced thromboembolic events.

Of the 16 subjects in EXTEND, 8 subjects had events that were venous in nature, 6 subjects had arterial events, and 2 subjects had both. The incidence of thromboembolic events in EXTEND as of this 2010 cut-off date was 3.14/100 PY (95% CI [1.92, 4.85]); this is consistent with published literature for patients with chronic ITP.

Table 8.600
Incidence Rates Per 100 Person Years for Thromboembolic Events Across 773A, 773B, REPEAT, RAISE and EXTEND (Subjects Exposed to Eltrombopag)

	Events Included	No. of subjects with at least one event	Total person days exposure	Incidence rate (with 95% CI) per 100 person years
Total exposure	DVT, PE, TIA, MI, IS	20	232,487	3.14 (1.92, 4.85)
	TIA, MI, IS	8	233,511	1.25 (0.54, 2.47)
	DVT, PE	14	234,646	2.18 (1.19, 3.66)
	DVT	10	235,187	1.55 (0.74, 2.86)
	PE	6	235,268	0.93 (0.34, 2.03)
	TIA	2	234,032	0.31 (0.04, 1.13)
	MI	4	234,821	0.62 (0.17, 1.59)
	IS	3	235,714	0.46 (0.10, 1.36)
360 days	DVT, PE, TIA, MI, IS	15	111,472	4.91 (2.75, 8.11)
	TIA, MI, IS	3	112,249	0.98 (0.20, 2.85)
	DVT, PE	12	112,078	3.91 (2.02, 6.83)
	DVT	8	112,408	2.60 (1.12, 5.12)
	PE	6	112,464	1.95 (0.72, 4.24)
	TIA	2	112,282	0.65 (0.08, 2.35)
	MI	0	112,855	N/A
	IS	1	112,822	0.32 (0.01, 1.80)

Note: Total exposure includes number of days on-therapy and up to 6 weeks follow-up for 773A and 773B, plus number of days on-therapy and up to 4 weeks follow-up for EXTEND, REPEAT and RAISE.
For subjects with an event, only time until the start of the first event is included.
For subjects with a fatal AE (other than a TEE) recorded during study treatment, the time until the date of death is included. If the fatal AE occurred during the follow-up period, the time until the last follow-up visit is included or, if there are no follow-up visits the date of last dose of study medication is used.
Incidence Rate per 100 person years=(No. subj. with an event / Total person days exposure) * 365.25 * 100
pmb33162: /arenv/arprod/sb497115/tra_subm/apr10_update/drivers/ae_ir_tee.sas 01JUL2010 14:58

Table 8.600
Incidence Rates Per 100 Person Years for Thromboembolic Events Across 773A, 773B, REPEAT, RAISE and EXTEND (Subjects Exposed to Eltrombopag)

	Events Included	No. of subjects with at least one event	Total person days exposure	Incidence rate (with 95% CI) per 100 person years
180 days	DVT, PE, TIA, MI, IS	9	65,569	5.01 (2.29, 9.52)
	TIA, MI, IS	2	65,824	1.11 (0.13, 4.01)
	DVT, PE	7	65,782	3.89 (1.56, 8.01)
	DVT	4	65,917	2.22 (0.60, 5.67)
	PE	4	65,872	2.22 (0.60, 5.68)
	TIA	2	65,824	1.11 (0.13, 4.01)
	MI	0	66,037	N/A
	IS	0	66,037	N/A

Note: Total exposure includes number of days on-therapy and up to 6 weeks follow-up for 773A and 773B, plus number of days on-therapy and up to 4 weeks follow-up for EXTEND, REPEAT and RAISE.
For subjects with an event, only time until the start of the first event is included.
For subjects with a fatal AE (other than a TEE) recorded during study treatment, the time until the date of death is included. If the fatal AE occurred during the follow-up period, the time until the last follow-up visit is included or, if there are no follow-up visits the date of last dose of study medication is used.
Incidence Rate per 100 person years=(No. subj. with an event / Total person days exposure) * 365.25 * 100
pmb33162: /arenv/arprod/sb497115/tra_subm/apr10_update/drivers/ae_ir_tee.sas 01JUL2010 14:58

Cataracts

Based on sponsor review of the ocular data from EXTEND, a total of 40 subjects had a cataract event during EXTEND. Of these 40 subjects, 15 subjects had progression of preexisting cataracts, 17 subjects had an incident cataract, and 8 subjects had an incident cataract which also progressed during the observation period in EXTEND. These data will be reviewed and adjudicated by the Ocular Clinical Events Committee in the final EXTEND clinical study report.

