28 January 2016
EMA/CHMP/722220/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revolade

International non-proprietary name: eltrombopag / eltrombopag olamine

Procedure No. EMEA/H/C/001110/X/0022/G

Note

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

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Administrative information

Name of the medicinal product:	Revolade
Applicant:	Novartis Europharm Ltd Frimley Business Park Camberley GU16 7SR UNITED KINGDOM
Active substance:	eltrombopag / eltrombopag olamine
International Nonproprietary Name/Common Name:	eltrombopag / eltrombopag olamine
Pharmaco-therapeutic group (ATC Code):	vitamin k and other hemostatics, other systemic hemostatics (B02BX05)
Therapeutic indication(s):	Revolade is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1). Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1). Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for

	haematopoietic stem cell transplantation (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet, powder for oral suspension
Strength(s):	12.5 mg, 25 mg, 50 mg, 75 mg and 25 mg
Route(s) of administration:	Oral use
Packaging:	blister (PA/alu/PVC/alu), sachet (PET/OPA/alu/LDPE)
Package size(s):	14 tablets, 28 tablets and 84 (3 x 28) tablets (multipack), 30 sachets + 1 mixing bottle + 1 oral syringe + 1 screw cap with syringe-port capability

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List of abbreviations

AAG	α1-acid glycoprotein
API	Active pharmaceutical ingredient
BCRP	Breast cancer resistance protein
BDL	Below the limit of detection
CoA	Certificate of analysis
CYP	Cytochrome P450
DL	Detection limit
DSC	Differential scanning calorimetry
EP	European Pharmacopoeia
FMEA	Failure mode and effects analysis
GC	Gas chromatography
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HPLC	HIGH PERFORMANCE LIQUID CHROMATOGRAPHY
HSA	Human serum albumin
ICH	INTERNATIONAL CONFERENCE ON HARMONISATION
IPC	IN-PROCESS CONTROL TEST
IR	INFRA-RED
IRF-1	Interferon regulatory factor-1
ITP	Idiopathic thrombocytopenic purpura
LoD	LIMIT OF DETECTION
LOEL	Lowest observed effect level
LoQ	Limit of quantitation
NIR	Near infra - red
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OATP1B1	Organic anion transporting polypeptide 1B1
PfOS	Powder for Oral Suspension
Pgp	P-glycoprotein

pp	Post-partum
STAT	Signal transducer and activator of transcription
TPO	Thrombopoietin
TPO-R	Thrombopoietin receptor
UGT	Uridine diphosphate glucuronosyltransferase
US	United States
UVR	Ultraviolet radiation
XRPD	X-Ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The Marketing Authorisation Holder, Novartis Europharm Limited, (MAH) submitted to the European Medicines Agency (EMA) on 5 February 2015 an application for a group of variations in accordance with Article 7(2) of Commission Regulation (EC) No 1234/2008, consisting of an extension of the marketing authorisation and a Type II C.1.6a variation for Revolade.

The MAH applied for a group including:

- an extension of indication for paediatric (age 1 year and above) chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who had an insufficient response to other treatments (e.g. corticosteroids, immunoglobulins);

- an extension of the marketing authorisation to include new tablet strength (12.5mg) and a new powder for oral suspension formulation (25mg).

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2 c and d) thereof – Extension of marketing authorisation.

Article 10 of Commission Regulation (EC) No 1234/2008 – "Prior Approval" procedure for major variation of type II.

Article 7(2) of Commission Regulation (EC) No 1234/2008 - Grouping of variations.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies or bibliographic literature substituting/supporting certain tests or studies.

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/0307/2012 was completed.

The PDCO issued an opinion on compliance for the PIP P/0307/2012.

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 applicant submitted a critical report addressing the possible similarity with authorised orphan

medicinal products.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 23 March 2006, 12 January 2007, 15 November 2007 and 21 July 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

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

- The application was received by the EMA on 5 February 2015.
- The procedure started on 26 February 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 25 May 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2015.
- PRAC assessment overview, adopted by PRAC on 11 June 2015.
- During the meeting on 25 June 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 June 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 September 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 20 October 2015.
- During the meeting on 19 November 2015, the CHMP agreed on the consolidated List of Outstanding Issues to be sent to the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 19 November 2015.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 December 2015.
- PRAC assessment overview, adopted by PRAC on 14 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 13 January 2016.
- During the meeting on 28 January 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Revolade.
- The CHMP adopted a report on similarity of Revolade (eltrombopag) with Nplate (romiplostim) on 25 June 2015.

2. Scientific discussion

2.1. Introduction

Immune (idiopathic) thrombocytopenic purpura (ITP) is a disease characterized by an isolated low platelet count (<100 Gi/L) and the absence of underlying causes of thrombocytopenia. It is the result of accelerated platelet destruction by the reticuloendothelial system, coupled with impairment of platelet production and can be classified into: newly diagnosed, persistent (3-12 months' duration) and chronic (more than 12 months' duration). In contrast to adults, ITP in children is most often acute, following a viral illness or immunization, and the disorder usually resolves within 6 months. However, in approximately 15% to 30% of children with acute ITP the disorder becomes chronic. Disease management in patients with chronic ITP is based primarily on platelet count and severity or risk of bleeding. Persistently low platelet counts of <30 Gi/L are associated with increased bleeding, such as bruising, mucosal bleeding and intra-cranial hemorrhage. While most children with chronic ITP experience only mild bleeding in the form of bruising and petechiae, the risk of severe haemorrhage is related to the duration of marked thrombocytopenia.

According to the EMA guideline on Clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia (EMA/CHMP/153191/2013) focus on the platelet count as the key parameter to assess the bleeding risk in patients with ITP. In general, medical treatment to elevate platelet counts is recommended if a patient's platelet counts are below 30 Gi/L. Although the primary goal of treatment in chronic ITP is to maintain a safe platelet count that prevents bleeding, it is also important to note that low platelet counts have a detrimental effect on quality of life. Patients with chronic ITP report anxiety with low platelet counts, suffer frustration due to activity restrictions, and experience activity limiting fatigue. Treatment guidelines therefore recommend consideration of psychosocial and lifestyle issues, in addition to bleeding symptoms and platelet count, in making treatment decisions.

Treatment of chronic ITP in children varies widely and no single universally recognized standard of care exists; guidelines base treatment recommendations on the results of a limited number of small, primarily single-arm studies. Recent guidelines from the American Society for Hematology and an international consensus report recommend a single dose of IVIg or a short course of corticosteroids for the initial pharmacological management of paediatric ITP. The guidelines also suggest the use of a single dose of anti-D in the treatment of Rh-positive, non-splenectomised children who require treatment. When ITP becomes a chronic disease with persistently low platelet counts, treatment with corticosteroids, IVIg, or anti-D, or other previously successful treatments may be continued in these patients. Response may be limited or transient, however, and repeated treatment with these agents may be expected to increase the risk of adverse events (AEs). For children who are unresponsive to initial ITP treatment and/or who have persistent or chronic ITP, several small single-arm clinical studies have demonstrated the efficacy of rituximab in raising platelet counts, although it is not licensed for use in paediatric patients with ITP. Alternatively, high dose dexamethasone is recommended for treatment of children who have persistent or chronic ITP, also based on limited number of small single-arm studies. Treatment guidelines recommend consideration of splenectomy in certain situations to treat paediatric chronic ITP. However, the potentially serious complications (e.g., serious infection) are acknowledged and therefore a delay of at least 12 months from initial ITP diagnosis is suggested, depending on the severity of the disease and other quality of life considerations. According to international guidelines, 60% to 70% of paediatric subjects may be expected to have a long-term platelet response life-long risk of sepsis. Unfortunately, for some paediatric patients with chronic ITP, existing

therapies are ineffective in maintaining platelet counts in a safe haemostatic range, or AEs associated with commonly prescribed therapies prevent their long term use.

Thrombopoietin (TPO) is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous TPO, inducing proliferation and differentiation from bone marrow progenitor cells.

At the time of the MAA submission, GlaxoSmithKline submitted a Paediatric Investigation Plan (PIP) under Article 16(1) of the Paediatric Regulation (EC No 1901/2006) for the condition 'Idiopathic Thrombocytopenia Purpura' as required for the submission of the initial adult chronic ITP indication, and agreed by the Paediatric Committee (PDCO). The agreed PIP included the development of a powder for oral suspension (PfOS) in fixed single-dose sachets and a Phase II clinical study to investigate the safety, tolerability and efficacy of eltrombopag in paediatric patients diagnosed with chronic ITP from 1 year to less than 18 years old (Study TRA108062 herein after known as PETIT). The PETIT study was conducted in accordance with the study design agreed with the PDCO and was completed in February 2014. GSK submitted a Full PIP compliance check for the clinical study to the PDCO in August 2014 and received the opinion in November 2014. In addition to the PETIT study, GlaxoSmithKline conducted a Phase III study in the paediatric population, Study TRA115450 hereinafter known as PETIT2. This application presents data from PETIT2 and PETIT.

The indication in ITP is to be revised as follows: Revolade is indicated for ~~adult~~ chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients **aged 1 year and above** who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1)".

The recommended starting dose of eltrombopag for the paediatric population aged 1 to 5 years is 25 mg once daily.

2.2. Quality aspects

2.2.1. Introduction

The applicant applied for a new strength of 12.5 mg of the already authorised pharmaceutical form: tablets and a new pharmaceutical form: Powder for Oral Suspension.

Tablets 12.5 mg

The finished product is presented as tablet containing 12.5 mg of eltrombopag (as olamine) as active substance.

Other ingredients are:

Tablet core: magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone, and sodium starch glycolate.

Tablet coating: hypromellose, macrogol 400, polysorbate 80, titanium dioxide (E171).

The product is available in aluminium blisters (PA/Alu/PVC/Alu) as described in section 6.5 of the SmPC.

Powder for oral suspension

The finished product is presented as powder for oral solution containing 25 mg of eltrombopag (as olamine) as active substance.

Other ingredients are: mannitol, sucralose, and xanthan gum.

The product is available in aluminium foil sachets co-packaged in a kit with a 40 ml reconstitution vessel, an oral dosing syringe and a threaded closure with syringe-port capability as described in section 6.5 of the SmPC.

2.2.2. Active Substance

All information related to eltrombopag olamine is identical to that provided in the approved initial marketing authorisation for Revolade (eltrombopag) tablets. Revolade 12.5 mg tablets and 25 mg powder for oral suspension use the commercially approved eltrombopag olamine active substance.

2.2.3. Finished Medicinal Product

Tablets 12.5 mg

Revolade tablets 12.5 mg are white, round, biconvex film coated immediate release tablets debossed on one side with an identifying code of 'GS MZ1' and '12.5'.
The new strength of 12.5 mg was developed for paediatric patients diagnosed with chronic idiopathic thrombocytopenia purpura from 1 year to less than 18 years old

A risk-based approach has been applied throughout the development of the finished product to assure that, in addition to meeting the expectations of patients and clinicians; the finished product is capable of meeting appropriate quality standards in routine manufacture at commercial scale. Where appropriate, structured methodologies such as FMEA (Failure Mode and Effects Analysis) and BRITEST (Batch Route Innovation Technology Evaluation and Selection Techniques) tools and statistical Design of Experiments have been used to identify risks and improve overall product understanding so that appropriate control strategy and risk management can be applied in line with current regulatory expectations outlined within ICH Q8 and Q9.

Eltrombopag free acid is poorly soluble in water and exhibits a propensity to form both organic solvates and hydrates. It is a di-acid containing both a phenol and a carboxylic acid moiety and can therefore form both mono and bis-salts. Screening for salts, metal counter ions and an array of organic bases identified the bis-monoethanolamine salt as suitable for further development.

Only one known solid state form (Form 1) of the active was observed. The XRPD and SSNMR findings indicate that the manufacturing process does not induce any change in the polymorphic form or purity. Also, no change is observed in the finished product during stability conducted at 30 °C /65% RH and 40 °C /75% RH storage conditions. Eltrombopag granule and tablet physicochemical evaluation through Dynamic Vapour Sorption (DVS), X-Ray Powder Diffraction (XRPD), Solid-State Nuclear Magnetic Resonance (SSNMR) and stability studies indicate that the manufacturing process does not adversely affect the form or its stability in the finished product.

No compatibility issues were identified between the active substance and the excipients employed in the finished product. Based on the scientific and prior knowledge on the excipients used in the finished product and based on the initial risk assessment conducted through BRITEST, no CQAs associated with excipients

were identified. The specifications of the inactive ingredients comply with the European Pharmacopoeia (Ph. Eur.). The film coating material is composed of ingredients that have monographs in Ph. Eur. or USNF.

The formulation and excipient grades used for development, clinical, pivotal stability and intended for commercialisation are the same. During the development, the excipient grades and quantities were found to be satisfactory for processing and to provide finished product of the required CQAs using the defined process.

The solubility of eltrombopag olamine presented some challenges to the development of a suitable dissolution method. The active substance has a low aqueous solubility, particularly in acidic conditions.

A discriminating dissolution method has been developed for release and stability testing.

The same acceptance criterion as the approved 25 mg, 50 mg and 75 mg tablets will be applied to commercial 12.5 mg tablets, based on the results from the long-term stability studies.

The manufacturing process development presents the process knowledge and understanding of the variables of input and output attributes and parameters of the unit operations that define the Design Space for the finished product manufacturing process together with Quality Critical Process Parameters (QCPP) and Critical Quality Attributes (CQA) that should be controlled.

The primary packaging is aluminum blisters (PA/Alu/PVC/Alu). The primary packaging and the materials used are the same as for the already authorized strengths.

Powder for oral suspension

The finished product is an elongated sachet containing reddish-brown to yellow powder, which when reconstituted with water, forms a reddish-brown suspension.

The new pharmaceutical form was developed for paediatric patients diagnosed with chronic idiopathic thrombocytopenia purpura from 1 year to less than 18 years old.

The attributes of the active substance which have the potential to impact finished product CQAs were evaluated based on scientific understanding and prior knowledge. The active substance used for the powder for oral solution is the same as that used in the commercial tablets.

The paediatric formulation selected was a dry powder for oral suspension that is readily reconstituted with water. Single or multiple sachets can be used to meet different dose range (up to a maximum dose of 75 mg) with the initial dose based on the child's body weight and/or age with subsequent doses based on platelet response. The formulation and composition of the blend for both the clinical and the proposed commercial formulation are the same.

Eltrombopag PfOS has been developed using a quality risk management approach. In line with the principles outlined in ICH Q9, quality risk management throughout the product lifecycle to drive product development and continuous improvement is applied. Quality risk management has been used to drive decisions around the finished product formulation and manufacturing process. It has been used to direct experimental activities to further product and process knowledge and understanding. It has been also used to develop a control strategy that results in a robust finished product manufacturing process.

The product is packaged into heat-sealed foil laminate sachets. The laminate material comprises a polyester (PET) / oriented polyamide (OPA) / aluminium foil (AL) / low density polyethylene heat seal layer (LDPE). The

product contact material is the polyethylene heat seal layer. To facilitate reconstitution and dosage of the finished product, ancillary components, a reconstitution bottle, a non-sterile oral dosing syringe and a threaded closure with syringe-port capability, are also provided within the secondary package. In addition, the product contact materials comply with the European Directives pertaining to materials for use in contact with food and with Ph. Eur. regulations. These are considered to demonstrate safety of the materials.

The reconstitution bottle manufactured from high density polyethylene (HDPE) resin was selected due to its robust nature and inherent low risk of extractable and leachable concern. A round bottle shape was selected to allow adequate headspace for the reconstitution procedure with water as well as to minimize residual product after dispensing due to low internal bottle surface area. A threaded closure with syringe-port capability manufactured from low density polyethylene (LDPE) was selected for its ability to facilitate a clean liquid-tight connection of an oral dosing syringe. The CE marked non- sterile oral dosing syringe with printed graduation markings was chosen to facilitate accurate dispensing of the reconstitution and rinse volumes. An evaluation of potential leachables from the product contact ancillary components was conducted and a risk assessment was carried out to highlight areas for extractable profiling. The risk assessment found the product contact materials to be very low risk for leachables.

Manufacture of the product and process controls

Tablets 12.5 mg

The manufacturing process consists of 10 main steps: dry mixing, granulation, wet milling, drying, milling, compression mix blending (pre-lubrication), compression mix blending (lubrication), compression, film coating and packaging. The process is considered to be a standard manufacturing process.

The information about the manufacturing process is adequately described. No validation data are provided which is deemed acceptable based on the significant level of manufacturing experience obtained during development, scale-up, and production of clinical supplies. The validation scheme for the finished product has been provided.

Powder for oral suspension

The manufacturing process consists of two main steps: blending and sachet filling. The process is considered to be a standard manufacturing process.

The 3 commercial scale batch analysis data confirm that the manufacturing process is well controlled and reliably produces product which meets its defined DP CQAs.

Product specification

Tablets 12.5 mg

The finished product release specifications include appropriate tests for this kind of dosage form description, identification (IR), assay (HPLC), impurities content (HPLC), uniformity of dosage units (Ph Eur), dissolution (UV, Ph Eur) and microbial limit tests (Ph Eur).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. All information related to reference standards is identical to that provided in the approved initial Revolade tablets.

The analytical methods used to test the tablets are a combination of traditional methods and methods developed using Quality by Design (QbD) principles. The following two methods have used a QbD approach: Impurities Content by HPLC, Dissolution by UV.

Batch analysis results are provided for 8 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Powder for oral suspension

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (IR), uniformity of dosage units (HPLC), assay (HPLC), impurities content (HPLC), dissolution (UV, Ph Eur) and microbial enumeration test (Ph Eur).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for impurities testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications through traditional final product release testing.

Stability of the product

Tablets 12.5 mg

Stability data of three batches of the 12.5 mg with the commercial film coats and tablet debossing of finished product stored under long term conditions for up 48 months at 30 °C / 65% RH, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. All batches were manufactured at production scale at the proposed commercial manufacturing site, and packaged in the proposed market blister pack. Stability data for batches of white 25 mg, 50 mg, 75 mg and 100 mg tablets, identical to those proposed for marketing except for the film coating and tablet debossing, have also been presented as supportive data. The batches of 12.5 mg tablets have the same white coating as the commercial tablets while the 12.5 mg tablet primary stability batches are not debossed. Both sets of 25 mg tablets have the same white coating while the 25 mg tablet primary stability batches are not debossed. The 50 mg tablet primary stability batches are also not debossed, and have the same white coating as the 25 mg tablets while the commercial film coated 50 mg tablets described above are coated brown, the commercial film coated 75 mg tablets are coated pink. A matrixed protocol was used with the 50 mg, 75 mg and 100 mg white, non-debossed tablets. The matrixing adheres to the guidelines provided in ICH Q1D which describes designs for stability testing of new finished products.

Samples were tested for description, identification (IR), impurities content (HPLC) and dissolution. The analytical procedures used are stability indicating.