All 40 subjects with a cataract event had at least 1 risk factor for cataractogenesis reported by the examining ophthalmologist, had documented use of corticosteroids, or were 60 years or older.

Neoplasms

In order to present a causality analysis of all neoplasms occurring after more than 2 years exposure in the cITP indication, data from the EXTEND study was used since the treatment duration for all other global adult cITP studies was 2 years or less. Five SAEs (in 5 patients) and 6 non-serious AEs (in 5 patients) concerned events from the EXTEND study within the MedDRA Neoplasms SOC with an onset after 720 days of eltrombopag treatment. There were 6 non-serious reports (in 5 patients) containing PTs within the Neoplasms SOC.

It is highly unlikely that any of the described SAEs were associated with the study medication

Safety in special populations

Supportive Safety in Paediatric Chronic ITP

There were a total of 174 paediatric subjects enrolled in both studies and 171 subjects received at least 1 dose of eltrombopag at any time during the studies.

In the Safety Population, the median average daily dose of blinded study medication was 47.5 mg in the eltrombopag group. The median average daily dose in each study cohort was as follows: Cohort 1: 53.3 mg; Cohort 2: 50.0 mg; and Cohort 3: 27.1 mg. In the All Eltrombopag Treated Population, the average daily dose was 55.3 mg across all cohorts and the median average daily dose in each cohort was as follows: Cohort 1: 64.0 mg; Cohort 2: 57.6 mg; and Cohort 3: 37.0 mg.

No notable differences in average daily dose were seen in East Asian subjects when compared with non-East Asian subjects, despite the reduced starting doses in East Asian subjects.

Overall, there were 128 (75%) subjects who received $\geq$24 weeks of treatment with eltrombopag.

Adverse Events

The safety profile observed in paediatric subjects with chronic ITP is consistent with what has been reported for eltrombopag in adults with chronic ITP; no new safety signals have been identified in the paediatric ITP population with doses of eltrombopag up to 75 mg.

Overall, the number of subjects in the randomized period (Safety Population) who reported an AE was similar between the treatment groups (82.0% placebo; 81.3% eltrombopag). There were few serious adverse events (SAEs) in either treatment group (12% placebo; 8% eltrombopag) and few AEs that led to discontinuation of study treatment (2% placebo; 3% eltrombopag).

The AEs reported were consistent with the established safety profile of eltrombopag or the population under study. The most common AEs in the eltrombopag group (≥10% of subjects) were headache, upper respiratory tract infection, and nasopharyngitis with the latter 2 being reported in a higher proportion of subjects receiving eltrombopag when compared with the placebo group. The most common AEs reported in the placebo group (≥10% of subjects) were headache, epistaxis, vomiting, nausea, and upper abdominal pain, all of which were reported in a higher proportion of subjects when compared to the eltrombopag group.

In the Safety Population, SAEs were reported more frequently in the placebo group (12%) than in the eltrombopag group (8.4%). With the exception of epistaxis, which was reported in 2 placebo subjects, no SAE was reported by more than 1 subject in either treatment group. In the eltrombopag group, ALT increases and events of neutropenia were the most common SAEs, whereas bleeding events were more common in the placebo group.

In the Safety Population, elevations in ALT ≥3x ULN were more frequent in the eltrombopag group (4.7%) compared with the placebo group (0%). No subject had an elevation of ALT ≥3x ULN in conjunction with total bilirubin elevation ≥1.5x ULN during the Randomised Period. Of the 5 subjects with an elevation of ALT ≥3x ULN in the Randomised Period of PETIT2, 2 subjects (1 White; 1 East Asian) had increases in ALT ≥5x ULN, which met the protocol defined liver chemistry stopping criteria. For both subjects, the events were reported as AEs, and resolved following discontinuation of study treatment.

Detailed ocular assessments were performed throughout the studies and subjects meeting predefined criteria were reviewed by the ocular Clinical Events Committee (CEC). Based on the CEC review, 2 eltrombopag subjects and no placebo subjects had a cataract event. Both subjects had either reported corticosteroid use as a risk factor or were receiving corticosteroids as an ongoing ITP medication. While eltrombopag cannot be excluded as a causative factor in these events, concurrent use of corticosteroids, a known cataractogenic medication, confounds the interpretation of these cases.

No thromboembolic events were reported.

Renal abnormalities were infrequent and were mild and transient. The data do not indicate a relationship between eltrombopag treatment and renal abnormalities. One malignancy event (thyroid papillary carcinoma) was reported 20 months after the discontinuation of eltrombopag treatment. The investigator considered the event unrelated to study treatment. No events indicative of bone marrow fibrosis were reported.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

The incidence of AE leading to withdrawal was higher in splenectomised, see below table.

Table 2-10 Incidence Rates per 100 Subject Years for Adverse Events across Adult ITP Studies for Subjects with and without Splenectomy.

Events included	Splenectomised Patients			Non- Splenectomised Patients		
	No. of subjects with first event (N=209)	Total person days exposure	Incidence rate (95% CI) per 100 person years	No. of subjects with first event (N=400)	Total person days exposure	Incidence rate (95% CI) per 100 person years
Drug-Related AEs	106	79, 226	48.87 (40.01, 59.1)	164	197, 132	30.39 (25.91, 35.41)
Serious AEs	71	100, 435	25.87 (19.97, 32.25)	109	262, 944	15.14 (12.43, 18.26)
Drug-Related serious AEs	18	134, 043	4.9 (2.91, 7.75)	33	298, 004	4.04 (2.78, 5.68)
AEs leading to withdrawal	29	133, 377	7.94 (5.32, 11.41)	56	305, 124	6.70 (5.06, 8.71)
Fatal AEs	6	135, 717	1.61 (0.59, 3.51)	6	308, 725	0.71 (0.26, 1.55)

Data Source: Table 8.610; Table 8.611

Post marketing experience

Based on IMS (Intercontinental Medical Statistics) Health data, the cumulative postmarketing exposure from 08 November 2008 (1st worldwide approval) through 31 December 2013 is estimated to be 28,127 patient-years. This estimate was produced in April 2014 and was based on the latest data available at that time (December 2013).

The most recently received PSUR with regard to Revolade covered the reporting period 01 October 2013 to 30 September 2014. According to the PSUR, an estimated 3,976 subjects in total have been exposed to Revolade in sponsored ongoing and completed interventional studies of which 640 are from completed studies (including the studies presented in this Assessment Report); 648 are from ongoing studies in patients with ITP.

Cumulative post-marketing exposure to Revolade is estimated to be to 35,612 patient years. Revolade is currently approved for the treatment of chronic ITP in over 95 countries worldwide including the United States, EU, and Japan. From the Table 1-4 below, the cumulative patient years of therapy in the US for both 25 mg and 50 mg combined is 8,715 patient years as compared to 6,886 patient years of therapy in EU5. The 16-month lag in approvals between the EU and US would be expected to contribute less utilization in the EU regardless of any indication limitations. From cumulative patient years of therapy it is challenging to separate the differences in cumulative patient years of therapy as due to either launch timings versus indication limitations.

Table 1-4 Total cumulative exposure in patients with chronic ITP in EU and in countries where the authorised indication does not have limitations with regard to non-splenectomised patients

	Top 12 Revolade Markets (Not in any particular order)											
	EU5, Canada, Turkey - Where splenectomy limitation exists							Countries where splenectomy limitation is not in the cITP indication				
1000s of Tabs	Germany	France	UK	Spain	Italy	Canada	Turkey	U.S.A.	Japan	Brazil	Colombia	Russia
12.5mg	-	-	-	-	-	-	-	138	6,409	-	-	-
25mg	543	513	190	293	293	143	138	2,456	652	129	1	25
50mg	587	526	150	269	227	97	187	2,088	-	188	-	52
75mg	24	-	-	-	-	-	-	550	-	-	-	-
Total	1,155	1,039	339	562	520	240	325	5,232	7,061	317	1	77

Promacta/Revolade Est. cITP Patient Years of Therapy, by Strength												
	Top 12 Revolade Markets (Not in any particular order)											
	EU5, Canada, Turkey - Where splenectomy limitation exists							Countries where splenectomy limitation is not in the cITP indication				
Est. Patient Years of Therapy	Germany	France	UK	Spain	Italy	Canada	Turkey	U.S.A.	Japan	Brazil	Colombia	Russia
12.5mg	-	-	-	-	-	-	-	264	12,291	-	-	-
25mg	1,042	984	364	562	562	274	265	4,711	1,251	248	1	48
50mg	1,126	1,009	287	515	435	186	359	4,005	-	360	-	100
75mg	46	-	-	-	-	-	-	1,055	-	-	-	-
Total	2,214	1,993	651	1,077	998	460	624	10,035	13,541	608	1	148

Source: IMS data

Doses of 12.5 mg daily to 75 mg daily are approved for treatment of chronic ITP worldwide. Revolade is also currently approved for treatment of adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia in order to maintain optimal interferon-based therapy in over 45 countries worldwide including the United States and all European Union Member States at doses of 25 mg daily to 100 mg daily. Revolade is also currently approved for the treatment of severe aplastic anaemia in the United States at doses of 25 mg daily to 150 mg daily.