The results of accelerated and long-term primary stability studies demonstrate the chemical and physical stability of Eltrombopag Tablets, 12.5 mg, when stored for up to 48 months at 30 °C/65% RH, or for up to 6 months at 40 °C/75% RH. No significant changes were observed in description, eltrombopag content, drug-related impurities content, and dissolution, and all results complied with specification. Some batches of 50

mg and 75 mg tablets required Stage 2 dissolution testing at the initial and/or various subsequent timepoints, however, all results complied with specification.

A photo stability study in accordance with ICH Q1B Option 2 has also been performed, and storage at 5°C and 50°C has been performed at abbreviated time points. No significant changes were observed in description, eltrombopag content, and drug-related impurities content, and all results complied with specification.

Based on available stability data, the proposed shelf-life 4 years without storage conditions as stated in the SmPC (section 6.3) are acceptable.

Powder for oral suspension

Stability data of 3 commercial scale batches of finished product stored under long term conditions for up 12 months at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of the medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, identification (IR), uniformity of dosage units (HPLC), assay (HPLC), impurities content (HPLC), dissolution (UV) and microbial enumeration tests (Ph Eur). The analytical procedures used are stability indicating.

With regard to the reconstituted suspension, the results of long-term and accelerated primary stability studies demonstrate the chemical and physical stability when stored for up to 12 months at 30 °C /65% RH, or for up to 6 months at 40 °C /75% RH. No significant changes were observed in description, eltrombopag content, drug-related impurities content, dissolution, pH, reconstitution time, viscosity, water content, eltrombopag content in reconstituted suspension, drug-related impurities content in reconstituted suspension or microbial enumeration tests, and all results comply with specification.

In addition, data has been generated for description, eltrombopag content, drug-related impurities content, dissolution, pH, reconstitution time, viscosity and water content following short-term storage of one of the three primary stability batches of the finished product under stress conditions of 50 °C, a freeze/thaw cycle (comprised of two repeated cycles each consisting of 7 days storage at -20 °C followed by 7 days storage at 30 °C /65% RH for total of 28 days exposure) and exposure to ICH Q1B Option 2 photostability conditions (only description, eltrombopag content, drug-related impurities content tested). The results demonstrate the chemical and physical stability of Eltrombopag PfOS at all storage conditions. No significant changes were observed in description, eltrombopag content, drug-related impurities content, dissolution, pH, reconstitution time, viscosity and water content, and all results comply with the specification.

In-use stability data were presented for two batches of the finished product following reconstitution. The results of the stability studies demonstrate the chemical and physical stability of the suspension when stored at ambient temperature/humidity/light. No significant changes were observed in description, eltrombopag content, drug-related impurities content, pH and reconstitution time, and all results comply with specification.

Based on available stability data, the proposed shelf-life of 24 months, following reconstitution, the product should be administered immediately, within 30 minutes of reconstitution as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used in both pharmaceuticals forms.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

All information related to eltrombopag olamine is identical to that provided in the approved initial marketing authorisation for Revolade (eltrombopag) tablets. Revolade 12.5 mg tablets and 25 mg powder for oral suspension use the commercially approved eltrombopag olamine active substance.

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner for both new presentations.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process.

The proposed designed space is the same as the already authorised tablet strengths.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic and Pharmacokinetic evaluation with eltrombopag following oral administration was completed as part of the nonclinical development program in support of the initial MAA for the treatment of ITP and MAA variation for HCV-related thrombocytopenia. The reports for these studies were submitted and reviewed previously either as part of the initial MAA or as part of subsequent variations. No new nonclinical toxicology studies have been submitted in this application. Juvenile toxicity studies conducted with eltrombopag were submitted as part of the initial MAA.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Eltrombopag is a potent and selective TPO-R agonist and requires expression of TPO-R for its activity.

No additional studies on primary pharmacodynamics were needed in relation to this extension of indication.

Secondary pharmacodynamic studies

N/A

Safety pharmacology programme

Data from the initial MAA are summarised here.

Oral administration of eltrombopag did not produce clinically relevant findings in safety pharmacology studies in animals evaluating the cardiovascular, respiratory and nervous systems. Eltrombopag inhibits hERG channel tail current and decreases upstroke amplitude, maximum rate of depolarization and action potential durations in isolated Purkinje fibres in vitro; however, there were no effects of eltrombopag on electrocardiographic parameters in dogs following single or repeat dosing for up to 52 weeks. In addition, there was no effect on cardiac repolarisation in healthy human subjects given eltrombopag at doses up to 150 mg daily for 5 days and no clinically significant effect on cardiac repolarisation in adult ITP patients evaluated in clinical trials at doses up to 75 mg or adult patients with chronic HCV infection evaluated in clinical trials at doses up to 100 mg once daily. Routine ECGs were not performed in paediatric ITP clinical trials; however, no adverse events indicative of altered cardiac repolarisation were reported in paediatric ITP clinical trials at doses up to 75 mg once daily.

Pharmacodynamic drug interactions

Eltrombopag exhibited minimal effects on a broad range of common drug targets. Thus, pharmacodynamic drug interactions are unlikely to be of clinical significance.

2.3.3. Pharmacokinetics

A comprehensive package of nonclinical pharmacokinetic, distribution, metabolism and excretion studies was conducted in the mouse, rat and dog, the principle species used for toxicological assessment of eltrombopag and is summarised here. Across the nonclinical species, absorption of eltrombopag was low to moderate and plasma clearance was generally low with moderate to long half-lives. Absolute oral bioavailability of eltrombopag as a solution was low in the rat while high in the dog. Following repeat administration, systemic exposure of eltrombopag increased greater than dose-proportionally in rats and approximately dose-proportionally in mice and dogs. There was no marked difference in systemic exposure between males and females of these species.

Eltrombopag-related material was widely distributed into peripheral tissues in the mouse and rat, but the concentrations in most tissues were lower than in blood. Drug-related material did not extensively penetrate into central nervous system or the lens of the eye, nor was it selectively retained in melanin containing tissues. There was no evidence of tissue accumulation of drug-related material in mice, including eyes, kidneys and skin upon repeat administration. Eltrombopag was highly bound to plasma proteins in nonclinical species as well as in human (>99.9%), and had low association with blood cells. Eltrombopag was highly bound (>99.9%) to human serum albumin (HSA) at physiologic albumin concentrations (600 µM), and the

binding was not concentration-cdependent. Eltrombopag did not bind to human α1-acid glycoprotein (AAG) at physiologic AAG concentrations of 15 µM. At diseased state AAG concentrations (150 µM), eltrombopag binding to AAG was moderate (77% to 90%).

In vitro (hepatocytes) and ex-vivo (isolated perfused animal liver or kidney), eltrombopag was metabolized by oxidation, glucuronidation or conjugation with cysteine or glutathione. There was no evidence for the formation of any human specific metabolites in hepatocytes. In vivo, eltrombopag was the predominant circulating component in the nonclinical species. Minor metabolites derived from oxidation or glucuronidation were also in circulation. In the rat, there was adequate coverage for the circulating metabolites in humans.

In the nonclinical species, eltrombopag was primarily eliminated as unchanged drug in the faeces with renal elimination of cleavage products contributing a minor route. No notable gender-related differences in metabolism were observed in mice, rats or dogs. In addition to unchanged eltrombopag, human faeces also contained glutathione, glutamyl cysteine and cysteine conjugates of eltrombopag. These conjugates were not detected in the animal faeces, but were observed in mouse (glutathione conjugate) and rat bile (glutathione and glutamyl cysteine conjugates). Minor metabolites derived from glucuronidation or oxidation were also detected in the mouse, rat and dog bile. Gut microbes readily cleaved eltrombopag. One of the cleavage products, SB-611855, was quickly absorbed, metabolized and eliminated as conjugates in urine following oral administration to mice. Eltrombopag was not renally eliminated in any species studied.

In vitro, eltrombopag inhibited cytochrome P450 (CYP) enzymes CYP2C8 and CYP2C9 and several uridine diphosphate glucuronosyl transferase (UGT) enzymes. Eltrombopag was neither an inhibitor nor a substrate of human P-glycoprotein (Pgp) and was not a substrate of human organic anion transporting polypeptide (OATP1B1), although it was an inhibitor of this transporter and the potential for such an interaction was confirmed clinically. In addition, eltrombopag was an in vitro inhibitor and a substrate of human breast cancer resistance protein (BCRP). These data suggest that systemic interactions between eltrombopag and certain co-administered compounds, such as selected statins and substrates and inhibitors of human BCRP (e.g., doxorubicin) following oral administration at therapeutic doses are possible. However, subsequent in vitro evaluation indicated that the potential for clinical interaction between eltrombopag and doxorubicin appears to be low.

The in vitro oxidative metabolism in human liver microsomes was primarily mediated by CYP1A2 and CYP2C8. CYP1A genes were well conserved among species. Rat CYP1A2 demonstrated 83% homology to human CYP1A2 [Martignoni, 2006]. Although the mechanism and ontogeny of eltrombopag clearance in rat has not been established, the biotransformation profile in rats was similar to that in humans, and the increased eltrombopag exposure in young pups coincides with CYP1A2 ontogeny in this species. It has been reported that CYP1A2 expression in rats is low at birth and increases gradually until Days 15 to 26 pp, when enzyme expression reached and exceeded adult levels [de Zwart, 2008]. The slow post-natal maturation of CYP1A2 metabolic capability in rats likely contributed to the very high exposures of eltrombopag in pups on the juvenile toxicity study. Rats do not have homologous enzymes to human CYP2C8 [Martignoni, 2006].

In vitro studies have also demonstrated that UGT1A1 and UGT1A3 were the primary enzymes responsible for glucuronidation of eltrombopag. The potential for pharmacokinetic interactions due to inhibition of these CYPs and UGTs by other drugs are adequately described in the label and post-marketing plan. Gut microbes readily cleaved eltrombopag. Antibiotic treatment in mice altered excretion patterns of eltrombopag, but did not notably change its systemic exposure, suggesting that interaction between eltrombopag and antibiotics is unlikely.

2.3.4. Toxicology

Eltrombopag has undergone a comprehensive nonclinical toxicological evaluation to support its clinical use in the treatment of adult ITP patients. The species used in the definitive toxicology evaluations (mice, rats and dogs) were selected on the basis of similarities in their pharmacokinetic and metabolic profiles to humans and the extensive historical background data for these species. In addition to the nonclinical data package in adult animals, dose range and definitive juvenile toxicity studies in rats were conducted to support administration of eltrombopag in paediatric patients. Due to age-dependent development of hepatic excretory pathways and reduced hepatic clearance which led to higher exposures of eltrombopag and poor tolerability in very young rats, juvenile toxicity studies were conducted in two phases to cover an age range of preterm infant to adolescent: (1) Day 4 pp to Day 31 pp and (2) Day 32 pp to Day 63 pp. While it was not possible to assess potential effects of exaggerated pharmacology in these species due to the unique species-specificity of eltrombopag (i.e., chimpanzee and human are the only pharmacologically responsive species), the potential for effects associated with excessive TPO-R agonism has been evaluated in clinical studies, including paediatric ITP patients.

The principal nonclinical toxicology findings associated with oral administration of eltrombopag to adult animals were cataracts (mice and rats), renal tubular toxicity (mice and rats) and hepatotoxicity (mice, rats and dogs). Endosteal hyperostosis and bone marrow erythroid hyperplasia (rats) and decreased reticulocyte counts (rats and dogs) were observed at non-tolerated doses. Embryofetal toxicity was observed in rats.

The existing nonclinical development program submitted in support of the adult ITP indication contains a nonclinical safety assessment of oral administration of eltrombopag at a daily dose of up to 75 mg, which is also the maximum recommended therapeutic dose for the treatment of paediatric ITP patients. A nonclinical safety assessment of eltrombopag at this dose in paediatric ITP patients is provided. Exposure to eltrombopag in paediatric ITP patients ≥ 11 years of age was similar to adult ITP patients at equivalent doses; however, increased exposure was observed in paediatric ITP patients at 1 to 11 years of age. Due to this difference in exposure, comparisons have been made to the maximum systemic exposure observed at the maximum recommended therapeutic dose of 75 mg/day in paediatric ITP patients at 1 to 5 years of age (AUC = 242 µg.h/mL, Cmax = 17.4 µg/mL).

Two juvenile toxicity studies were conducted in rat pups dosed eltrombopag from Day 4 to 32 pp and one juvenile toxicity study at higher doses from Day 32 to 63 pp. Dose-normalized exposures to eltrombopag in juvenile rats, especially the younger pups (starting treatment on Day 4 postpartum [pp]), were higher than those in adult rats. The exposure increased slightly less than dose-proportionally in the younger pups, but greater than dose-proportionally in the older pups (starting treatment on Day 32 pp). No notable differences in systemic exposures were observed between male and female young rats of either age at any dose.

In a 4 week dose range study in juvenile rats at doses ≥ 30 mg/kg/day (2274 µg.h/mL; ≥ 9-fold maximum clinical exposure in paediatric ITP patients at an oral dose of 75 mg) some unscheduled deaths occurred, as well as evident toxicity clinical signs (decreased activity, weakness, thinness and cold to touch). Pale yellow discoloration of the fur/skin (attributed to the colour of eltrombopag), carcass, salivary gland and thymus, revealing hepatic affectation, was reverted in the 30 mg/kg/day dose group during the 4- week recovery period. Ocular opacities (consistent with cataracts) were noted grossly in five pups at these high exposures (30 mg/kg/day) during treatment with eltrombopag or during the 4-week off-treatment period. There were no treatment related findings at 10 mg/kg/day (977 µg.h/mL; 4-fold the maximum proposed clinical exposure in paediatric ITP patients). Therefore, monitoring of adult patients and paediatric ITP patients for cataracts is recommended in the current prescribing information.

In the second definitive 4 week juvenile toxicity study in rat pups dosed from Day 4pp to Day 31pp, a dose of 15 mg/kg/day (1202 µg.h/mL; 5-fold maximum clinical exposure in paediatric ITP patients) was associated with slight reduction in red cell counts, haemoglobin and mean cell haemoglobin concentration values (5%, 7% and 3%, respectively) for males, an increase in absolute reticulocyte counts for females (20%), and increases in red cell distribution width for males (14%) and females (21%). These findings were not considered adverse due to the small magnitude of change and evidence of regenerative response.

Due to age-dependent development of hepatic excretory pathways, and additional 4 week juvenile toxicity study was conducted at higher doses in slightly older rats. Pups were dosed eltrombopag orally once daily from Day 32 to 63 postpartum. There were no unscheduled deaths or treatment-related effects on clinical observations, body weight, food consumption or ophthalmology at doses up to 40 mg/kg/day. At the highest dose group (40 mg/kg/day; 850 µg.h/mL; at 3-fold maximum clinical exposure in paediatric ITP patients), effects on red blood cell parameters to the same extent than observed in the previous study in younger pups were also noted. In addition, decreases in serum cholesterol and triglyceride concentrations (up to 52%) were also observed in rats given 40mg/kg/day. The decreases in serum cholesterol and triglyceride concentrations were not associated with effects on organ weights, particularly reproductive organ weights (testes, prostate and ovaries) or any adverse microscopic findings in developing organ systems, i.e. neurologic, skeletal, immune, pulmonary, renal (function) or the reproductive system (including testes, epididymides, prostate, seminal vesicles, ovaries, vagina and uterus - horns, body and cervix). Importantly, there were no adverse events of abnormal cholesterol or triglyceride concentrations in the paediatric ITP program. Taken together, these data suggest that the risk of a potential effect of eltrombopag on developing organ systems, reproductive organs or sexual maturation in pediatric ITP patients is minimal and does not warrant inclusion of this information or additional precautions in the SmPC.

At 40 mg/kg/day dose group, increased urinary protein was noted in males, and was considered to be related to an increased incidence of tubular hyaline droplets observed in the kidneys of males given 15 and 40 mg/kg/day. According to published literature submitted by the Applicant (Durham, 2002), hyaline droplets are a common spontaneous finding in male rats. Immunohistochemical staining indicated that the hyaline droplets contained alpha-2 microglobulin, a male-rat specific protein. Therefore, humans are not supposed to be at risk since they do not synthesize this protein (Durham, 2002; Lehman-McKeeman LD, 1992). Since the changes were only accompanied by slight proteinuria and were not accompanied by histologic evidence of renal damage, kidney findings could be considered non-adverse.

As a conclusion from these three juvenile toxicity studies, toxicity was observed at lower eltrombopag doses in the youngest animals dosed from Day 4 to 32 pp (NOAEL=15 mg/kg/day), when compared to older animals, administered from Day 32 to 63 pp (NOAEL=40 mg/kg/day). The exposure at the NOAEL in juvenile rats (1202 µg.h/mL or 850 µg.h/mL for rat pups dosed from Day 4 pp or Day 32 pp, respectively) was slightly higher than in adult rats (661 µg.h/mL). The slow post-natal maturation of CYP1A2 metabolic capability in rats likely contributed to the very high exposures of eltrombopag in pups on the juvenile toxicity study. CYP1A2 expression in rats is low at birth and increases gradually until Days 15 to 26 pp, when enzyme expression reached and exceeded adult levels [de Zwart, 2008].

With regard to the powder for oral suspension (PfOS) formulation which has been developed for administration in younger patients (ages 1 to 5 years old) or patients who cannot swallow tablets, no further actions are required since no new impurities or degradation products have been detected in the eltrombopag PfOS, and levels of known impurities/degradants are within the existing specification limits for eltrombopag tablets. Regarding the new tablet strength (12.5mg), no additional nonclinical studies are considered necessary. Eltrombopag 25mg, 50mg and 75 mg tablets are already registered.

In summary, in juvenile rats, eltrombopag was associated with adverse effects at exposures up to 3- to 5-fold maximum clinical exposure in paediatric ITP patients at an oral dose of 75 mg.

2.3.5. Ecotoxicity / environmental risk assessment

No new environmental risk assessment is required for eltrombopag with regard to the paediatric use and new formulation as no substantial increase in the use can be anticipated.

2.3.6. Discussion on non-clinical aspects

The existing nonclinical development program submitted in the adult ITP MAA contains a nonclinical safety assessment of oral administration of eltrombopag at a daily dose of up to 75 mg, which is also the maximum recommended therapeutic dose for the treatment of paediatric ITP patients. In addition to the nonclinical data package in adult animals, dose range and definitive juvenile toxicity studies in rats were conducted to support administration of eltrombopag in paediatric patients. Due to age-dependent development of hepatic excretory pathways and reduced hepatic clearance which led to higher exposures of eltrombopag and poor tolerability in very young rats, juvenile toxicity studies were conducted in two phases to cover an age range of preterm infant to adolescent: (1) Day 4 pp to Day 31 pp and (2) Day 32 pp to Day 63 pp.