Hepatotoxicity

In the EU PSUR 6, a cumulative review of hepatotoxicity was conducted by searching the GSK global safety database (OCEANS) to identify eltrombopag post-marketing and spontaneous cases with preferred terms (PTs) in the drug-related hepatic disorders – a comprehensive search SMQ received cumulatively through 31 August 2013. A total of 352 cases reporting 552 hepatic events were identified and reviewed. In 212 cases (60.2%) the hepatic events were serious and in 140 cases the hepatic events were nonserious.

Relevant laboratory data were provided in 223 of the 352 cases. Of these, 60 reported ALT or AST levels ≥5x ULN. In 38 of these 60 cases, the events resolved or improved, including 32 cases demonstrating a positive de-challenge. In 32 of these 60 cases, the reporter considered the events related to eltrombopag. In 15 cases, the events were considered unrelated and no causality assessment was reported in 13 cases. In summary, the identified reports generally describe mild and transient elevations in LFTs, which resolve upon eltrombopag discontinuation. However, several reports of hepatic failure and severe hepatic injury, some of which required liver transplantation or resulted in death, were identified. Many of these reports describe liver failure or severe liver injury in patients receiving eltrombopag for thrombocytopenia associated with preexisting chronic liver disease.

This review did not identify any new trends or changes compared with previous analyses of hepatotoxicity. The data was consistent with the known safety profile of eltrombopag.

In addition, during the 5-year renewal period, a review of cases of hepatotoxicity received between 01 September 2013 and 11 March 2014 was consistent with the known safety profile of eltrombopag.

The risk of hepatotoxicity is described in the Warnings and Precautions section of the eltrombopag reference safety information (RSI).

Thromboembolic Events

In March 2011, a search of the GSK global safety database was performed for cases with eltrombopag as the suspect drug and the MedDRA version 13.1 SMQ for embolic and thrombotic events. One hundred forty-six (146) reports were retrieved and reviewed that had at least one event within this MedDRA SMQ. The review focused on thromboembolic events (TEEs) and was reported in detail in PSUR-2 (01 October 2010 to 31 March 2011). No new trends or changes in incidence or severity of TEEs emerged based on the analysis of those 146 reports. No specific risk factors were identified that allow a differentiation between those subjects with ITP who experienced a TEE and those who did not.

Subsequent reviews of thromboembolic events were conducted in PSURs 3, 4, and 5 and PBRER-1/EU PSUR-6. These reviews did not identify any new trends or changes the safety profile of eltrombopag. The benefit/risk profile of eltrombopag for the treatment of previously treated patients with chronic ITP to increase platelet counts and reduce or prevent bleeding continued to be favourable.

In addition, during the 5-year renewal period, a review of cases of TEEs received between 01 September 2013 and 11 March 2014 was consistent with the known safety profile of eltrombopag. The risk of TEEs is described in the Warnings and Precautions section of the eltrombopag RSI.

Cataract

Cataract is considered an important identified risk, which has been closely monitored. Post-marketing and spontaneous reports were retrieved from the GSK worldwide safety database (OCEANS) with eltrombopag as the suspect drug and MedDRA SMQ lens disorder. From spontaneous sources, there were 13 reports and 20 adverse events received from spontaneous sources related to eye disorders with preferred terms of cataract (3), visual acuity reduced (2), visual impairment (6), and vision blurred (7) from SMQ lens disorder, and preferred terms of blindness and vitreous floaters (1 each) were also reported in these cases. The majority of these 17 post-marketing and spontaneous cases presented patients with specific

information regarding blurred vision or vision impairment. In cases where cataract or visual acuity was specifically reported, limited information was provided. Overall, the reports from spontaneous and post marketing sources provide limited information on the potential risk of cataract.