At poorly tolerated doses in juvenile rats (≥ 9-fold maximum clinical exposure), reductions in body weight gain or body weight loss and discoloration of skin, fur and other organs (attributed to the colour of eltrombopag) were observed and reversed following an approximate 4 week off-treatment period. Ocular opacities (consistent with cataracts) were observed grossly in some pups at these high exposures during treatment with eltrombopag or during the 4 week off-treatment period.

In rat pups dosed from Days 4 to 31 pp, effects were slight reductions in body weight gain, slight discoloration of the skin and fur (attributed to the colour of eltrombopag) and decreases in red cell parameters with a regenerative increase in reticulocyte counts (20%) at 5-fold maximum clinical exposure. These findings were not considered adverse due to the small magnitude of change and evidence of regenerative response. In rat pups dosed from Days 32 to 63 pp, decreases in red blood cell parameters, serum cholesterol and triglyceride concentrations (up to 52%) were observed at 3-fold maximum clinical exposure. An increased incidence of renal tubular hyaline droplets (confirmed to be α-2μ-globulin) was seen at parity with clinical exposure and increased urine protein excretion at 3-fold clinical exposure, however, these microscopic changes in the kidney have been shown to be a male rat-specific effect and are thus of limited relevance to humans [Durham, 2002]. The decreases in serum cholesterol and triglyceride concentrations were not associated with effects on organ weights, particularly reproductive organ weights (testes, prostate and ovaries) or any adverse microscopic findings in developing organ systems, i.e. neurologic, skeletal, immune, pulmonary, renal (function) or the reproductive system (including testes, epididymides, prostate, seminal vesicles, ovaries, vagina and uterus - horns, body and cervix). Importantly, there were no adverse events of abnormal cholesterol or triglyceride concentrations in the paediatric ITP program. Taken together, these data suggest that the risk of a potential effect of eltrombopag on developing organ systems, reproductive organs or sexual maturation in pediatric ITP patients is minimal and does not warrant inclusion of this information or additional precautions in the SmPC. Ocular opacities (consistent with cataracts) were noted grossly in five pups at these high exposures (30 mg/kg/day) during treatment with eltrombopag or during the 4-week off-treatment period. There were no treatment related findings at 10

mg/kg/day (977 µg.h/mL; 4-fold the maximum proposed clinical exposure in paediatric ITP patients) (See also discussion on clinical safety).

As a conclusion from these three juvenile toxicity studies, toxicity was observed at lower eltrombopag doses in the youngest animals dosed from Day 4 to 32 pp (NOAEL=15 mg/kg/day), when compared to older animals, administered from Day 32 to 63 pp (NOAEL=40 mg/kg/day). The exposure at the NOAEL in juvenile rats (1202 µg.h/mL or 850 µg.h/mL for rat pups dosed from Day 4 pp or Day 32 pp, respectively) was slightly higher than in adult rats (661 µg.h/mL). The slow post natal maturation of CYP1A2 metabolic capability in rats likely contributed to the very high exposures of eltrombopag in pups on the juvenile toxicity study. CYP1A2 expression in rats is low at birth and increases gradually until Days 15 to 26 pp, when enzyme expression reached and exceeded adult levels [de Zwart, 2008].

With regard to the powder for oral suspension (PfOS) formulation which has been developed for administration in younger patients (ages 1 to 5 years old) or patients who cannot swallow tablets, no further actions are required since no new impurities or degradation products have been detected in the eltrombopag PfOS, and levels of known impurities/degradants are within the existing specification limits for eltrombopag tablets. Regarding the new tablet strength (12.5mg), no additional nonclinical studies are considered necessary. Eltrombopag 25mg, 50mg and 75 mg tablets are already registered.

Results showed that in juvenile rats, eltrombopag was associated with adverse effects at exposures up to 3- to 5-fold maximum clinical exposure in paediatric ITP patients at an oral dose of 75 mg.

In conclusion there are no findings in juvenile rats to suggest a greater risk of toxicity with eltrombopag treatment in paediatric vs. adult ITP patients. This information has been included in the SmPC section 5.3.

2.3.7. Conclusion on the non-clinical aspects

Current information on the non-clinical aspects of Revolade can adequately support the introduction of a new tablet strength of 12.5mg and PfOS formulation of 25mg to be indicated for the treatment of thrombocytopenia in paediatric patients with ITP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
TRA111718 Relative Bioavailability and Food Effect	Relative bioavailability of eltrombopag Powder for Oral Suspension (PfOS) formulation relative to the commercial 25 mg tablet. The effect of a high calcium meal separated by 2 hours on the bioavailability of PfOS	OL, R, 5-period, balanced CO	Healthy volunteers	**Treatment A** eltrombopag/25mg/tablet (25mg)/commercial/oral/single dose/fasting **Treatment B** eltrombopag/25mg/powder (25mg)/oral/single dose/fasting **Treatment C** eltrombopag/ 25mg/powder (25mg)/oral/single dose/with a high calcium meal **Treatment D** eltrombopag/25mg/powder (25mg)/oral/single dose/2 hours prior to a high calcium meal **Treatment E** eltrombopag/25mg/powder (25mg)/oral/single dose/2 hours after a high calcium meal	40 Eltrombopag: 40	Completed with final CSR
TRA108062 PETIT	Efficacy, Safety, PK, PD, QoL, PGx	Dose Finding Phase: NR, OL Randomized Period: R, DB, PC Eltrombopag Only Period: OL	Subjects between 1 and <18 years of age with chronic ITP	Dose Finding Phase: Eltrombopag tablet, 12.5mg to 75mg (adjusted based on platelet count) once daily for children 6 to 17 years old; Eltrombopag PfOS for children 1 to 5 years old. Maximum dose of 75mg once daily. Randomized Period: Eltrombopag 12.5mg to 75mg (adjusted based on platelet count) or matching PBO once daily for children 6 to 17 years old. Eltrombopag PfOS or matching PBO for children 1 to 5 years old. Maximum dose of 75mg once daily. Eltrombopag Only Period: Eltrombopag tablet, 12.5mg to 75mg once daily. Eltrombopag PfOS to maximum dose of 75mg once daily..	Dose Finding Phase: 15 eltrombopag; Randomized Period: 67 (45 eltrombopag; 22 placebo) Eltrombopag Only Period: 67	Completed with final CSR
TRA115450 PETIT2	Efficacy, Safety, PK, PD, PGx,	Randomized Period: R, DB, PC Eltrombopag Only Period: OL	Subjects between 1 and <18 years with a confirmed diagnosis of chronic ITP for at least 1 year	Randomized Period: Eltrombopag tablet, 12.5mg to 75mg once daily (adjusted based on platelet count) or matching PBO for children 6 to 17 years old; Eltrombopag PfOS or matching PBO for children 1 to 5 years old. Maximum dose of 75mg once daily. Eltrombopag Only Period: Eltrombopag tablet, 12.5mg to 75mg once daily; Eltrombopag PfOS to maximum dose of 75mg once daily	Randomized: 92 (63 eltrombopag; 29 placebo) Eltrombopag Only Period: 87	Completed with final CSR

2.4.2. Pharmacokinetics

This submission provides information in support to register a new tablet strength (12.5 mg) and a new Powder for Oral Suspension (PfOS; 25 mg). In addition, the effect of a high calcium, moderate fat and calorie meal on the pharmacokinetics of a single oral 25 mg dose of eltrombopag PfOS has been evaluated when eltrombopag is administered concurrently, two hours before, or two hours after the meal.

The PK analyses of plasma eltrombopag concentration-time data were conducted using non-compartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 5.2.

Primary Endpoints were plasma eltrombopag $AUC_{0-\infty}$ and C_{max}.

Secondary Endpoints were plasma eltrombopag AUC_{0-t}, $\%AUC_{ex}$, t_{lag}, t_{max}, $t_{1/2}$, and CL/F. The area under the plasma concentration-time curve from time zero to the last quantifiable time point (AUC_{0-t}) was calculated by a combination of linear and logarithmic trapezoidal methods.

Log_e-transformed C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, and CL/F of eltrombopag were separately analyzed using a mixed effects linear analysis of variance (ANOVA) model with fixed effect terms for sequence, period and treatment and subject treated as a random effect in the model using SAS® version 9.1.3 software. Point estimates and their associated 90% CIs were constructed for the differences between test and reference treatments. The point estimates and their associated 90% CIs were then back transformed to provide the ratios of geometric least square (GLS) means and associated 90% CIs for the ratios of test/reference for the selected PK parameters. Plasma eltrombopag t_{lag} and t_{max} were analyzed using the nonparametric Hodges-Lehmann method to compute point estimates and associated 90% CIs for the median differences between test and reference treatments.

A cross-over study design was submitted to evaluate the relative bioavailability between both formulations (tablet and suspension) and to evaluate the effect of a high calcium, moderate fat and calorie meal on the pharmacokinetics of a single oral 25 mg dose of eltrombopag PfOS in healthy adult subjects when eltrombopag is administered concurrently, two hours before, or two hours after the meal.

In general, the pre-study validations of the two bioanalytical methods were consistent and demonstrated an adequate precision and accuracy (both intra- and inter-day) within the calibrated range, which showed an adequate selectivity, and the absence of matrix effect and carry-over. The results from the cross-validation demonstrated the inter-laboratory reliability between the methods from the two laboratories. The in-study validation shows an acceptable calibration standards and QC values in the valid runs. The ISR was performed in all three studies and were acceptable. In general, the analysis of study samples is acceptable and the re-analysis of the study samples was well justified and handled.

2.4.1. Absorption

- **Bioequivalence**

Eltrombopag 12.5 mg tablets

Eltrombopag Tablets, 25 mg, 50 mg and 75 mg were approved by the European Medicines Agency (EMA) in March 2010 and are commercially available.

Eltrombopag 12.5 mg tablets administered in the clinical paediatric studies TRA108062/PETIT and TRA115450/PETIT2 (both studies are included in this application) were the same as the intended commercial product.

The Applicant claims a biowaiver of the 12.5 mg, considering that the requirements of the Guideline on investigation of bioequivalence are fulfilled.

Eltrombopag tablets, 12.5 mg are the same immediate release tablet dosage form as the 25 mg, manufactured at the same commercial site by the same manufacturer, and using the same manufacturing process as the 25 mg tablet.

With regard to the linearity, plasma eltrombopag AUC and C_{max} increased with increasing dose and the evaluation of proportionality was dose dependent. Plasma eltrombopag $AUC\tau$ increased in a dose proportional manner between 50 mg and 200 mg and C_{max} increased in a dose proportional manner between 50 mg and 150 mg. At doses below 50 mg, plasma eltrombopag $AUC_{0-\infty}$ and C_{max} increased in a slightly greater than dose-proportional manner. Eltrombopag olamine has a low solubility over the pH range 1 to 7.4 (see the following table). It is considered to have moderate permeability so the bioavailability may be considered to be limited by its dissolution rate.

Because of this low aqueous solubility, polysorbate 80 was added to acidic media in an attempt to generate meaningful dissolution profiles. At 60 minutes, less than 30% and 60% of eltrombopag were dissolved in the 0.1 N HCl and pH 4.5 media containing 2% polysorbate 80, respectively, for a 50 mg tablet.

Because of that, a QC dissolution method was developed using a surfactant. The dissolution medium is phosphate buffer pH 6.8 with 0.5% polysorbate 80 at 50 rpm. The dissolution results demonstrated similar dissolution profiles between both strengths.

Influence of food

Clinical Study Report TRA111718

This study was a randomized, open-label, five-period, balanced cross-over study conducted in healthy adult subjects.

The primary objectives were to evaluate the bioavailability of a power for oral suspension PfOS formulation relative to the commercial eltrombopag 25 mg tablet formulation and to evaluate the effect of a high calcium, moderate fat and calorie meal on the pharmacokinetics of a single oral 25 mg dose of eltrombopag PfOS when eltrombopag is administered concurrently, two hours before, or two hours after a meal.

Each subject was randomized to one of ten treatment sequences (see the table below). Each treatment period was separated by a wash-out of 10 to 14 days.

Sequence	N	Period 1[1]	Period 2[1]	Period 3[1]	Period 4[1]	Period 5[1]
1	4	A	E	B	D	C
2	4	B	A	C	E	D
3	4	C	B	D	A	E
4	4	D	C	E	B	A
5	4	E	D	A	C	B
6	4	C	D	B	E	A
7	4	D	E	C	A	B
8	4	E	A	D	B	C
9	4	A	B	E	C	D
10	4	B	C	A	D	E

A: eltrombopag 25 mg tablet fastedB: eltrombopag 25 mg PfOS fastedC: eltrombopag 25 mg PfOS administered with high calcium meal D: eltrombopag 25 mg PfOS administered 2 hours before high calcium meal E: eltrombopag 25 mg PfOS administered 2 hours after high calcium meal

1. There was a 10 to 14-day washout between each treatment period

For Treatments A and B, subjects were required to fast at least eight hours before administration of each treatment. Water was permitted during the fast, except for one hour prior to dosing. Subjects fasted for an additional four hours after eltrombopag dosing.

For Treatment C, subjects were required to fast eight hours before administration of the standard high calcium meal. Water was permitted during the fast. Each subject was served a standard high calcium meal and ingested this meal within 30 minutes. Within 5 minutes after completion of the meal, each subject took eltrombopag.

For Treatment D, subjects were required to fast at least eight hours before administration of eltrombopag. Water was permitted during the fast, except for one hour prior to dosing. Subjects fasted for an additional two hours after eltrombopag dosing. Two hours after dosing, each subject was served a standard high calcium meal and ingested this meal within 30 minutes

For Treatment E, subjects were required to fast 8 hours before administration of the standard high calcium meal. Water was permitted during the fast. Each subject was served a standard high calcium meal and ingested this meal within 30 minutes. Two hours after completion of the meal, each subject took eltrombopag.

In all treatment, each subject took eltrombopag with 240 mL of water.

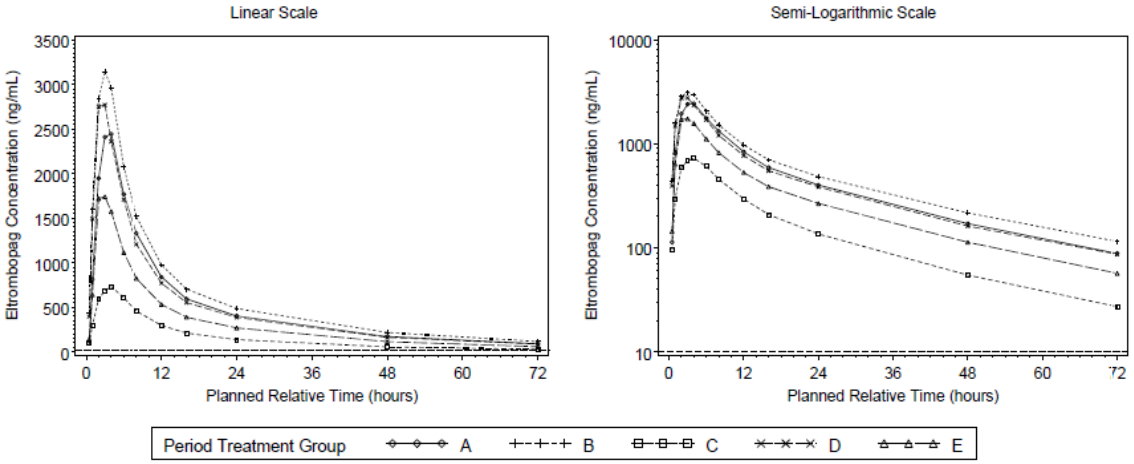
The standard high calcium meal composition is presented below.

Food	Kilocalories	Calcium (mg)	Fat (gm)
1 cup Cheerios	111	100	1.8
½ cup (4 oz) 2% milk	61	150	2.3
1 slice toast	69	20	1.2
2 teaspoon jam	37	2.7	0
1 teaspoon butter	34	1	3.8
½ cup (4 oz) calcium fortified orange juice	60	175	0
TOTALS	**372**	**448**	**9.1**

Blood samples for pharmacokinetic analysis of eltrombopag were collected following a single dose administration in each treatment period at Pre-dose, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 48.0, 72.0 hours post-dose.

Results

The mean plasma eltrombopag concentration-time plot (Linear and Semi-Log) (overlay treatment) is presented below.



Following oral administration of eltrombopag as a tablet or PfOS, plasma eltrombopag concentrations were quantifiable within 0.5 to 1 hour after dosing, with median t_{max} values of 2 to 4 hours. Eltrombopag was eliminated slowly with $t_{1/2}$ geometric mean values ranging from 18.9 to 20.7 hours (see the table below). Median $\%AUC_{ex}$ was 6 to 7% across the treatments; all individual %AUCex were less than 20%, except for Subject 1071 who had an %AUCex of 20.8% for Treatment B. Moderate inter-subject variability (37% to 57% CVb) was observed for plasma eltrombopag $AUC_{0-\infty}$ and C_{max} across the treatments (see the table below).