Period reviews of cataract were conducted in PSURs 1, 3, 4, and 5, and PBRER/EU PSUR-6. These reviews have not identified any new trends or changes in the safety profile of eltrombopag.

During the 5-year renewal period, a review of cases of cataract received between 01 September 2013 and 11 March 2014 was consistent with the known safety profile of eltrombopag. The risk of cataract is described in the Warnings and Precautions section of the eltrombopag RSI.

Important Potential Risks; Potential for Increased Bone Marrow Reticulin Formation,

Reviews of bone marrow reticulin fibrosis were conducted in PSURs 1, 2, 3, 4 and 5. In PBRER/EU PSUR 6, a cumulative review of bone marrow reticulin fibrosis was conducted by searching the GSK global safety database (OCEANS) to identify eltrombopag cases with PTs in the haematopoietic cytopenias affecting more than one type of blood cell SMQ, the malignancy-related conditions SMQ, and the blood premalignant disorders SMQ received through 31 August 2013. A total of 48 cases were identified that described possible bone marrow reticulin fibrosis. In 21 of the 48 cases, information on the Bauermeister grade of the bone marrow was provided. For the majority of cases in which the information was available (21 cases), bone marrow reticulin fibrosis was Bauermeister Grade 1 (13 cases). In the remaining cases, limited information on the degree of bone marrow fibrosis was provided. Furthermore, in most reports, the degree of bone marrow reticulin fibrosis at baseline was not provided. Finally, other cases were complicated by concurrent medical conditions including myelodysplastic syndrome, AML, chronic lymphocytic leukemia, multiple myeloma, and unspecified malignancy.

During the 5-year renewal period, a review of cases of bone marrow reticulin formation and bone marrow fibrosis received between 01 September 2013 and 11 March 2014 was consistent with the known safety profile of eltrombopag. The potential for bone marrow reticulin formation and bone marrow fibrosis is described in the Warnings and Precautions section of the eltrombopag RSI.

Haematological Malignancies

Cumulative reviews of haematological malignancies were conducted in PSURs 2 and 3. The review in PSUR 3 identified a total of 126 cases of haematological malignancies. Of these 126 cases, 112 were found to contain insufficient information for assessment, describe patients with pre-existing haematological malignancy, or were unlikely to be caused by eltrombopag based on timing of the event relative to treatment.

This review concluded that no safety signal with regard to haematological malignancy was identified based on nonclinical and clinical experience with eltrombopag.

Subsequent reviews of haematological malignancies were conducted in PSURs 4, 5 and PBRER/PSUR 6. These reviews did not identify any new trends or changes the safety profile of eltrombopag.

In addition, a review of cases of haematological malignancies received between 01 September 2013 and 11 March 2014 was consistent with the known safety profile of eltrombopag. The risk of haematological malignancies is described in the Warnings and Precautions section of the eltrombopag RSI.

2.5.1. Discussion on clinical safety

The safety profile of eltrombopag in the original MAA submission has been evaluated based on data from 26 completed or ongoing clinical studies in 1616 eltrombopag-treated and 247 placebo-treated healthy

volunteers and patients with ITP, hepatitis C, or chemotherapy-induced thrombocytopenia. The doses of eltrombopag used in these studies ranged from 3 mg to 200 mg. The duration of treatment with eltrombopag ranged from 1 day in healthy volunteers up to 560 days in subjects with chronic ITP.

Adverse reactions observed during eltrombopag treatment included headache (13%); nausea, alanine aminotransferase increased and aspartate aminotransferase increased (4%); diarrhoea and fatigue (3%); paraesthesia, constipation, rash, pruritus, blood bilirubin increased, cataract, arthralgia, myalgia and hyperbilirubinaemia (2%), abdominal pain upper, alopecia, dry eye, oedema peripheral, muscle spasm, bone pain, hepatic function abnormal and insomnia (1%).

Safety concerns included hepatobiliary laboratory abnormalities, thromboembolic events, post-therapy recurrence of thrombocytopenia, bone marrow reticulin formation and risk of bone marrow fibrosis, haematological malignancies, cataracts and loss of response to eltrombopag.

Eltrombopag administration can cause abnormal liver function. In clinical studies with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were observed. Findings were mostly mild (Grade 1-2), reversible, and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality.