Table: Summary of Select Plasma Eltrombopag Pharmacokinetic Parameters

Plasma Eltrombopag PK Parameter	Treatment A (N=38)	Treatment B (N=38)[3]	Treatment C (N=37)	Treatment D (N=40)	Treatment E (N=39)
AUC(0-∞)[1] (µg.h/mL)	34.2 (29.9, 39.1) [42%]	41.1 (35.2, 48.0) [49%]	10.6 (8.89, 12.6) [57%]	33.9 (29.6, 38.8) [44%]	22.1 (18.9, 25.8) [51%]
Cmax[1] (µg/mL)	2.55 (2.27, 2.87) [37%]	3.30 (2.88, 3.78) [44%]	0.700 (0.586, 0.835) [57%]	2.87 (2.53, 3.26) [41%]	1.74 (1.53, 1.98) [42%]
tmax (h)[2]	3.00 (2.00, 6.00)	3.00 (2.00, 6.00)	4.00 (2.00, 6.00)	2.00 (1.00, 4.00)	3.00 (2.00, 6.00)
tlag (h)[2]	0.00 (0.00, 1.00)	0.00 (0.00, 0.50)	0.00 (0.00, 0.52)	0.00 (0.00, 0.50)	0.00 (0.00, 0.50)
t1/2 (h)[1]	20.5 (19.3, 21.9) [20%]	20.6 (19.1, 22.1) [22%]	18.9 (17.4, 20.6) [26%]	20.7 (19.4, 22.2) [21%]	19.9 (18.5, 21.3) [22%]

Source Data: Table 11.4

1. Data presented as geometric mean (95% CI) [CVb%]
2. Data presented as median (minimum, maximum)
3. N=37 for AUC(0-∞) and t1/2

Assessment of the relative bioavailability of eltrombopag powder for oral suspension versus tablet formulation and assessment of impact of administering eltrombopag powder for oral suspension with and two hours apart from a high-calcium meal is presented below

Plasma Eltrombopag PK Parameter	Relative Bioavailability	Impact of Administering Eltrombopag		
		With high Calcium Meal	2 hours before high calcium meal	2 hours after high calcium meal
	Treatment B vs A	Treatmen C vs B	Treatment D vs B	Treatment E vs B
AUC(0-∞)[1] (µg.h/mL)	1.22 (1.08, 1.38)	0.254 (0.224, 0.287)	0.804 (0.711, 0.908)	0.531 (0.470, 0.601)
Cmax[1] (µg/mL)	1.31 (1.14, 1.50)	0.211 (0.184, 0.243)	0.859 (0.750, 0.984)	0.524 (0.457, 0.601)
tmax (h)[2]	-0.500 (-1.00, 0)	1.00 (0.50, 1.50)	-0.50 (-0.50, 0)	0 (-0.50, 0)
tlag (h)[2]	0 (-0.25, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
t1/2 (h)[1]	1.01 (0.959, 1.06)	0.902 (0.858, 0.948)	0.995 (0.947, 1.05)	0.958 (0.912, 1.01)

1. Data Presented as geometric least squares mean ratio (90% CI)
2. Data Presented as median difference (90% CI)

A: eltrombopag 25 mg tablet fasted
B: eltrombopag 25 mg PfOS fasted
C: eltrombopag 25 mg PfOS administered with high calcium meal
D: eltrombopag 25 mg PfOS administered two hours before high calcium meal
E: eltrombopag 25 mg PfOS administered two hours after high calcium meal

The results for AUC_{0-t} are presented below:

Plasma Eltrombopag PK Parameter	Relative Bioavailability	With high Calcium Meal	2 hours before high Calcium Meal	2 hours after high Calcium Meal
	Treatment B vs A	Treatment C vs B	Treatment D vs B	Treatment E vs B
AUC_{0-t} (ug.h/mL)	1.22 (1.08, 1.38)	0.253 (0.224, 0.286)	0.803 (0.712, 0.905)	0.532 (0.471, 0.600)

On average, plasma eltrombopag $AUC_{0-\infty}$ and AUC_{0-t} was 22% higher and C_{max} was 31% higher following single dose administration of the PfOS 25 mg fasted relative to single dose administration of the tablet 25 mg fasted.

Administration of a single 25 mg dose of the eltrombopag PfOS with a high-calcium meal reduced plasma eltrombopag $AUC_{0-\infty}$ and AUC_{0-t} 75% and C_{max} 79% compared to fasting.

Administration of a single 25 mg dose of the eltrombopag PfOS 2 hours after a high-calcium meal reduced plasma eltrombopag $AUC_{0-\infty}$ and AUC_{0-t} 47% and C_{max} 48% compared to fasting.

Administration of a single 25 mg dose of the eltrombopag PfOS 2 hours prior to a high-calcium meal reduced plasma eltrombopag $AUC_{0-\infty}$ and AUC_{0-t} 20% and C_{max} 14% compared to fasting.

Although administration of a single 25 mg dose of the eltrombopag PfOS 2 hours prior to a high-calcium meal reduced plasma eltrombopag $AUC_{0-\infty}$ and AUC_{0-t} approximately 20% and C_{max} 14% compared to fasting, these data support administration of Eltrombopag PfOS at least 2 hours before high-calcium meals; whereas, a longer time separation (4 hours) is still required if eltrombopag is administered after a high-calcium meal as this reduction is considered not clinical relevant.

The results obtained with the PfOS could be extrapolated to the tablets formulation as both formulations have similar absorption-time profile and support a revised recommendation to administer eltrombopag tablets at least 2 hours prior or 4 hours after polyvalent metal cation-containing products.

Population PK and PK/PD analyses

The goal of the clinical pharmacology evaluation described in this application is to support selection of eltrombopag starting doses and dose titration schedules based on population pharmacokinetic (popPK) data and the relationship between plasma eltrombopag exposure and platelet response (popPK/PD) analyses in pediatric ITP patients 1 to 17 years of age enrolled in PETIT and PETIT 2 Studies.

Study Design and Methodology

PopPK and PK/PD analyses included concentration-time and platelet count-time data following eltrombopag dosing in pediatric ITP patients 1 to 17 years of age enrolled in Studies TRA108062/PETIT and TRA115450/PETIT-2. Subjects were enrolled into age cohorts: Cohort 1: 12 to 17 years, Cohort 2: 6 to 11 years, Cohort 3: 1 to 5 years. Subjects received eltrombopag for at least 24 weeks. Subjects underwent weekly visits until platelet counts were stable and then underwent monthly visits thereafter.

Subjects 1 to 5 years of age received the eltrombopag Powder for Oral Suspension (PfOS) formulation and were dosed on a mg/kg basis; starting doses ranged from 0.7 to 1.5 mg/kg once daily. Subjects 6 to 17 years of age received tablets, and starting doses ranged from 25 to 50 mg once daily. East Asian subjects initiated eltrombopag at approximately 30 to 50% lower doses. Doses were increased at 2-week intervals if platelet counts were <50 Gi/L; the maximum eltrombopag dose was 75 mg once daily.

Doses were decreased at any time platelet counts were >200 Gi/L and dosing was interrupted when platelet counts were >400 Gi/L. Serial PK samples were collected at Week 6 in Study TRA108062/PETIT, and a single PK sample was collected at all visits in both studies. Platelet counts were collected at all visits. Plasma eltrombopag concentration-time and platelet count-time data were analyzed by nonlinear mixed-effects modelling using NONMEM software Version 7.2. PK and PD parameters were estimated using the first order conditional estimation method with interaction (FOCE-I).

Population PK Model Results

The initial PopPK modelling was done with data from one study, TRA108062/PETIT. The final model developed with data from TRA108062/PETIT was used to predict concentrations of Study TRA115450/PETIT2 as an external validation. Following successful external validation, data from both study TRA108062/PETIT and TRA115450/PETIT-2 were combined to obtain final PopPK model parameter estimates for eltrombopag in pediatric subjects with ITP.

Plasma eltrombopag PK were described by a 2-compartment model, with first-order absorption and elimination. Inter-individual variability (IIV) was included on apparent oral clearance (CL/F), volume of the central compartment (V2/F), and intercompartmental exchange flow rate (Q/F). In addition, Inter-occasion variability (IOV) was included on CL/F, with three occasions defined as serial PK profiles, sparse PK samples collected Weeks 1-6, and sparse PK samples collected at $\geq$Week 7.

Lower plasma eltrombopag CL/F was observed for pediatric ITP patients of East/Southeast Asian ancestry (30% lower CL/F) and female sex (20% lower CL/F). The race and sex effects identified in the pediatric analysis are consistent with previous analyses in adults, where East/Southeast Asian adults had 33% lower CL/F and female adults had 19% lower CL/F. These CL/F differences translate to a mean (95% CI) 43% (25%, 67%) higher AUC(0-τ) in East/Southeast Asian pediatric subjects and a 25% (14%, 41%) higher AUC(0-τ) in female pediatric subjects.

Plasma eltrombopag CL/F (L/hr), Q (L/hr), V2/F (L), and volume of the peripheral compartment (V3/F) (L) increased with body weight. The estimated exponents for weight on clearance (0.691) and volume (0.791) parameters were close to allometric values (0.75 for clearance and 1.0 for volume parameters).

The PfOS had 29% lower bioavailability relative to the tablet. The lower bioavailability of the PfOS relative to the tablet in the pediatric analysis is confounded by age because the PfOS formulation was only used in subjects 1 to5 years of age and the tablet formulation was only used in subjects 6 to 17 years of age. Because age and formulation were correlated, each was tested separately as a covariate (in models that also included weight, sex, and race). The final model included formulation on F1 because the objective function value (OFV) for this model was significantly lower than the model that included age on CL/F.

All parameters were estimated with good precision (%RSE <20%), except IIV of V2/F and Q/F (%RSE=40% for IIV of V2/F and 31% for IIV of Q/F).

Goodness of fit (GOF) plots showed the 2-Study PopPK final model adequately described the data and produced unbiased population and individual predictions. Random effects were normally distributed and were not correlated. No unexplained covariate-parameter relationships were observed. The non-parametric bootstrap estimates of the model parameters were similar to the NONMEM estimates.

The observed median and 5th and 95th percentiles were within the 90% confidence intervals of the VPC, and 9.9% of the observed concentrations fell outside the 90% prediction interval of the simulated values. Based on GOF, bootstrap, and VPC, the final model was deemed to have acceptable predictive performance for simulation purposes.

Population PK/PD Model Results

Data from both study TRA108062/PETIT and TRA115450/PETIT-2 were combined to obtain final PopPK/PD model parameter estimates for eltrombopag in pediatric subjects with ITP.

The relationship between plasma eltrombopag exposure and platelet response was described by a 7-compartment life-span model, including three PK compartments (absorption, central, and peripheral) and four PD compartments. The four PD compartments represented three bone marrow compartments (one platelet precursor production and two maturation compartments) and one blood platelet compartment in which the increase in the rate of platelet precursor production (KIN) was linearly related to plasma eltrombopag concentrations. A mixture model with different SLOP parameters for two sub-populations, responders (SLOP estimated) and nonresponders (SLOP=0), was implemented.

SLOP, KOUT (platelet maturation rate), and P1 (the proportion of subjects identified as responders) were estimated, and KIN was fixed to adult value. IIV was included on SLOP and KOUT. The estimate of SLOP (0.651 mL/μg) was consistent with prior analysis in adults (0.579 mL/μg). The majority of subjects (96%) were identified as responding to eltrombopag treatment. KOUT increased with increasing age, which influenced the time to steady-state platelet count. The time to $\geq$80% of steady-state platelet count was 4 weeks for subjects 6 to 17 years of age and 6 weeks for subjects 1 to 5 years of age (Figure 3). No significant covariates were identified on SLOP. The first-order platelet degradation rate (KDEG) is calculated as KIN/BASL, and the average value of KDEG was 0.102/hr (1.43 Gi/L/hr/14 Gi/L). Based on this KDEG, the average half-life of platelets was approximately 7 hours. All parameters were estimated with good precision (%RSE <20%), except the effect of baseline age on KOUT (BAGE~KOUT, %RSE=30%).

GOF plots showed the final PopPK/PD model adequately described the data and produced unbiased population and individual predictions. Random effects were normally distributed and were not correlated. No unexplained covariate-parameter relationships were observed. The observed median and 5th and 95th percentiles were within the 90% confidence intervals of the VPC, and 9.3% of the observed concentrations fell outside the 90% prediction interval of the simulated values. Based on GOF and VPC, the final model was deemed to have acceptable predictive performance for simulation purposes.

Comparison between Pediatric and Adult PopPK and PopPK/PD Results

The typical value of plasma eltrombopag CL/F estimated in the pediatricPopPK analysis was consistent with the value estimated in a prior analysis in adult subjects with ITP. V2/F, Q/F, and V3/F parameter estimates varied from the values estimated in adults, and the pediatric model included a single first-order Ka as opposed to dual sequential Ka model in adults. A PK model, including dual sequential Ka and an absorption lag time was tested, and the V2/F estimate from this model was 10.0 L(similar to adult value), but this model was not accepted as the final model because of the high RSE of Ka2 and no obvious change in GOF plots. The effects of race and sex on plasma eltrombopag CL/F estimates were consistent between pediatric and adult analyses. For East Asian pediatric subjects, a 30% lower CL/F translates to a 43% higher AUC(0-τ), similar to the 33% lower CL/F and 49% higher AUC(0-τ) in East Asian adult subjects. For female pediatric subjects, a 20% lower CL/F translates to a 25%higher AUC(0-τ), similar to the 21% lower CL/F and 23% higher AUC(0-τ) in female adult subjects.

Based on the PopPK analysis, the bioavailability of the PfOS in pediatric subjects with chronic ITP was estimated as 29% lower than the tablet. This is in contrast to the 22% higher bioavailability of the PfOS relative to the tablet observed in healthy adult subjects. The relative bioavailability estimate in pediatric subjects is confounded by age because the PfOS formulation was only used in subjects 1 to 5 years of age and the tablet formulation was only used in subjects 6 to 17 years of age.

Adolescents 12 to 17 years of age had similar and children 1 to 11 years of age had higher plasma eltrombopag AUC(0-τ) and Cmax values compared to adults for the same 50 mg dose. Plasma eltrombopag tmax and t1/2 values were consistent between pediatric and adult subjects with ITP.

The typical value of SLOP estimated in the pediatric PopPK/PD analysis was consistent with the value estimated in a prior analysis in adult subjects with ITP. The estimate of KOUT in the pediatric analysis was lower than the value estimated in adults, and KOUT was dependent on age. A higher proportion of pediatric subjects with ITP were identified as responders compared to the adult analysis, and this may be a result of the longer treatment duration in the pediatric studies ($\geq$24 weeks) versus adult studies (6 weeks) included in analyses. No covariates were identified on SLOP in the pediatric analysis; whereas, age and sex were identified as covariates on SLOP in adults.

In summary the pharmacokinetics of eltrombopag have been evaluated in 168 paediatric ITP subjects dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT-2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. The effects of race and sex on plasma eltrombopag CL/F estimates were consistent between paediatric and adult patients. East Asian paediatric ITP patients had approximately 43% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients. Female paediatric ITP patients had approximately 25% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to male patients. The pharmacokinetic parameters of eltrombopag in paediatric subjects with ITP are shown in Table below.

Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in paediatric subjects with ITP (50 mg once daily dosing regimen)

Age	**C_{max} (µg/ml)**	**$AUC_{(0-\tau)}$ (µg.hr/ml)**
12 to 17 years (n=62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n=68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n=38)	11.6 (10.4, 12.9)	162 (139, 187)

Data presented as geometric mean (95%CI). $AUC_{(0-()}$ and C_{max} based on population PK post-hoc estimates

PK and PK/PD Simulation Results

Steady-state plasma eltrombopag PK profiles were simulated for a 24-hour dosing interval, with PK sampling at 0, 1, 2, 4, 6, 8, 12, and 24 hours after dosing, based on individual post-hoc PK parameter estimates from the final pediatric PopPK model. Plasma eltrombopag Cmax, C, and tmax were extracted from the profiles, AUC(0-τ~~∞~~) was calculated as Dose/CL/F for tablet formulation and Dose/CL/F*F1 for PfOS formulation, and t1/2 was calculated from CL/F, V2/F, Q/F, and V3/F. For the purpose of comparison, the same simulation was done for adults, based on individual post-hoc PK parameter estimates from the final adult ITP PopPK model and including adult subjects with ITP enrolled in Studies TRA100773A, TRA100773B, and TRA108109.

Simulations were completed for a 50 mg once daily dosage regimen to compare between age cohorts and adult subjects. Simulations were also completed for the final once daily dosage regimen recorded in the PopPK/PD dataset, the maximum 75 mg once daily regimen, and for various dosage regimens based on age plus race and weight bands.

Adolescents 12 to 17 years of age had similar plasma eltrombopag AUC(0-τ~~∞~~) and Cmax values as adults for the same 50 mg dose. When normalized to a 50 mg dose (DN), children 1 to 11 years of age, females, and East/Southeast Asian subjects had higher plasma eltrombopag DN-AUC(0-τ~~∞~~) and DN-Cmax values. Median plasma eltrombopagtmax values were 4 hours across age cohorts and consistent with adult values. Geometric mean plasma eltrombopag t1/2 value ranged from 46.9 to 51.9 h across age cohorts, consistent with the 44.0 h estimate in adults.

- Summary of Plasma Eltrombopag PK for the Final Dosage Regimen

The majority of subjects aged 6 to 17 years of age and approximately half of subjects aged 1 to 5 years of age received eltrombopag doses ≥50 mg as their final eltrombopag regimen. Overall, East/Southeast Asian subjects received lower or similar eltrombopag final doses and had higher plasma eltrombopag exposures than non- East/Southeast Asian subjects. Geometric mean plasma eltrombopag AUC(0-τ~~∞~~) values at the final doses ranged from 104 to 188 µg.h/mL.

The highest dose administered to pediatric subjects with chronic ITP was 75 mg once daily. In clinical studies, children in all age cohorts escalated to the 75 mg once daily regimen. Geometric mean plasma eltrombopag AUC(0-τ_{ss}) values for the 75 mg once daily regimen ranged from 154 to 242 µg.h/mL.

Plasma eltrombopag AUC(0-τ_{ss}) values were estimated for various dosage regimens to complement the platelet count simulations based on age and race and based on weight bands (AUC(0-τ_{ss}) plots. Geometric mean plasma eltrombopag AUC(0-τ_{ss}) values at the proposed starting doses ranged from 77.2 to 137 µg.h/mL.

- Platelet Count Simulation Results to Support Eltrombopag Starting Dose and Dose Titration Schedules

Simulations based on the final PopPK/PD model were completed to inform starting doses and dose titration schedules in pediatric subjects with ITP. Each simulation dataset included individual subject demographic and baseline characteristics for the 168 subjects included in the analysis, and 100 simulation datasets were included for each dosing scenario.

Median predicted platelet count versus time profiles were more consistent across groups when eltrombopag starting doses were based on age and race as compared to starting doses based on weight bands. In clinical trials, subjects 1 to 5 years of age were dosed on a mg/kg basis. According to the MAH, simulations support eltrombopag dosing on a mg basis. An eltrombopag 25 mg once daily starting dose resulted in similar proportions of subjects achieving threshold platelet counts as 1.5 mg/kg once daily based on simulation, similar to the starting dose used for Cohort 3 (1 to 5 years) in the pediatric clinical trials.

Simulations support dose titration every two weeks because the proportion of subjects predicted to be at each dose level following dose titration is similar for dose titration at 2- , 3-, and 4-week intervals. Incorporation of additional dose escalation steps resulted in a slightly lower proportion of subjects predicted to receive the highest 75 mg dose, but this strategy requires multiple tablet strengths to accommodate the various dose steps (e.g. a 37.5 mg dose requires 25 mg and 12.5 mg tablets) or administration of different tablet doses on alternating days. In addition, the time to achieve therapeutic platelet counts is increased for some subjects when more dose escalation steps are implemented.

Proposed Eltrombopag Starting Dose and Dose Titration Schedules

Simulations support eltrombopag starting doses based on age and race to maintain consistent platelet counts across groups. Based on the final doses administered in clinical studies, the majority of subjects will require dose escalation to achieve target platelet response. The proposed dose titration schedule will allow subjects to achieve therapeutic platelet counts within 1 to 2 dose escalations.

Simulations support dose titration every 2 weeks using dose titration steps that allow administration of a single tablet strength in children 6 to 17 years of age and administration of the full 25 mg sachet dose in children 1 to 5 years of age.

2.4.2. Pharmacodynamics

No new Pharmacodynamics studies have been provided.

2.4.3. Discussion on clinical pharmacology

Pharmacokinetics

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52 %.