Among 446 adult chronic ITP patients receiving eltrombopag, 20 subjects experienced thromboembolic events, which included deep vein thrombosis, pulmonary embolism, acute myocardial infarction, cerebral infarction, embolism, transient ischaemic attack, and suspected PRIND (prolonged reversible ischemic neurologic deficiency). The risk of thromboembolic events has been found to be increased in patients with chronic liver disease treated with eltrombopag. These findings have been considered unlikely to be relevant to the ITP patient population (conclusion supported by an *ad hoc* expert group).

The induction of reticulin formation and the potential development of bone marrow fibrosis is a serious safety concern. There are limited data suggesting that eltrombopag is associated with reticulin formation in the bone marrow (collagen formation in 2 cases); however, whether this is a finding likely to have clinical consequences on the long term is still uncertain. In addition, for Mpl ligands such as eltrombopag, there is a theoretical concern that they may stimulate the growth of haematopoietic malignancies or increase progression of MDS to acute myelogenous leukaemia (AML).

The Applicant has now characterized the safety profile of eltrombopag from the MA up to 11-March-2014; including data from the main studies in the adult population, data from the long-term safety study (TRA105325/EXTEND) in adults, the results of the paediatric population, and the post-marketing experience has been submitted in a brief synopsis.

As of 01 February 2010, across the adult ITP clinical development program, 446 subjects were exposed to eltrombopag, of which approximately 60% (273 subjects) were non splenectomised at baseline. Of them, a total 428 patients were included in the main clinical studies TRA100773A, TRA1007773B, and RAISE. The occurrence of adverse events is higher in splenectomized than non-splenectomized patients (77% vs 65%) and the same occur with regard to drug-related adverse events (37% vs 28%). This might well be explained by the more advanced disease status of splenectomized patients, but there is not data to confirm it. With regard to SAEs and AEs leading to discontinuation, the percentages do not seem remarkably different.

No major differences were observed in the safety profile between splenectomised and non-splenectomised subjects. A comparative exercise between non-splenectomised and splenectomised patients reveals a safety profile similar in both groups although the incidence of serious AEs appears higher in splenectomized (25.87 [19.97, 32.25]) than in non-splenectomized (15.14 [12.43,18.26])

patients. This is not unexpected given the more advanced and potentially severe disease status of patients undergoing surgery.

Results from the EXTEND study on the proportion of patients that permanently interrupted treatment with eltrombopag show similar results in non-splenectomized (4% [8/187]) and splenectomized patients (6% [7/115]). These 15 subjects maintained platelet counts ≥50 Gi/L for a range of 5 months to 2.5 years after interrupting eltrombopag and any other ITP medications. Seven subjects (4%) in EXTEND underwent splenectomy despite treatment with eltrombopag

The Applicant has provided an adequate overview of the safety profile with regard to the temporality of the adverse events, those associated with the tolerance and resolve while the therapy continues and which are more specific to long term use. All this information as already reflected in the SmPC, and does not require any further changes whether or not there was a broader use in the non-splenectomised population. In order to provide awareness to the physician that clinical decisions on treatment should be put in the context of safety in the long term, a statement is now included in the SmPC to point out that clinical studies comparing eltrombopag to other treatment options (e.g. splenectomy) have not been conducted. The long-term safety of eltrombopag should be considered prior to starting therapy.

The experience from 28,000 patients-years of exposure in the world-wide post marketing setting has not raised any new safety finding and corroborates the profile described in the SmPC. The splenectomy status is unknown for these patients, but keeping in mind that in many regions the approved label does not limit its use to splenectomised patients, both should be represented to an extent. A review of the cumulative events in patients who were splenectomized after eltrombopag initiation did not reveal a change in the pattern of the events. The majority of the most frequently reported events in patients who were splenectomized after eltrombopag initiation were listed as per the SmPC, and the instructions on use of product and monitoring of platelet counts has been adequately described in the SmPC.

All experience accumulated confirms the important identified risks of hepatotoxicity, thromboembolic events, and the potential risks of bone marrow reticulin formation and haematological malignancies.

Assessment of paediatric data on clinical safety

The safety profile observed in children, who were predominantly non-splenectomised, is not considered as relevant to the adult population, which is the objective of this variation procedure. These data are under evaluation in a parallel procedure (EMEA/H/C/1110/X/22/G).

2.5.2. Conclusions on clinical safety

The safety profile of eltrombopag in cITP patients is well characterized. In general, eltrombopag is well tolerated and most common toxicities are predictable. A priori, no major differences would be expected between splenectomised and non-splenectomised patients. Long-term safety, in particular bone marrow and haematological effects, remains of concern and will continue to be monitored through the PSURs and the RMP.