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59 %) with 31 % of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20 % of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

The MAH has performed a pharmacokinetic study comparing relative bioavailability and food effect of an eltrombopag powder for oral suspension (PfOS) formulation with the currently marketed 25mg tablet formulation. Eltrombopag bioavailability was higher following administration of the powder for oral suspension (PfOS) compared to the tablet formulation in a randomised, balanced cross-over study conducted in 40 healthy adult subjects (TRA 111718). The geometric mean (90% CI) plasma eltrombopag area under the concentration-time curve from time zero to infinity [AUC(0-inf.)] was 22% (8%, 38%) higher and the maximum concentration (Cmax) was 31% (14%, 50%) higher. The information is included in the SmPC section

The relative bioavailability of the PfOS to the tablet formulation was also estimated in the paediatric population PK analysis. In contrast to the results in healthy adult subjects, the bioavailability of the PfOS in children was estimated as 29% lower than the tablet. The interpretation of the results of the relative bioavailability in this paediatric study appears to be complicated by the fact that the oral suspension formulation was used only in very young children of 1 to 5 years of age and the tablet formulation was used in subjects of aged 6 to 17 years. Since the eltrombopag oral suspension and tablet formulations do not seem to be bioequivalent, platelet counts will need to be closely monitored when a patient switches between formulations.

Administration of a single 25 mg dose of the ~~eltrombopag oral~~eltrombopag oral suspension with a high-calcium moderate fat and moderate calorie meal reduced plasma eltrombopag AUC(0-inf.) 75% and Cmax 79% compared to fasting. This decrease of exposure was attenuated when a single 25 mg dose of eltrombopag powder for oral suspension was administered 2 hours before a high-calcium meal (mean $AUC_{0-\infty}$ was decreased by 20% and mean C_{max} by 14%). The results obtained with the PfOS could be extrapolated to the tablets formulation as both formulations have similar absorption-time profile and support a revised recommendation to administer eltrombopag tablets at least 2 hours prior or 4 hours after polyvalent metal cation-containing products. Administration of a single 50 mg dose of eltrombopag in tablet form with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 59% and mean C_{max} by 65%.

Food low in calcium (< 50 mg calcium) including fruit, lean ham, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content This information has been included in the SmPC (see sections 4.2 and 4.5).
The population pharmacokinetic model developed for pediatric ITP patients describes adequately the observations obtained. The model was adapted from a previously validated two-compartment model developed in an adult population. The model has been adequately developed and supports the starting dose and the dose adjustment recommendations.

The 7-compartment life-span model, including three PK compartments (absorption, central, and peripheral) and four PD compartments, adequately described platelet count response following eltrombopag administration. Three bone marrow and one circulating platelet compartments describe are able to the pharmacodynamics variable, where the increase in platelet precursor production rate (KIN) was linearly related to plasma eltrombopag concentration. Moreover, the drug- (SLOPE) and system-related (kin, kout) pharmacodynamics parameters seem comparable between adult and paediatric population.

Data from the 168 paediatric subjects with chronic ITP who provided PK and platelet count data in the two eltrombopag clinical studies were pooled for population PK and PK/PD analyses. Plasma eltrombopag PK following repeat oral administration to paediatric subjects with ITP were described by a 2-compartment model with first order absorption and elimination. Eltrombopag CL/F, volume of the central compartment (V2/F), inter-compartmental exchange flow rate (Q/F), and volume of the peripheral compartment (V3/F) increased with body weight. Mean (95% CI) plasma eltrombopag CL/F was 30% (20%, 40%) lower in East Asian subjects compared to other races and 20% (12%, 29%) lower in female subjects. These CL/F differences translate to a mean (95% CI) 43% (25%, 67%) higher AUC(0-τ_{ss}) in East Asian subjects and 25% (14%, 41%) higher AUC(0-τ_{ss}) in female subjects.

2.4.4. Conclusions on clinical pharmacology

Clinical pharmacology data support additional recommendations in the SmPC regarding switching between pharmaceutical formulations and the food effect on the treatment.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Eltrombopag starting doses for PETIT2 (Table 5) were determined based on consideration of preliminary safety, efficacy and PK data from the open-label, Dose Finding Phase of the PETIT study, while PETIT was ongoing. A reduced dose was used for East Asian subjects in PETIT based on clinical pharmacology data in adult subjects.

Table 5 PETIT2 Eltrombopag Starting Doses for the Randomized Period

	Cohort 1 (Age 12-17)		Cohort 2 (Age 6-11)		Cohort 3 (Age 1-5)
	<27 kg	≥27 kg	<27 kg	≥27 kg	
Non-East Asian	37.5 mg	50 mg	37.5 mg	50 mg	1.2 mg/kg
East Asian	25 mg		25 mg		0.8 mg/kg

m5.3.5.1 TRA115450 CSR Section 4.5.2

Note: The maximum dose allowed for any subject was 75 mg once daily.

Each subject's dose was adjusted as needed according to the dosing guidelines and based on their platelet response.

PETIT was a Phase II, multicenter, 3 part, staggered cohort, open-label and double blind, randomized, placebo controlled study stratified by 3 age-determined cohorts (Cohort 1: 11 – 17 years of age, Cohort 2: 6 – 10 years of age, Cohort 3: 1-5 years of age). The younger cohorts were not enrolled until safety, PK and platelet counts had been reviewed for the first 12 weeks of Part 1 in the older cohort(s).

-Part 1 (Dose Finding Phase): A 24-week open label treatment period for 5 subjects in each age cohort. A safety, PK and platelet count review took place after 12 weeks (3 months) of treatment. Subjects in the Dose Finding Phase did not participate in the Randomized Period.

-Part 2 (Randomized Period): A 7-week randomized, double-blind, placebo-controlled period involving 18 subjects per cohort. Sixty-seven subjects were enrolled in Part 2 (45 on eltrombopag, 22 on placebo).

-Part 3: An open-label treatment period where subjects randomized to eltrombopag in Part 2 received an additional 17 weeks of eltrombopag in Part 3 and subjects randomized to placebo in Part 2 received 24 weeks of eltrombopag in Part 3.

The starting doses for pediatric subjects in the Eltrombopag Dose Finding Phase of PETIT (Table 6) were selected according to age, weight and race based on adult PK and clinical data. Adolescents (12 to 17 years old) were the first cohort dosed. Each subject's eltrombopag starting dose was adjusted as needed according to the dosing guidelines and based on their platelet response. A safety, PK and platelet count review of instream data took place after 5 subjects in Cohort 1 had received 12 weeks of treatment. Since no safety concerns were identified after 12 weeks, the initial 5 subjects continued treatment with open-label eltrombopag to complete 24 weeks and the next younger cohort (Cohort 2) began enrolment.

The same procedure was followed in terms of safety review and subsequent enrolment and dosing in the youngest cohort (Cohort 3) for the Dose Finding Phase. In addition, initiation of Cohort 3 took place only after data from the previous Cohorts 1 and 2 had been evaluated by the Data Safety Monitoring Board.

Table 6 PETIT Starting Doses for the Eltrombopag Dose Finding Phase

	Cohort 1 (Age 12-17)	Cohort 2[a] (Age 6-11)		Cohort 3[a] (Age 1-5)
		<27kg	≥27kg	
Non-East Asian	25 mg	12.5 mg	25 mg	0.7 mg/kg
East Asian	12.5 mg			0.5 mg/kg

m5.3.5.1 TRA108062 CSR, Section 4.5.1.1

Note: The maximum dose allowed for any subject was 75 mg once daily.

a. The maximum dose allowed was 2 mg/kg rounded to the nearest available tablet strength, not exceeding 75 mg once daily.

Each subject's dose was adjusted as needed according to the dosing guidelines and based on their platelet response. Conservative starting doses were used in the Eltrombopag Dose Finding Phase, requiring several dose escalations throughout the study. During the 24 week treatment period, 14 of 15 subjects required ≥4 increases in eltrombopag dose. At the end of treatment, the majority (70%) of Cohort 1 and Cohort 2 subjects were receiving eltrombopag 75 mg once daily and Cohort 3 subjects were receiving doses 4- fold the starting dose (median of 66 mg or 3.0 mg/kg with a range of 34 to 75 mg [2.11 to 4.33 mg/kg]).

The majority of subjects (73.3%) achieved a platelet response during the 24 weeks of the Dose Finding Phase. Eltrombopag treatment was well tolerated; AEs were predominantly low grade and none led to withdrawal of eltrombopag. The need for multiple escalations to achieve platelet response, in combination with the safety and PK results, supported an increased starting dose in the Randomized Period (Table 7).

Table 7 PETIT Eltrombopag Starting Doses for the Randomized Phase

	Cohort 1 (Age 12-17)	Cohort 2 (Age 6-11)		Cohort 3 (Age 1-5)
		<27kg	≥27kg	
Non-East Asian	37.5 mg	25 mg	50 mg	1.5 mg/kg
East Asian	37.5 mg	12.5 mg	25 mg	0.8 mg/kg

m5.3.5.1 TRA108062 CSR, Section 4.5.1.1

Note: The maximum dose allowed for any subject was 75 mg once daily.

Dose Modification in PETIT2 and PETIT

The dose of eltrombopag in both studies was titrated based upon platelet response. The dose was increased if the platelet count remained below 50 Gi/L after 2 weeks at a given dose. For subjects receiving the tablet formulation, the following dose levels were available: 12.5 mg, 25 mg, 37.5 mg, 50 mg, 62.5 mg and 75 mg once daily. Initially increases were made to the next whole tablet dose (i.e., 25 mg, 50 mg or 75 mg). If an intermediate dose was required, then the dose could be adjusted by 12.5 mg, or the frequency reduced to less often than once daily.

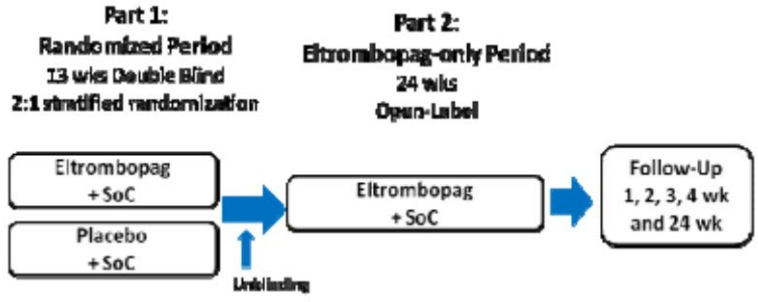
For subjects receiving the dry powder for oral suspension (PfOS) formulation, the dose was modified initially by a 30% increase or decrease. Intermediate dosing levels were allowed. The maximum dose for any subject was 75 mg once daily. The goal was to achieve and maintain platelet counts in the target range of 50 Gi/L to 200 Gi/L. The dose of eltrombopag was reduced whenever the platelet count exceeded 200 Gi/L and was interrupted if the platelet count exceeded 400 Gi/L. Eltrombopag was restarted at the next lower dose once the platelet count decreased below 150 Gi/L. Subjects who received eltrombopag during the Randomized Period continued on the same dose in the Eltrombopag-Only Period unless adjustments were warranted according to the dosing guidelines. For subjects who received placebo during the Randomized Period, the starting dose in the Eltrombopag-Only period was based on the above mentioned dosing guidelines (Table 5 and 7).

2.5.2. Main study(ies)

PETIT2

PETIT2 was a two part, double-blind, randomized, placebo-controlled and open-label Phase III study to investigate the efficacy, safety and tolerability of eltrombopag in paediatric subjects with previously treated chronic ITP.

Figure 2 PETIT2 Study Design Schematic



Abbreviations: SoC=Standard of Care

Methods

Study design:

Part 1(Randomized Period): 92 subjects were randomized 2:1 to receive eltrombopag) or placebo in a 13-week double-blind, placebo-controlled treatment period.

Part 2 (Eltrombopag-Only Period): subjects received eltrombopag in an open-label manner for 24 weeks. In total, subjects randomized to placebo in Part 1 received up to 24 weeks of eltrombopag treatment, and subjects randomized to eltrombopag in Part 1 received up to 37 weeks of eltrombopag treatment. After completion of Part 2, subjects were to complete a 24 to 28 week follow-up Period including an ophthalmic examination 24 weeks after the last dose of study treatment.

Study Participants

Subjects were eligible for enrolment in the study if they met all of the following key inclusion criteria: between 1 year and <18 years of age at Day 1; confirmed diagnosis of chronic ITP for at least 1 year, at screening, according to the guidelines published in the International Working Group Report; peripheral blood smear or bone marrow examination supported the diagnosis of ITP with no evidence of other causes of thrombocytopenia, refractory or relapsed after at least one prior ITP therapy, or subjects must have been unable, for a medical reason, to continue other ITP treatments, concomitant ITP medication (e.g. corticosteroids or azathioprine) administered at a stable dose for at least 4 weeks prior to Day 1, Day 1 (or within 48 hours prior) platelet count <30 Gi/L. In addition, subjects were allowed to receive additional rescue treatment at any time during the study, if required. Rescue treatment was defined as any of the following: addition of an ITP medication, increased dose of a concomitant ITP medication from baseline, platelet transfusion, or splenectomy.

Treatments

Both eltrombopag tablets and Powder for Oral Suspension (PfOS) (and matched placebo formulations) were used in this study. Starting doses varied based on age and weight. Additionally, East Asian subjects had lower starting doses based upon adult data showing increased exposure in East Asian patients and consequently response at lower doses. Eltrombopag was given once daily and doses were titrated based on platelet response. The maximum dose for both tablets and PfOS was 75mg daily.

The choice of rescue treatment was at the discretion of the investigator.

Outcomes/endpoints

The primary endpoint was the proportion of subjects on eltrombopag, compared to placebo, achieving platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 to 12 of Part 1, the Randomized Period, in the absence of rescue medication.

Other efficacy endpoints were analysis of the need for rescue treatment, the frequency and severity of bleeding, analysis of bleeding AEs, and the reduction or discontinuation of baseline concomitant ITP medications.

The safety and tolerability of eltrombopag was assessed by the analysis of the frequency of adverse events (AEs), clinical laboratory tests (haematology, chemistry, urinalysis), vital signs (blood pressure and heart rate), and ophthalmic examinations. PK endpoints were also included in the study.

Sample size

The study protocol assumed a response rate of 10% for placebo and 50% for eltrombopag based on the response rates at each nominal visit during the first 10 weeks of the placebo-controlled clinical study TRA102537/RAISE. Hence, for the randomized placebo-controlled part of the study, using a 2:1 randomization, a total sample size of 66 evaluable subjects was needed in order to provide at least 90%

power at the 5% level of significance (two-sided). This sample size was calculated using the Fisher's Exact Test option in PASS 2005. Allowing for an additional 10% of subjects to compensate for missing data and drop-outs, we planned to randomize approximately 75 subjects (50 on eltrombopag, 25 on placebo). Randomization was stratified into the 3 age-defined cohorts. The protocol stipulated a minimum of 25 subjects each for Cohort 1 and Cohort 2, and at least 12 subjects for Cohort 3. In this study, a positive response was defined for each assessment if the corresponding platelet count was ≥50 Gi/L. A platelet count <50 Gi/L was considered a negative response.

Randomisation

Patients in Part 1 -Randomized Period were randomized 2:1 to receive eltrombopag or placebo. The randomization was stratified by 3 age-defined cohorts: Cohort 1 enrolled subjects between 12 and 17 years old, Cohort 2 enrolled subjects between 6 and 11 years old, and Cohort 3 enrolled subjects between 1 and 5 years old. As each subject completed the Part 1 Week 12 visit, data up to Week 12 were reviewed and verified, and the database was locked for that subject prior to the Week 13 visit.

Blinding (masking)

Part I was double blinded. At week 13 visit the investigator was unblinded to the treatment assignment.

Statistical methods

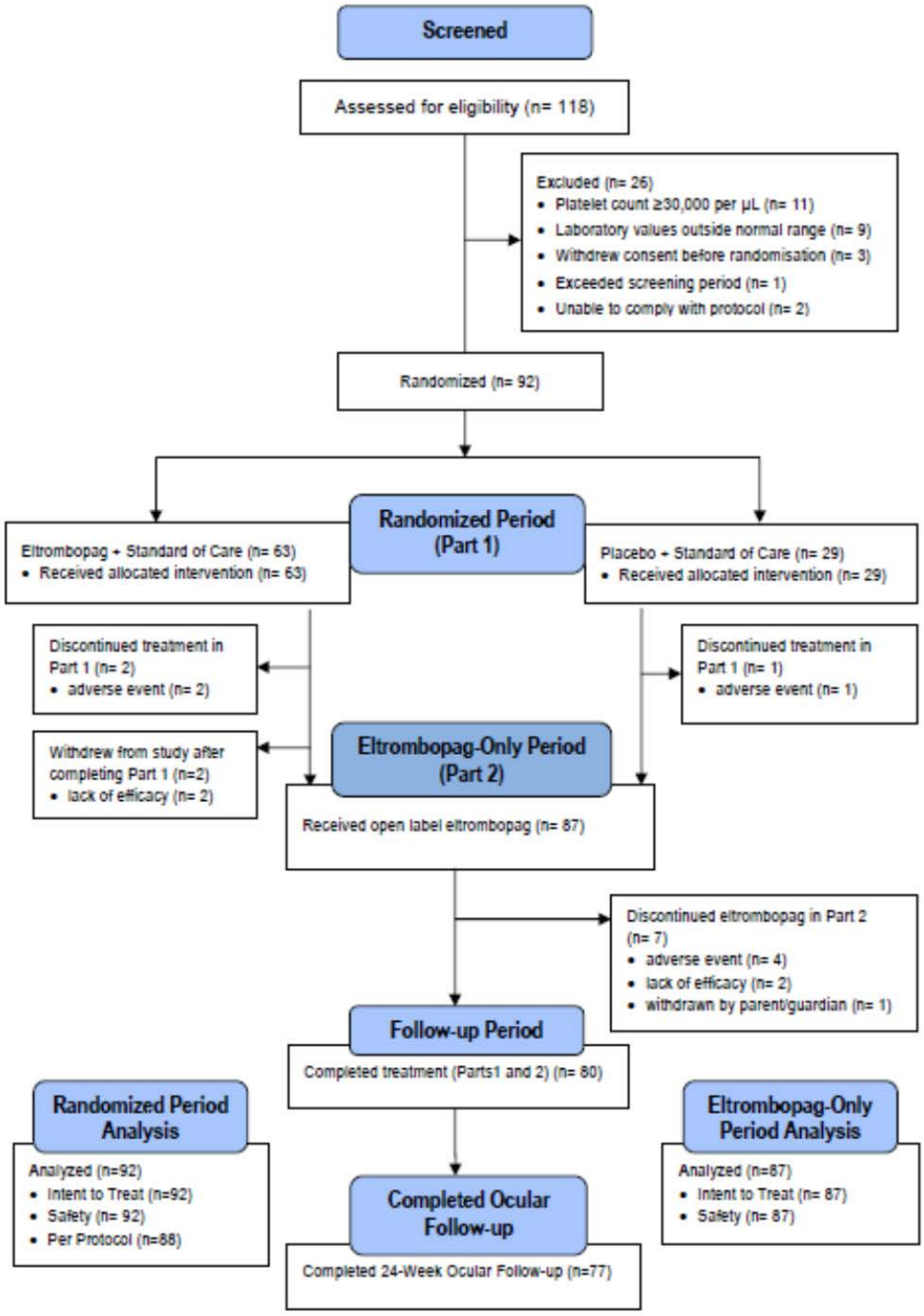
Planned analysis: All planned efficacy and safety analyses were performed when all of the subjects had either completed the 4-week follow-up visit or withdrawn from the study (first DBF). Additional safety analyses, including those pertaining to ocular data or AEs reported in the Follow-up Period were reported after all subjects completed the study (second DBF). There were no interim analyses.