In the SmPC, it is stated that clinical studies comparing eltrombopag to other treatment options (e.g. splenectomy) have not been conducted. The long-term safety of eltrombopag should be considered prior to starting therapy.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list, which remains unchanged.

2.6. Risk management plan

The CHMP agreed with the MAH that no RMP update is needed. The safety profile of patients treated with eltrombopag does not appear to differ based on splenectomy status, providing physicians with more options for treatment. Also the benefit risk remains positive and the indication remains second line for patients refractory to other treatments. Latest updated RMP includes information on all the clinical studies used to support this change to the indication and therefore has not been updated for this submission.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2 and 5.1 of the SmPC have been updated.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Eltrombopag was approved for the treatment of chronic ITP in adult patients based upon study results from 3 randomized, double-blind, placebo-controlled trials. These data demonstrated that eltrombopag treatment resulted in a significant elevation of platelet counts to safe levels up to 6 month treatment period in chronic ITP, in both splenectomised (116, 35 in placebo) and non-splenectomised patients (195, 65 in placebo). The results from these studies show the superiority of eltrombopag compared to placebo to increase the platelet count $\geq 50 \times 10^9$ /L and achieve a odds (95%IC) of response statistically superior either in splenectomized (6.02 (1.89,19.62) in RAISE study and 9.63 (1.72,53.76) in TRA100773B study) and non-splenectomized patients (9.41 (4.51,19.62) in RAISE study and 12.00(2.80, 51.46) in TRA 100773B study) , indeed the magnitude of the effect is greater in non-splenectomized patients.

Data from the EXTEND study, in which the 62% of the population enrolled were non-splenectomized patients, confirm efficacy, with 48% of non-splenectomized patients and the 31% of splenectomized patients showing platelet counts $\geq$50 Gi/L for >75% of the assessment and 67% of non-splenectomised and 51% of splenectomised patients showing platelet counts $\geq$ 50Gi/L for >50% of assessments.

Uncertainty in the knowledge about the beneficial effects

There are no new uncertainties about the beneficial effects.

Risks

Unfavourable effects

As of 01 February 2010, across the adult ITP clinical development program, 446 subjects were exposed to eltrombopag, of which approximately 60% (273 subjects) were not splenectomised at baseline. The occurrence of adverse events was higher in splenectomized patients than non-splenectomized (77% vs

65%) and the same occur with regard to drug related adverse events (37% vs 28%). With regard to SAE and AE leading to discontinuation the percentages do not seem remarkably different.

Similar safety profiles were seen for non-splenectomized and splenectomized patients, with the exception of urinary tract infections that were more common in non-splenectomized subjects. A review of the cumulative events in patients who were splenectomized after eltrombopag initiation did not reveal a change in the pattern of the events, the majority of the most frequently reported events in patients who were splenectomized after eltrombopag initiation were listed as per the SmPC and the instructions on use of product and monitoring of the platelet counts has been adequately described in the SmPC.

No new risks were identified; main safety concerns in the adult population remain and include: hepatotoxicity, thromboembolic events, hepatic decompensation, and post therapy reocurrence of thrombocytopenia. Appropriate risk minimization measures are addressed in the SmPC and RMP.

Uncertainty in the knowledge about the unfavourable effects

There are still uncertainties in relation to hepatotoxicity, potential haematological changes (leukocytosis and anaemia, cases of thrombocytosis), recurrence of thrombocytopenia, malignancies (haematological) and renal tubular toxicity/renal failure. These uncertainties encompass to non-splenectomised and splenectomised patients. Appropriate risk minimization measures are already addressed in the SmPC and RMP.

No new uncertainties have been identified, long term safety remains of concern and appropriate statements on the context of other treatment options are included in the SmPC.