The primary analysis was to compare eltrombopag with placebo in the assessment of the proportion of subjects that achieved platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 through 12 of the Randomized Period (Part 1). The study was designed to assess the null hypothesis H0 of no difference or reject it in favour of the alternative hypothesis H1: there was a difference, (two-sided at 5% level) in the eltrombopag group relative to placebo for the primary efficacy endpoint.

Results

Participant flow

Figure 2 Flow of Subjects in Study



Recruitment

Ninety-two subjects were enrolled in the Randomized Period, the 13-week double-blind, placebo-controlled treatment phase, with 63 subjects randomized to the eltrombopag treatment group and 29 subjects

randomized to placebo. Twenty-eight (97%) placebo subjects and 59 (94%) eltrombopag subjects entered Part 2, the Eltrombopag-Only Period. The ITT and safety populations were both 87 subjects for the Eltrombopag-Only Period since all patients received eltrombopag.

Conduct of the study

Six subjects (7%) withdrew from the study, without completing the Follow-Up Period, for reasons of withdrawal of consent (4 subjects) or lack of efficacy (2 subjects). Of these 6 subjects, one subject withdrew consent following discontinuation of study treatment (placebo) in the Randomized Period; 2 subjects withdrew due to lack of efficacy after completion of the Randomized Period but prior to entering the Eltrombopag-Only Period; and 3 subjects withdrew consent after completing the treatment periods but prior to completing the Follow-up Period.

There were 5 subjects who did not continue into the Eltrombopag-Only Period. Of these 5 subjects, 3 subjects had discontinued investigational product during the Randomized Period due to AEs. The remaining two subjects completed treatment in the Randomized period, but withdrew from study prior to entering the Eltrombopag-Only Period, as discussed above.

Seventy-seven subjects (84%) completed all 3 periods of the study including the 24-Week Ocular Follow-up Visit.

Baseline data

The largest proportion of subjects (26 subjects, 28%) were enrolled in Thailand followed by Russia (13 subjects, 14%) and Italy (12 subjects, 13%).

Few subjects had difficulty tolerating eltrombopag during the Randomized Period. The only reason for discontinuation of investigational product in both groups was AEs: one placebo subject discontinued treatment due to AE of abdominal haemorrhage, and 2 eltrombopag subjects discontinued treatment due to AEs of increases in aminotransferases.

Numbers analysed

Outcomes and estimation

- Efficacy

Primary endpoint

A statistically greater proportion of eltrombopag subjects in the PETIT2 study achieved a sustained platelet response (≥50 Gi/L in the absence of rescue) for at least 6 of 8 weeks between Weeks 5 to 12 of the Randomized Period, compared with placebo subjects (Table 9).

Table 9 **Analysis of Platelet Count Response (>=50 Gi/L) for at least 6 of 8 Weeks during Weeks 5 through 12 of the Randomized Period (PETIT2, ITT Population)**

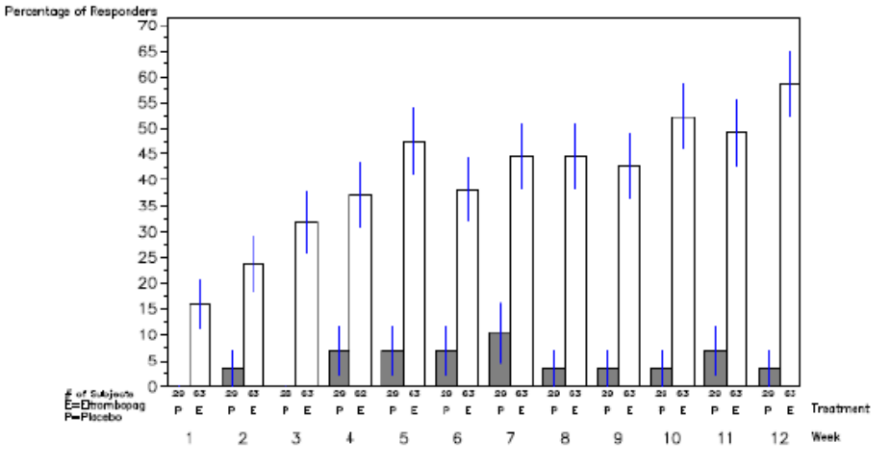
	Placebo N=29	Eltrombopag N=63
Subjects with a Primary Response[a], n (%)	1 (3.4)	25 (39.7)
Odds Ratio (Eltrombopag/Placebo)	17.96	
95% CI[b]	(2.29, 140.93)	
p-value[c]	<0.001	

m5.3.5.1 TRA115450 CSR Section 6.1

a. Primary Response defined as achieving a platelet count of ≥50 Gi/L for at least 6 of the 8 weeks between Weeks 5 through 12
b. Adjusted for age cohort and treatment.
c. Stratified Cochran-Mantel-Haenszel Chi-square test adjusted for age cohort and treatment.

The proportion of subjects in the eltrombopag group with a platelet response at Week 1 was 15.9%, which increased to 47.6% by Week 5 and remained between 38% and 59% through Week 12 (Figure 4). In comparison, the proportion of subjects in the placebo group with a platelet response at each week was 10% or less throughout the Randomized Period.

Figure 4 **Platelet Response at Each Week during the Randomized Period (PETIT2, ITT Population)**



m5.3.5.1 TRA115450 CSR. Section 6.1

Primary Efficacy Analysis by Age Cohort Strata and Subgroup

The sensitivity of the primary efficacy analysis was evaluated in 3 analyses. Results of all 3 analyses were consistent with the primary efficacy analysis.

Eltrombopag treatment was effective in producing a sustained response in each of the 3 age cohorts and the response was consistent across the cohorts (Table 10).

Table 10 Primary Efficacy Analysis by Age Cohort Strata (PETIT2, ITT Population, Randomized Period)

	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)	
	Placebo N=10	Eltrombopag N=23	Placebo N=13	Eltrombopag N=26	Placebo N=6	Eltrombopag N=14
Subjects with platelet counts ≥50 Gi/L for at least 6 of the 8 weeks						
No. of Responders	1 (10.0)	9 (39.1)	0 (0.0)	11 (42.3)	0 (0.0)	5 (35.7)
95% CI	(0, 0.45)	(0.20, 0.61)	NA	(0.23, 0.63)	NA	(0.13, 0.65)

m5.3.5.1 TRA115450 CSR, Section 6.1.1.2
Abbreviations: NA = not applicable

Subgroup analyses based on gender, race, use of ITP medication at baseline, baseline splenectomy status, and baseline platelet counts (≤15 Gi/L, >15 Gi/L) demonstrated that there was a treatment effect of eltrombopag compared with placebo and the response was consistent across the subgroups for each of these defined covariates.

Secondary Efficacy Results for the Randomized Period

Platelet Response

A repeated measures analysis of platelet response (platelet count ≥50 Gi/L in absence of rescue) 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).

The proportion of eltrombopag subjects with platelet counts ≥50 Gi/L at least once during the first 12 weeks of the Randomized Period (74.6%) was significantly greater compared with placebo subjects (20.7%; odds ratio: 11.73; 95% CI: 3.99, 34.50; p<0.001).

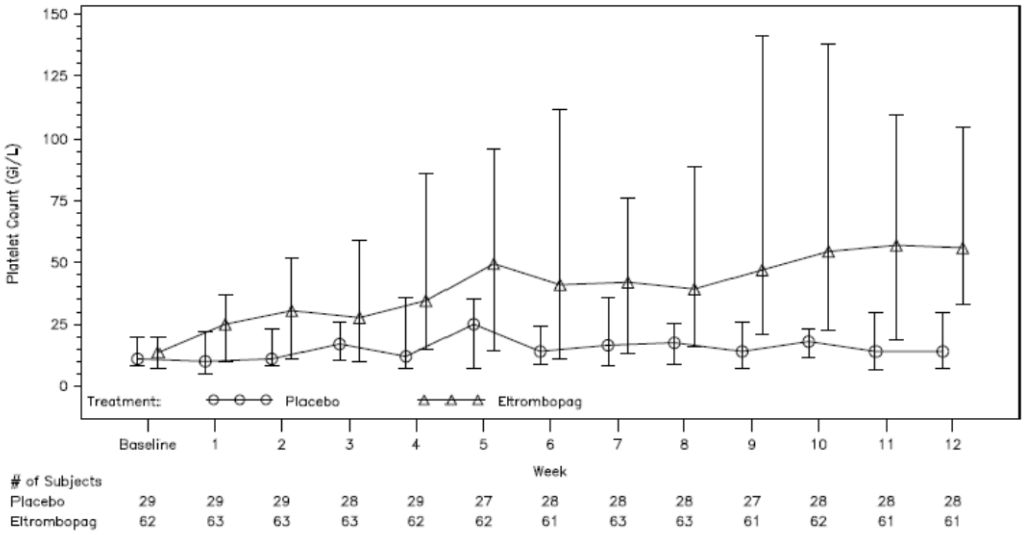
The time to response, defined as first platelet count ≥50 Gi/L in the absence of rescue, was evaluated for subjects who achieved a platelet response at any time during the 12 weeks of the Randomized Period as a post hoc analysis. The eltrombopag group had a median time to response of 22.5 days, with a range of 7 to 95 days. In comparison, the placebo group had a median time to response of 32.5 days (range: 15-50 days).

The proportion of subjects achieving a platelet response at least once during the first 6 weeks of the Randomized Period (61.9% of eltrombopag subjects vs. 17.2% of placebo subjects) was consistent with the 12-week analysis (odds ratio: 8.29; 95% CI: 2.74, 25.09; p<0.001).

Median platelet count at baseline was similar between treatment groups (eltrombopag: 11.00 Gi/L [range: 1.0 to 29.0 Gi/L]; placebo: 13.65 Gi/L [range: 1 to 38 Gi/L]. The median platelet count in eltrombopag subjects began to rise after one week of treatment (median: 25.00 Gi/L; range: 0 to 342 Gi/L) compared with 10 Gi/L (range: 1 to 140 Gi/L) in placebo subjects, and remained higher than in placebo subjects throughout the 12-week Randomized Period (Figure 5).

Eltrombopag subjects had a median platelet count between 25 and 60 Gi/L at any week during the Randomized Period. In comparison, placebo subjects had a median platelet count between 10 and 25 Gi/L at any week during the Randomized Period.

Figure 5 **Summary of Median (Interquartile Range) Platelet Counts by Week and Treatment (PETIT2, Double-Blind ITT Population)**



m2.7.3 ISE, Section 2.1.3.1

Weighted Mean Platelet Counts

Weighted mean platelet counts were compared between treatment groups using an ANCOVA model adjusted for the actual baseline platelet count, age cohort and treatment. Eltrombopag subjects had a significantly higher mean area (63.9) under the platelet-time curve compared with the placebo subjects (23.7; 95% CI: 24.15, 57.88; p<0. 001), confirming that the mean magnitude of the platelet count response was higher for eltrombopag compared with placebo.

Continuous Response

The median duration of continuous response during the Randomized Period was 3 weeks (range: 0 to 12 weeks) for the eltrombopag group and 0 weeks (range: 0 to 8 weeks) for the placebo group, with the difference being statistically significant (p<0.001).
When these data were examined by age cohort, the median duration of maximum continuous response was consistently longer for eltrombopag subjects compared with placebo subjects. For the eltrombopag cohorts, Cohort 2 had a median of 3 weeks similar to that for the overall eltrombopag group. Cohort 1 and Cohort 3 had medians of 2 weeks and 1.5 weeks, respectively.

Rescue Treatment
Rescue treatment was defined as either addition of an ITP medication, an increase in dose of concomitant ITP medication from baseline, platelet transfusion or splenectomy.
A statistically lower proportion of eltrombopag subjects (19.0%) received rescue treatment compared with placebo subjects (24.1%) during the Randomized Period (odds ratio: 0.44; 95% CI: 0.21, 0.93; p=0.032). Of the subjects who received rescue therapy, the majority of the eltrombopag subjects (9/12, 75%) were rescued once, whereas the majority of placebo subjects (5/7, 71%) were rescued 2 or more times. Most subjects received a new ITP medication as rescue (9 eltrombopag and 7 placebo). Of the subjects who received new ITP medications, the majority received a corticosteroid (8 eltrombopag and 4 placebo). Three subjects were rescued with either an increase in baseline ITP medication (2 subjects) or a platelet transfusion (1 subject). All 3 subjects were treated with eltrombopag. Based on the analysis of rescue treatment at each assessment, there was no pattern with respect to the timing of rescue during the Randomized Period.

Reduction in Incidence and Severity of Bleeding
Bleeding was evaluated using the WHO Bleeding Scale below, as well as analyses of bleeding-related AEs. There was no statistically significant difference between the treatment groups in the proportion of subjects

with any bleeding (WHO Grade 1 to 4) or clinically significant bleeding (WHO Grade 2 to 4) over the 12-week Randomized Period. Eltrombopag was significantly different from placebo ($p<0.05$) in the analysis of time to WHO Grade 1 to 4 bleeding via the Anderson Gill counting process. However, this was not significant when a similar analysis of time to significant bleeding (i.e., WHO Grade 2 to 4) was performed.
The proportions of subjects with any bleeding (WHO Grade 1 to 4) and clinically significant bleeding (WHO Grade 2 to 4) at baseline and Week 12 are shown in Table 11. While there was a decrease in bleeding and clinically significant bleeding in both treatment groups, the magnitude of change from baseline to Week 12 was greater in the eltrombopag group.
No eltrombopag subject and 3 placebo subjects (1 in each age cohort) experienced WHO Grade 3 bleeding. All 3 subjects had the Grade 3 bleed within the first 3 weeks of the study. One of the placebo subjects with WHO Grade 3 bleeding also had a Grade 4 SAE of abdominal hemorrhage that started one day after the last dose of study treatment (WHO bleeding assessment was not done at the time of the SAE). No other WHO Grade 4 bleeding was reported in either group.

Table 11 WHO Bleeding Scale by Assessment during the Randomized Period (PETIT2, ITT Population)

	Placebo N=29	Eltrombopag N=63
Baseline [a]		
n	29	63
Subjects by WHO Grade, n (%):		
Grade 1-4 (bleeding symptoms)	20 (69.0)	45 (71.4)
Grade 2-4 (clinically significant)	6 (20.7)	16 (25.4)
Week 12		
n	28	61
Subjects by WHO Grade, n (%):		
Grade 1-4 (bleeding symptoms)	16 (55.2)	23 (36.5)
Grade 2-4 (clinically significant)	2 (6.9)	3 (4.8)

m5.3.5.1 TRA115450 CSR, Section 6.2.3.1
a. Baseline defined as Day 1 assessment if available, else the latest available Screening assessment.

Secondary Efficacy Results for the Eltrombopag-Only Period

Platelet Response
The majority of subjects overall and in each age cohort responded at least once over the 24 weeks of the Eltrombopag-Only Period which is consistent with results for eltrombopag subjects during the Randomized Period.
Platelet response was analyzed between Weeks 4 and 24 of the Eltrombopag-Only Period to allow subjects randomized to placebo during the Randomized Period time to escalate to their therapeutic dose of eltrombopag. Subjects had a median of 11 weeks of response (range: 0 to 21 weeks) during this time period (Table 12). Results were consistent across the age cohorts. The median duration of continuous response was 6.0 weeks (range: 0 to 24 weeks) for all subjects during Week 1 to Week 24 of the Eltrombopag-Only period (Table 12).

Table 12 Platelet Count Response during the Eltrombopag-Only Period (PETIT2, ITT Population)

Endpoint	Eltrombopag N=87
Platelet counts ≥50 Gi/L, without rescue, at least once; n(%)	70 (80.5)
Platelet count ≥50 Gi/L for at least 50% of assessments between Weeks 13 and 24; n(%)	49 (56.3)
Platelet count ≥50 Gi/L for at least 75% of assessments between Weeks 13 and 24; n(%)	38 (43.7)
Median (min - max) total weeks with platelet count ≥50 Gi/L between Weeks 4 and 24	11 (0-21)
Median (min - max) duration (weeks) of continuous platelet count ≥50 Gi/L between Weeks 1 and 24	6 (0-24)

m5.3.5.1 TRA115450 CSR, Section 6.3.1.1, Section 6.3.1.2 and Section 6.3.1.4; m5.3.5.3 ISE, Section 2.1.4.1

Reduction in Baseline Concomitant ITP Therapy

Decreases or discontinuations in concomitant ITP therapy were only allowed during the Eltrombopag-Only Period. Fifteen of the 87 subjects participating in the Eltrombopag- Only Period were taking concomitant ITP medications at baseline. For subjects randomized to placebo in the Randomized Period, baseline for the Eltrombopag-Only Period was defined as the Part 1 Week 13 assessment.

For subjects randomized to eltrombopag, baseline for the Eltrombopag-Only Period was defined as Part 1 Day 1.

Of the 15 subjects, 9 attempted reduction or discontinuation of a baseline concomitant medication (defined as a decrease in the dose or frequency from the baseline dose or frequency of an ITP medication for at least one day) during the Eltrombopag-Only Period. Of these, 8 (53.3%) subjects had a sustained reduction or permanent discontinuation of at least 1 baseline ITP medication. Seven (46.7%) subjects permanently discontinued all baseline ITP medications without receiving rescue therapy: 5 discontinued corticosteroids, 1 discontinued dapsone and 1 discontinued cyclosporine. One subject had a sustained reduction of a baseline ITP medication (corticosteroid) for ≥18 weeks without requiring on-therapy rescue.

Rescue Treatment

During the Eltrombopag-Only Period, 12.6% of eltrombopag subjects required rescue treatment. This was lower than the proportion of eltrombopag subjects (19.0%) who required rescue treatment during the Randomized Period.

Reduction in Incidence and Severity of Bleeding

Overall, the proportion of subjects with any bleeding and clinically significant bleeding decreased from baseline to Week 24 of the Eltrombopag-Only Period (Table 13). At the majority of the time points of the Eltrombopag-Only Period less than 30% of subjects with an assessment reported any bleeding. Five or fewer subjects reported Grade 2 bleeding at each weekly visit; no subject had the most severe WHO Grade 3 or 4 bleeding.

Table 13 WHO Bleeding Scale by Assessment during the Eltrombopag-Only Period (PETIT2, ITT Population)

	Eltrombopag N=87
Baseline [a]	
n	87
Subjects by WHO Grade, n (%):	
Grades 1-4 (bleeding symptoms)	55 (63.2)
Grades 2-4 (clinically significant)	17 (19.5)
Week 24 [b]	
n	79
Subjects by WHO Grade, n (%):	
Grades 1-4 (bleeding symptoms)	19 (24.1)
Grades 2-4 (clinically significant)	5 (6.3)

m5.3.5.1 TRA115450 CSR, Section 6.3.4

a. For subjects randomized to placebo in Part 1, baseline was defined as Part 1, Week 13 assessment. For subjects randomized to eltrombopag in Part 1, baseline was defined as Part 1 Day 1 assessment, if available, or the latest available screening assessment.

b. Week 24 is equivalent to Week 37 of eltrombopag treatment for PETIT2 subjects randomized to eltrombopag

Ancillary analyses N/A

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 4: Summary of efficacy for trial PETIT II

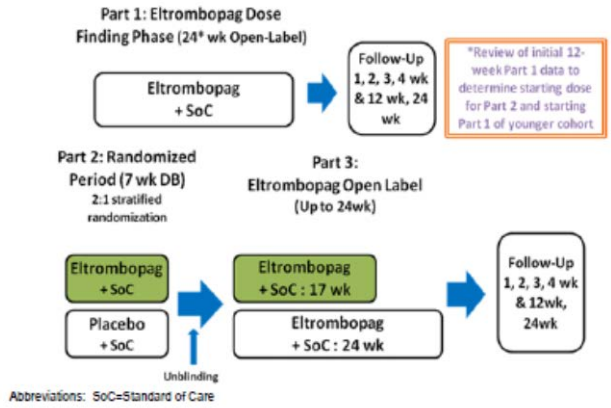
Title: PETIT II double blind randomized placebo controlled and open-label phase III study to investigate the efficacy, safety and tolerability of eltrombopag in paediatric subjects with previously treated chronic ITP			
Study identifier	TRA115450 (PETIT2)		
Design	PETIT2 was a two part, double-blind, randomized, placebo-controlled and open-label Phase III study		
	Duration of main phase: Duration of Extension phase:		13 weeks 24 weeks O-L eltrombopag only phase + 24 week Follow up visit
Hypothesis	Superiority		
Treatments groups	eltrombopag placebo		92 subjects were randomized 2:1 to receive eltrombopag (63 subjects) or placebo (29 subjects) in a 13-week double-blind, placebo-controlled treatment period. The randomization was stratified by 3 age-defined cohorts: Cohort 1 enrolled subjects between 12 and 17 years old, Cohort 2 enrolled subjects between 6 and 11 years old, and Cohort 3 enrolled subjects between 1 and 5 years old. - Part 2 (Eltrombopag-Only Period): 87 subjects received eltrombopag in an open-label manner for 24 weeks. In total, subjects randomized to placebo in Part 1 received up to 24 weeks of eltrombopag treatment, and subjects randomized to eltrombopag in Part 1 received up to 37 weeks of eltrombopag treatment.
Endpoints and definitions	Primary endpoint	Sustained platelet response at Week 12	Double blind phase: Defined as propotion of patients with platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 to 12, in the absence of rescue medication O-L eltrombopag only phase: sustained platelet response during
	Secondary endpoint	Use of rescue medication, bleeding AEs, reduction or disontinuation of baseline concomitant ITP medication	
Database lock			

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT			
Descriptive statistics and estimate variability	Treatment group	eltrombopag	placebo	<group descriptor>
	Number of subject	63	29	<n>
	Subjects with a primary response N (%)	25 (39.7%)	1 (3.4%)	<point estimate>
	ORR (eltrombopag/placebo)	17.96 (2.29, 140.23) P<0.001		
	Cohort 1 (1-5)	9 (39.1%)	1 (10%)	<point estimate>
	Cohort 2 (6-11)	11 (42.3%)	0 (0%)	<variability>
	Cohort 3 (12-17)	5 (35.7%)	0 (0%)	<point estimate> <variability>
Secondary endpoints	Rescue medication	19.0% 24.1% (odds ratio: 0.44; 95% CI: 0.21, 0.93; p=0.032)		
	Platelet response >50Gi/L at least once during 12 weeks	74.6% 20.7% odds ratio: 11.73; 95% CI: 3.99, 34.50; p<0.001		
	Bleeding events during 12weeks (G1-4)	23 (36.5%)	16 (55.2%)	
Eltrombopag only period	Platelet response for at least 75% of the time between W13-24	38 (43.7%)		
	Rescue medication	12.6%		
	Bleeding events (G1-4)	19 (24.1%)		
	Sustained or permanent discontinuation of ITP medication	8 out of 15 patients		

Supportive study(ies)

TRA108062 (PETIT) was the first administration of eltrombopag in paediatric patients. The main objective of this study was to assess the efficacy, safety, tolerability and pharmacokinetic profile of eltrombopag in paediatric subjects with chronic ITP and to determine dosing regimens in the paediatric population.

Figure 3 PETIT Study Design Schematic



PETIT was a Phase II, multicenter, 3 part, staggered cohort, open-label and double blind, randomized, placebo controlled study stratified by 3 age-determined cohorts (Cohort 1: 11 – 17 years of age, Cohort 2: 6 – 10 years of age, Cohort 3: 1-5 years of age).

-Part 2 (Randomized Period): A 7-week randomized, double-blind, placebo-controlled period involving 18 subjects per cohort (Note: Efficacy analyses were done on the first 6 weeks of data. The 7-week treatment period provided 1 additional week after the Week 6 time point to review, clean and lock the data prior to each subject transitioning to Part 3. The safety analyses were done on all 7 weeks). Sixty-seven subjects were enrolled in Part 2 (45 on eltrombopag, 22 on placebo).

-Part 3: An open-label treatment period where subjects randomized to eltrombopag in Part 2 received an additional 17 weeks of eltrombopag in Part 3 and subjects randomized to placebo in Part 2 received 24 weeks of eltrombopag in Part 3. Therefore, all subjects received 24 weeks of eltrombopag treatment during Part 2/3, referred to hereafter as the Eltrombopag Only Period. A total of 65 subjects continued to receive open-label eltrombopag in Part 3 of the study.

The primary endpoint was the proportion of subjects achieving platelet counts ≥50 Gi/L at least once between Days 8 and 43 (Weeks 1 to 6) of the Randomized Period of the study. The safety and tolerability of eltrombopag over 24 weeks of eltrombopag dosing was assessed by analysis of the nature and frequency of adverse events (AEs), laboratory abnormalities, vital signs, ocular examinations and clinical monitoring/observation. PK endpoints were also included in the study and are reported separately.

Both eltrombopag tablets and Powder for Oral Suspension (PfOS) (and matched placebo formulations) were used in this study. Starting doses varied based on age and weight. Additionally, East Asian subjects had lower starting doses based upon adult data showing increased exposure in East Asian patients and consequently response at lower doses. Eltrombopag was given once daily and doses were titrated based on platelet response. The maximum dose for both tablets and PfOS was 75mg daily.

Statistical Methods

Planned analysis: After the initial 5 subjects in each age cohort completed 12 weeks (3 months) of treatment in the Dose Finding Phase, a medical review of the safety, PK and platelet count data took place for the purpose of making a decision regarding the starting dose and dosing strategy for the rest of the cohort and the initiation of the next age cohort.

After all subjects in Cohort 1 completed the Randomized Period and the initial 5 subjects in Cohort 2 completed 12 weeks (3 months) of treatment in the Dose Finding Phase, unblinded data was provided to external Independent DSMB for a safety review. The purpose of the DSMB was to identify safety issues that could preclude the initiation of the lower age cohort or to determine modification or interruption of study procedures.

All planned efficacy and safety analyses were performed when all of the subjects had reached Week 4 follow-up visit. Safety data pertaining to ocular follow-up to 6 months was reported separately after all subjects completed the study. There were no interim analyses of data for subjects enrolled into Parts 2 and 3 of the study.

Sample size calculation:
The primary endpoint was the proportion of subjects achieving platelets ≥50 Gi/L at least once at any time between Days 8 and 43 of the Randomized Period. The response rates were assumed to be approximately 20% for placebo and 70% for eltrombopag based on conservative estimates of observed rates during the first 6 weeks of the treatment period of the placebo controlled clinical study TRA102537 (RAISE). Hence, for the Randomized Period, using a 2:1 randomization, a total sample size of 33 evaluable subjects was required in order to provide 90% power at the 5% level of significance (two-sided).

A secondary endpoint was the proportion of subjects with platelets ≥50 Gi/L in more than 60% of assessments from Days 15 to 43 (Weeks 2 to 6). The response rates were assumed to be approximately 10% for placebo and 50% for eltrombopag based on conservative estimates of observed rates during the first 6 weeks of the treatment period of the controlled clinical study TRA102537 (RAISE). Hence, for the Randomized Period, using a 2:1 randomization, a total sample size of 42 evaluable subjects was required to provide 90% power at the 5% level of significance (two-sided).

To ensure sufficient power for both the primary and secondary platelet count endpoints, and with a further 30% increase to compensate for missing data and drop-outs, 54 subjects (36 on eltrombopag, 18 on placebo) were to be randomized in total to the three cohorts; 18 subjects (12 on eltrombopag, 6 on placebo) in each of 1-5 year olds, 6-11 year olds and 12-17 year olds.

Including the 15 subjects required across all 3 cohorts in the Dose Finding Phase, the total number of subjects in the study was planned to be approximately 70.

Baseline demographics for subjects in the Eltrombopag Only Period were the same as for the Randomized Period

Table 12 Baseline Demographics (Double-Blind ITT Population)

	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)		All Cohorts		
	Placebo (N=8)	Eltrombopag (N=16)	Placebo (N=9)	Eltrombopag (N=19)	Placebo (N=5)	Eltrombopag (N=10)	Placebo (N=22)	Eltrombopag (N=45)	Total (N=67)
Age (yrs)									
Median	14.5	13.0	10.0	9.0	3.0	3.5	10.0	9.0	10.0
Min-Max	13-17	12-17	6-11	6-11	2-5	1-5	2-17	1-17	1-17
Sex, n (%)									
Female	3 (37.5)	8 (50.0)	8 (88.9)	14 (73.7)	2 (40.0)	5 (50.0)	13 (59.1)	27 (60.0)	40 (59.7)
Male	5 (62.5)	8 (50.0)	1 (11.1)	5 (26.3)	3 (60.0)	5 (50.0)	9 (40.9)	18 (40.0)	27 (40.3)
Ethnicity, n (%)									
Hispanic/latino	2 (25.0)	0	0	0	1 (20.0)	3 (30.0)	3 (13.6)	3 (6.7)	6 (9.0)
Not hispanic/latino	6 (75.0)	16 (100.0)	9 (100.0)	19 (100.0)	4 (80.0)	7 (70.0)	19 (86.4)	42 (93.3)	61 (91.0)
Weight (kg)									
Median	71.30	54.45	35.40	32.60	19.70	17.90	41.95	37.20	38.20
Min-Max	41.2-82.4	37.2-89.8	20.4-64.0	21.7-60.9	14.5-23.7	11.9-24.1	14.5-82.4	11.9-89.8	11.9-89.8
Race, n (%)									
White[a]	7 (87.5)	15 (93.8)	8 (88.9)	17 (89.5)	5 (100.0)	8 (80.0)	20 (90.9)	40 (88.9)	60 (89.6)
East Asian	1 (12.5)	0	1 (11.1)	1 (5.3)	0	1 (10.0)	2 (9.1)	2 (4.4)	4 (6.0)
Mixed Race	0	1 (6.3)	0	0	0	1 (10.0)	0	2 (4.4)	2 (3.0)
African American/African	0	0	0	1 (5.3)	0	0	0	1 (2.2)	1 (1.5)

Data Source: Table 6.3002 and Table 6.3011

a. Includes Caucasian/ European Heritage and Arabic/North African Heritage

All subjects with an ITP diagnosis <12 months had a diagnosis for at least 6 months. Median duration of ITP at screening was 28.4 months (range 6-171 months) The majority of subjects had platelet counts ≤ 15 Gi/L (50% placebo, 51.1% eltrombopag) at baseline. Prior splenectomy (0% placebo, 11% eltrombopag) was more prevalent on the eltrombopag arm. The largest proportion of subjects (38 subjects, 57%) was enrolled in US followed by the Spain (13 subjects, 19%).

Table 13 Baseline Characteristics (Double-Blind ITT Population)

	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)		All Cohorts		
	Placebo (N=8)	Eltrombopag (N=16)	Placebo (N=9)	Eltrombopag (N=19)	Placebo (N=5)	Eltrombopag (N=10)	Placebo (N=22)	Eltrombopag (N=45)	Total (N=67)
ITP medication use, n (%)									
Yes	0	2 (12.5)	2 (22.2)	1 (5.3)	0	2 (20.0)	2 (9.1)	5 (11.1)	7 (10.4)
No	8 (100.0)	14 (87.5)	7 (77.8)	18 (94.7)	5 (100.0)	8 (80.0)	20 (90.9)	40 (88.9)	60 (89.6)
Platelet count, n (%)									
≤15Gi/l	4 (50.0)	7 (43.8)	6 (66.7)	11 (57.9)	1 (20.0)	5 (50.0)	11 (50.0)	23 (51.1)	34 (50.7)
>15Gi/l	3 (37.5)	9 (56.3)	3 (33.3)	6 (31.6)	4 (80.0)	5 (50.0)	10 (45.5)	20 (44.4)	30 (44.8)
Missing	1 (12.5)	0	0	2 (10.5)	0	0	1 (4.5)	2 (4.4)	3 (4.5)
Splenectomy status, n (%)									
Yes	0	3 (18.8)	0	2 (10.5)	0	0	0	5 (11.1)	5 (7.5)
No	8 (100.0)	13 (81.3)	9 (100.0)	17 (89.5)	5 (100.0)	10 (100.0)	22 (100.0)	40 (88.9)	62 (92.5)
Time since ITP diagnosis, n (%)									
<12 months	0	1 (6.3)	2 (22.2)	2 (10.5)	0	5 (50.0)	2 (9.1)	8 (17.8)	10 (14.9)
≥12 months	8 (100.0)	15 (93.8)	7 (77.8)	17 (89.5)	5 (100.0)	5 (50.0)	20 (90.9)	37 (82.2)	57 (85.1)

Data Source: Table 6.3005

ITP=Idiopathic thrombocytopenia

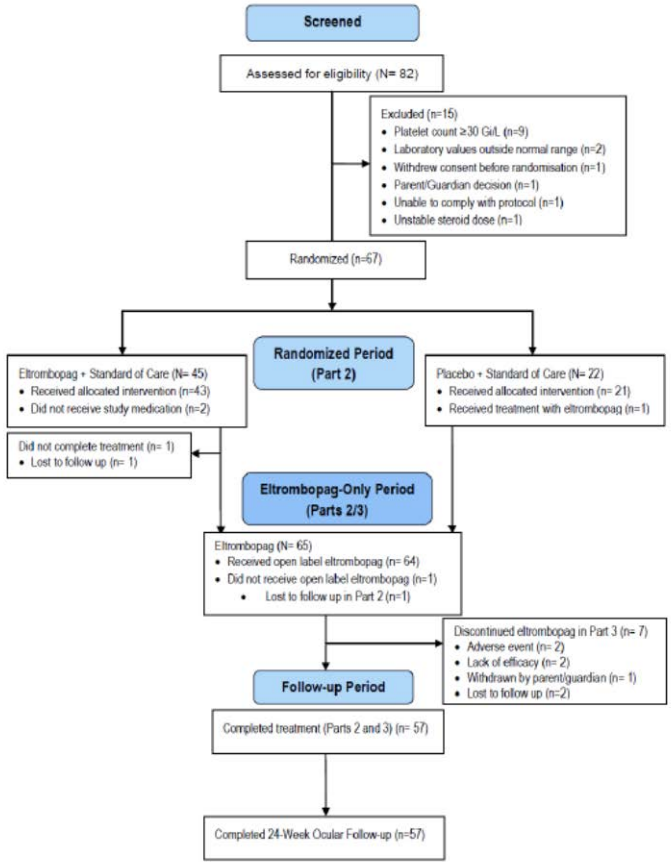
Table 15 Summary of Prior ITP Medications (Double-Blind ITT Population)

	Number of Subjects (%)							
	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)		All Cohorts	
Classification	Placebo (N=8)	Eltrombopag (N=16)	Placebo (N=9)	Eltrombopag (N=19)	Placebo (N=5)	Eltrombopag (N=10)	Placebo (N=22)	Eltrombopag (N=45)
Any ITP medication	**8 (100.0)**	**16 (100.0)**	**9 (100.0)**	**17 (89.5)**	**5 (100.0)**	**10 (100.0)**	**22 (100.0)**	**43 (95.6)**
IVIG	6 (75.0)	12 (75.0)	9 (100.0)	14 (73.7)	5 (100.0)	9 (90.0)	20 (90.9)	35 (77.8)
Corticosteroids	5 (62.5)	14 (87.5)	7 (77.8)	15 (78.9)	4 (80.0)	5 (50.0)	16 (72.7)	34 (75.6)
Anti-D	3 (37.5)	8 (50.0)	3 (33.3)	9 (47.4)	1 (20.0)	3 (30.0)	7 (31.8)	20 (44.4)
Rituximab	3 (37.5)	6 (37.5)	3 (33.3)	7 (36.8)	3 (60.0)	3 (30.0)	9 (40.9)	16 (35.6)
Other ITP	1 (12.5)	2 (12.5)	1 (11.1)	1 (5.3)	3 (60.0)	0	5 (22.7)	3 (6.7)
Azathioprine	0	1 (6.3)	0	1 (5.3)	0	1 (10.0)	0	3 (6.7)
Vincristine/vinblastine	1 (12.5)	1 (6.3)	1 (11.1)	0	0	0	2 (9.1)	1 (2.2)
Cyclophosphamide	0	0	0	1 (5.3)	0	0	0	1 (2.2)
Danazol	0	1 (6.3)	0	0	0	0	0	1 (2.2)
Mycophenolate	0	0	0	0	1 (20.0)	0	1 (4.5)	0

Data Source: Table 6.4002
Anti-D=Antibody against D antigen; ITP=Idiopathic thrombocytopenia; IVIG=intravenous immunoglobulin

Study disposition

Figure 2 Flow of Subjects in Part 2 and 3 of Study TRA108062



Data Source: Table 6.1001 to Table 6.1003, Table 6.1009 and Table 6.1010

More eltrombopag subjects than placebo subjects were withdrawn from the study prematurely: 1 patient (4.5%) in placebo vs 13 patients (19.4%) in eltrombopag treatment arm, being protocol violation and lost of FU the main reasons for eltrombopag treated arm.