Effects Table

Table 1. Effects Table for Revolade (1-02-2010)

Effect	Short Description	Unit	Treatment	Control Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Subjects Responders	Dose responses relationship 30mg 50mg 75mg	%	Splenectomized: 21,53,70 Non-splenectomized: 33,92, 88	Splenectomized:14 Non-splenectomized: 8		TRA100773A
Subjects responders		%	Splenectomized: 62 Non-splenectomized: 57	Splenectomized:15 Non-splenectomized:17	Splenectomised OR (95%IC): 9.3(1.72,53.76) Non-splenectomized OR(95%IC) 12.00(2.80,51.46)	TRA100773B
Subjects responders	OR (95%IC)				Splenectomised OR (95%IC): 6.02 (1.89,19.62) Non-splenectomized OR(95%IC) 9.41 (4.51,19.62)	RAISE
Subjects responders	Only 9 patients had prior	%	Splenectomized: 78	Splenectomized:N/A		Pooled paediatric Data

Effect	Short Description	Unit	Treatment	Control Placebo	Uncertainties / Strength of evidence	References
	splenectomy, all of them treated with eltrombopag		Non-splenectomized: 61	Non-splenectomized:24		(TRA108062/PETIT+PETIT2)
Unfavourable Effects						
AE		%	Splenectomized:77 Non-splenectomized:65	Splenectomized:75 Non-splenectomized:65		Pooled[1]
SAE			Splenectomized:6 Non-splenectomized:7	Splenectomized:15 Non-splenectomized:11		Pooled[1]
Drug-related AE			Splenectomized:37 Non-splenectomized:28	Splenectomized:25 Non-splenectomized:25		Pooled[1]
AE leading to withdrawal			Splenectomized:4 Non-splenectomized:7	Splenectomized:6 Non-splenectomized:8		Pooled[1]
TEE		Adjusted event (100P-Y) (95%IC)			3.14(1.92,4.95)	Reference[2]
Cataract		Number of casees			40	Extend (cut off 1-2-2010)
Hepatobiliary		%			2	Extend (cut off 1-2-2010)
Reticulin Formation and fibrosis	12 months				MF grade 0: 64 MF grade 1: 28 MF grade 2: 8 MF grade 3: 0	Extend (cut off 1-2-2010)
Reticulin Formation and fibrosis	36 months	%			MF grade 0: 86 MF grade 1: 14 MF grade 2: 0 MF grade 3: 0	Extend (cut off 1-2-2010)

Pooled[1]: TRA100773A, TRA100773B and RAISE

Reference[2]: EXTEND study (cut off 1-2-2010) and ITP program

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The short-term benefits of eltrombopag in terms of platelet count increments above the level of bleeding risk was initially demonstrated and replicated in two phase 3 randomized clinical trials which included both splenectomized and non-splenectomized subjects with cITP. Additional long-term analysis from the EXTEND Study show that the effect tend to be maintained in the long run, with a trend for a reduction of bleeding events, as well as reduction or discontinuation of concomitant ITP medication (mainly corticosteroid). However, remission is not to be expected in relation to eltrombopag treatment, thus Revolade should be considered a supportive treatment option and its long term use should be weighed against the option of splenectomy.

The main safety concerns, potential and identified, include hepatotoxicity, cataracts, potential haematological changes (leukocytosis and anaemia, cases of thrombocytosis), recurrence of thrombocytopenia, malignancies (haematological) and renal tubular toxicity/renal failure, increased reticulin formation and bone marrow fibrosis.

In the context of limited treatment options, benefits of the treatment are considered to overweigh the risks for patients with cITP.

Benefit-risk balance

The benefit / risk balance in the indication: *"Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). (See Section 4.2 and 5.1)* is positive

Discussion on the Benefit-Risk Balance

Eltrombopag has demonstrated to increase platelet counts above a level which reduces the risk of bleeding events in up to 60% of subjects. Responses were seen in splenectomised and non-splenectomized patients, although responses tend to be lower in splenectomised patients likely due to the more advanced status of the disease. The effect is considered clinically relevant, substantiated by an apparent favourable effect observed in the overall incidence of bleeding events. However, contrary to other treatment options available, eltrombopag does not interfere with the underlying pathophysiological autoimmune disorder of the condition, but rather stimulates platelet production with the aim to compensate peripheral platelet destruction. Thus, remission is unlikely during eltrombopag treatment. Although well tolerated, eltrombopag may be associated with the risk of thromboembolic complications, bone marrow fibrosis and progression to haematological malignancies.

Splenectomy remains as the standard second-line treatment for adults with ITP, given that it provides the highest overall success rate, with approximately two thirds of patients remaining in clinical remission 5-10 years after splenectomy. Laparoscopic surgery has sought to use minimally invasive techniques to reduce postoperative pain, reduce the duration of hospitalization, minimize complications and increase speed of recovery.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to extend the use of Revolade to non-splenectomized patients; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

This variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to extend the use of Revolade to non-splenectomized patients; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

Summary

Please refer to the Scientific Discussion Revolade-H-C-1110-II-23.