Table 9 Summary of End of Study Record (Double-Blind ITT Population)

	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)		All cohorts		
	Placebo (n=8)	Eltrombopag (n=16)	Placebo (n=9)	Eltrombopag (n=19)	Placebo (n=5)	Eltrombopag (n=10)	Placebo (n=22)	Eltrombopag (n=45)	Total (n=67)
Completion status	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed per-protocol[a]	7 (87.5)	14 (87.5)	9 (100.0)	15 (78.9)	5 (100.0)	7 (70.0)	21 (95.5)	36 (80.0)	57 (85.1)
Completed Follow-up	7 (87.5)	13 (81.3)	9 (100.0)	15 (78.9)	5 (100.0)	5 (50.0)	21 (95.5)	33 (73.3)	54 (80.6)
Completed all parts[b]	7 (87.5)	12 (75.0)	9 (100.0)	13 (68.4)	5 (100.0)	5 (50.0)	21 (95.5)	30 (66.7)	51 (76.1)
Prematurely withdrawn	1 (12.5)	3 (18.8)	0	4 (21.1)	0	5 (50.0)	1 (4.5)	12 (26.7)	13 (19.4)
Reason for premature withdrawal	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Protocol violation	0	1 (6.3)	0	3 (15.8)	0	1 (10.0)	0	5 (11.1)	5 (7.5)
Lost to follow-up	0	2 (12.5)	0	0	0	4 (40.0)	0	6 (13.3)	6 (9.0)
Withdrawal by parent/guardian	1 (12.5)	0	0	1 (5.3)	0	0	1 (4.5)	1 (2.2)	2 (3.0)

Data Source: Table 6.1005

a. Completed the treatment periods in Parts 2 and 3.
b. Completed Part 2, Part 3 and 6 month follow-up.

Table 11 Investigational Product Discontinuation During the Eltrombopag Only Period (All Eltrombopag Exposed ITT Population)

	Eltrombopag; n (%)			
	Cohort 1 (12-17 yrs) (N=24)	Cohort 2 (6-11 yrs) (N=28)	Cohort 3 (1-5 yrs) (N=15)	All Cohorts (N=67)
Investigational product				
Completed	21 (87.5)	24[a] (85.7)	12 (80.0)	57[a] (85.1)
Prematurely stopped	3 (12.5)	2 (7.1)	3 (20.0)	8 (11.9)
Reason for stopping permanently				
Lost to follow-up	1 (4.2)	0	2 (13.3)	3 (4.5)
Adverse event	0	2 (7.1)	0	2 (3.0)
Lack of efficacy	0	0	1 (6.7)	1 (1.5)
Physician decision	1[b] (4.2)	0	0	1 (1.5)
Withdrawal by parent/guardian	1[c] (4.2)	0	0	1 (1.5)

Data Source: Table 6.1010

a. Two subjects (Subject 93 and 230) were randomized but not treated.
b. Subject 22 discontinued by physician due to lack of efficacy
c. Subject 245 discontinued by parent due to lack of efficacy

Dosing

Starting doses for eltrombopag or matching placebo were as follows:

Cohort 1 (12 to 17 year olds): 37.5 mg once daily (12.5 mg if of East Asian Ancestry)

Cohort 2 (6 to 11 year olds): Weight <27 kg: 25 mg once daily (12.5 mg if of East Asian ancestry); Weight >27 kg: 50 mg once daily (25 mg if of East Asian ancestry)

Cohort 3 (1 – 5 year olds): 1.5 mg/kg once daily (0.8 mg/kg/day if of East Asian ancestry)

Doses titrations were permitted every 2 weeks based on platelet response. The maximum dose for all Cohorts was 75 mg.

Efficacy

Primary endpoint

Treatment with eltrombopag led to a statistically significant platelet response with 62.2% in the eltrombopag group compared with 31.8% in the placebo group achieving platelet counts ≥50 Gi/L at least once between Days 8 and 43 (Week 1 to 6) of the 6-week Randomized Period (Table 5). The odds of response were 4.31 times greater for eltrombopag treated subjects than placebo treated subjects (95% CI: 1.39, 13.34, p=0.011). Eltrombopag treated subjects in all 3 age cohorts achieved a platelet response (Table 15).

Table 5: Analysis of Platelet Count Response (>=50 Gi/L) between Days 8 and 43 (Weeks 1 to 6) of the Randomized Period – Logistic Regression Model (PETIT, Double-Blind ITT Population)

	Placebo N=22	Eltrombopag N=45
Subjects with Platelet Count ≥50 Gi/L at least once between Days 8 and 43		
Responders, n (%)	7 (31.8)	28 (62.2)
Odds-Ratio (Eltrombopag/Placebo)[a]	4.31	
95% CI	(1.39, 13.34)	
p-value (two-sided versus placebo)	0.011	

m5.3.5.1 TRA108062 CSR, Section 7.1

a. Logistic regression analysis adjusted for age cohort and treatment.

A higher proportion of eltrombopag treated patients than placebo treated patients had a platelet count response at each post-baseline assessment during the randomised study period

Primary Efficacy Analysis by Age Cohort and Subgroup

Eltrombopag treatment was effective in producing a response rate of approximately 60% in each age cohort, which is consistent with the overall analysis (Table 15).

Table 15 Platelet Response by Age Cohort for the First 6 Weeks of Dosing during the Randomized Period (PETIT, Double-Blind ITT Population)

	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)	
	Placebo (N=8)	Eltrombopag (N=16)	Placebo (N=9)	Eltrombopag (N=19)	Placebo (N=5)	Eltrombopag (N=10)
Responders [a], n (%)	0	10 (62.5)	3 (33.3)	12 (63.2)	4 (80.0)	6 (60.0)
95% CI	(0.63, 1.00)	(0.35, 0.85)	(0.07, 0.70)	(0.44, 0.90)	(0.28, 0.99)	(0.26, 0.88)

m5.3.5.1 TRA108062 CSR, Section 7.1.1

a. Platelet count ≥50 Gi/L at least once between Days 8 and 43.

Subgroup analyses by gender, race and time since ITP diagnosis demonstrated that the treatment effect of eltrombopag compared with placebo was consistent across the subgroups for each of these defined covariates.

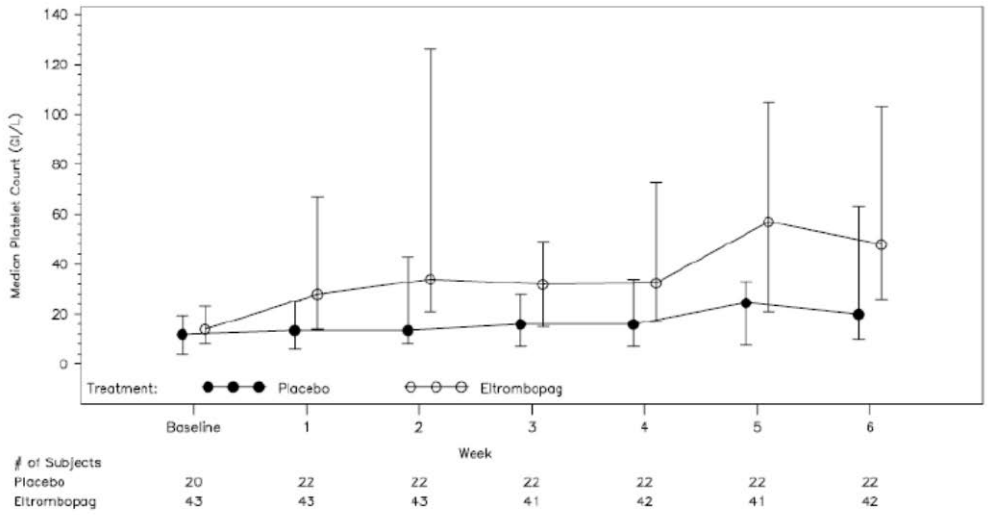
Secondary Efficacy Results for the Randomized Period

Platelet Response

In the PETIT study sustained platelet response was assessed by the proportion of subjects with platelet counts >50 Gi/L for at least 60% of assessments between Days 15 to 43 (Weeks 2 to 6) of the Randomized Period. The study demonstrated that a higher proportion of eltrombopag subjects than placebo subjects (35.6% vs. 0) had a sustained response during the Randomized Period. The odds of achieving a sustained platelet response was statistically significant (odds ratio: 5.84, 95% CI: 1.18, 28.90; p=0.002).

Median platelet count at baseline was similar between treatment groups (eltrombopag: 14 Gi/L [range: 2-29 Gi/L]; placebo: 12 Gi/L [range: 1-28 Gi/L]. The median platelet count in eltrombopag subjects began to rise after one week of treatment (median: 28 Gi/L; range: 2 to 239 Gi/L) compared with 13.5 Gi/L (range: 3 to 244 Gi/L) in placebo subjects, and remained higher than in placebo subjects throughout the 6 week Randomized Period (Figure 7). Eltrombopag subjects had a median platelet count between 28 and 57 Gi/L at any week during the Randomized Period. In comparison, placebo subjects had a median platelet count between 13.5 and 24.5 Gi/L at any week during the Randomized Period.

Figure 7 **Median Platelet Count by Week (Interquartile Range) During the Randomized Period (PETIT, Double-Blind ITT Population)**



m5.3.5.1 TRA108062 CSR, Section 7.2.1.1

Weighted Mean Platelet Count

Over the Randomized Period, eltrombopag subjects had a significantly higher mean area under the platelet-time curve (68.0) compared with placebo subjects (30.5; p=0.012), confirming that the mean magnitude of the platelet count response was higher for eltrombopag compared with placebo.

Weighted mean platelet counts (area under the platelet time curve adjusted for duration on treatment) were compared between treatment groups using an ANCOVA model adjusted for the actual baseline platelet count and age cohort and treatment variables.

Continuous Response

The median duration of continuous response during the Randomized Period was longer for eltrombopag subjects (1 week [range: 0 to 6 weeks]) compared with placebo subjects (0 weeks [range: 0-2 weeks]; p=0.0020). When analyzed by age cohort, eltrombopag had a longer treatment effect compared with placebo in Cohorts 1 and Cohort 2 (1 vs. 0 and 2 vs. 0 weeks, respectively). The median duration of continuous response in Cohort 3 was 1 week for both eltrombopag and placebo subjects.

Rescue Treatment

During the 6-week Randomized Period, the odds of initiating a rescue treatment were 90% lower in the eltrombopag group compared with the placebo group; this was statistically significant (p=0.002). Of the subjects who received rescue therapy, the majority of the eltrombopag subjects (4/6, 67%) were rescued once, whereas the majority of placebo subjects (8/11, 73%) were rescued 2 or more times. Rescue treatment for all subjects consisted of an additional ITP medication. A lower proportion of eltrombopag subjects (13.3%) initiated rescue with an additional ITP medication compared with placebo subjects (50.0%). At each assessment week, rescue treatment was largely limited to the use of one rescue therapy. There was no pattern with respect to the timing of rescue during the Randomized Period. An analysis by age cohort was consistent with the results of the overall treatment group.

Reduction in Incidence and Severity of Bleeding

During the Randomized Period, the odds of any clinically significant bleeding (Grade 2 to 4) were lower in eltrombopag subjects than in placebo subjects; the effect was statistically significant (p=0.013; Table 16). The odds of any bleeding (Grade 1-4) were lower in eltrombopag subjects than in placebo subjects; this effect was not statistically significant.

Given the limited number of severe and clinically relevant G3 or 4 bleeding events (with no differences between treatments), the observed differences are just due to a reduction in the incidence of mild bleedings

(G1 or 2 events). It is noted that due to the limited number of patients and the short period of follow up, relevant differences would be not be expected.

Table 16 Analysis of WHO Bleeding Grades during the Randomized Period - Logistic Regression Model (PETIT, Double-Blind ITT Population)

	Placebo N=22	Eltrombopag N=45
Any Bleeding (Grades 1-4); n (%)	20 (90.9)	33 (73.3)
Odds-Ratio Eltrombopag/Placebo	0.27	
95% CI	(0.05,1.41)	
P-value (two-sided versus Placebo)	0.122	
Clinically Significant Bleeding (Grades 2-4); n (%)	13 (59.1)	12 (26.7)
Odds-Ratio Eltrombopag/Placebo	0.21	
95% CI	(0.06, 0.72)	
P-value (two-sided versus Placebo)	0.013	

m5.3.5.1 TRA108062 CSR, Section 7.2.3.1

There were decreases in any bleeding and in clinically significant bleeding from baseline to Week 6 in both eltrombopag and placebo subjects (Table 17). Most bleeding during the Randomized Period was WHO Grade 1 or 2. Two subjects (1 in each treatment group) had WHO Grade 3. No subject had WHO Grade 4 bleeding.

Table 17 WHO Bleeding Scale by Assessment during the Randomized Period (PETIT, Double-Blind ITT Population)

	Placebo N=22	Eltrombopag N=45
Baseline[a]		
n	22	45
Subjects by WHO Grade, n (%):		
Grades 1-4 (bleeding symptoms)	18 (81.8)	35 (77.7)
Grades 2-4 (clinically significant)	6 (27.3)	9 (20.0)
Week 6		
n	22	42
Subjects by WHO Grade, n (%):		
Grades 1-4 (bleeding symptoms)	16 (72.7)	10 (22.2)
Grades 2-4 (clinically significant)	4 (18.2)	1 (2.2)

m5.3.5.1 TRA108062 CSR, Section 7.2.3.1

a. Baseline was defined as Day 1, if available, else the latest available screening assessment.

Secondary Efficacy Results for the Eltrombopag-Only Period

Platelet Response

The majority of subjects (80.6%) had a platelet count >50 Gi/L in the absence of rescue at least once during the 24 weeks of treatment of the Eltrombopag-Only Period (Table 18). The treatment effect was consistent across age cohorts (Cohort 1: 75.0%; Cohort 2: 82.1%; Cohort 3: 86.7%.

Sustained platelet response was assessed by the percentage of subjects with platelet counts >50 Gi/L for at least 60% of assessments between Week 2 and 24 of the Eltrombopag-Only Period. Twenty-four subjects (35.8%) had a sustained platelet response. These results are consistent with the results in the eltrombopag group during the Randomized Period. The platelet count response was maintained as indicated by the proportion of subjects with platelet count ≥50Gi/L for 50% to 75% of assessments (Table 18). Weighted mean platelet count was consistent with that observed during the Randomized Period.

Table 18 Platelet Count Response during the Eltrombopag-Only Period (PETIT, All Eltrombopag Exposed ITT Population)

Endpoints	Eltrombopag N=67
Platelet count ≥50 Gi/L at least once without rescue during the 24 weeks, n (%)	54 (80.6)
Platelet count ≥50 Gi/L for ≥60% assessments between Weeks 2 and 24; n (%)	24 (35.8)
Platelets count ≥50 Gi/L for ≥50% assessments between Weeks 13 and 24; n (%)	31 (46.3)
Platelet count ≥50 Gi/L for ≥75% Assessments between Weeks 13 and 24; n (%)	20 (29.9)
Weighted mean platelet count (SD), n=65	80.4 (44.18)
Median duration of continuous platelet count ≥50 Gi/L (min-max), weeks	4 (0-24)

m5.3.5.1 TRA108062 CSR, Section 7.3.1 and m5.3.5.3 ISE, Section 2.2.4.1

Reduction in Baseline Concomitant ITP Medication

Thirteen subjects participating in the Eltrombopag-Only Period were taking concomitant ITP medications at baseline (Table 19). Six of the thirteen had either sustained reduction or permanently stopped their baseline ITP medications and did not need rescue therapy. Three subjects permanently stopped taking all baseline ITP medications and did not need rescue therapy. For 2 of these subjects, the baseline ITP medication stopped was a corticosteroid and for one subject it was IVIg.

Table 19 Change from Baseline Up to Last Dose of Study Medication + 1 Day in Dose and/or Frequency of Concomitant ITP Medications during the Eltrombopag-Only Period (PETIT, All Eltrombopag Exposed ITT Population)

Number of Subjects (%)	Eltrombopag N=67
Taking an ITP medication at baseline [a]	13 (19.4)
Having a sustained reduction or permanently stopping at least one baseline ITP medication [b]	7 (53.8)
Permanently stopping all baseline ITP medications prior to Eltrombopag-Only Period	2 (15.4)
Having a sustained reduction or permanently stopping at least one baseline ITP medication and not needing subsequent rescue [b]	6 (46.2)
Permanently stopping all baseline ITP medications and not needing subsequent rescue [b]	3 (23.1)
Having a sustained reduction and not needing subsequent rescue [b,d]	4 (30.8)
Maximum Reduction 4-<6 weeks[c]	0
Maximum Reduction 6-<8 weeks[c]	1 (25.0)
Maximum Reduction 8-<12 weeks[c]	3 (75.0)
Maximum Reduction 12-<18 weeks[c]	0
Maximum Reduction ≥18 weeks[c]	0

m5.3.5.1 TRA108062 CSR, Section 7.3.2

Note: Sustained reduction defined as reduction from baseline in dose and/or frequency which is maintained for at least 4 weeks. Excludes sustained reductions started more than 1 day after last dose.

a. For subjects randomized to Placebo in Part 2, baseline was defined as Part 2 Week 7 assessment. For subjects randomized to Eltrombopag in Part 2, Baseline was defined as Part 2 Day 1.
b. Denominator is number of subjects taking an ITP medication at baseline.
c. Denominator is number of subjects with a sustained reduction and not needing subsequent rescue.
d. Subject 97 reduced baseline ITP medication of corticosteroid, which was subsequently discontinued; therefore, this subject is counted in both categories of sustained reduction and permanent discontinuation.

Rescue Treatment

During the Eltrombopag-Only Period, a total of 16 eltrombopag subjects (23.9%) initiated rescue with a new ITP medication.

Overall, rescue was infrequent at each assessment during the Eltrombopag-Only Period and was mostly limited to the use of one rescue therapy. There was no pattern with respect to the timing of rescue during the Eltrombopag-Only Period.

Reduction in Incidence and Severity of Bleeding

The proportion of eltrombopag subjects with any bleeding (WHO Grades 1-4) and clinically significant bleeding (WHO Grades 2-4) decreased from baseline to Week 24 of the Eltrombopag-Only Period (Table 20). No subject had WHO Grade 4 bleeding and 3 subjects had Grade 3 bleeding.

Table 20 WHO Bleeding Scale by Assessment during the Eltrombopag-Only Period (PETIT, All Eltrombopag Exposed ITT Population)

	Eltrombopag N=67
Baseline	
n	67
Subjects by WHO Grade, n (%):	
Grades 1-4 (bleeding symptoms)	53 (79.1)
Grades 2-4 (clinically significant)	16 (23.9)
Week 24	
n	60
Subjects by WHO Grade, n (%):	
Grades 1-4 (bleeding symptoms)	14 (23.3)
Grades 2-4 (clinically significant)	3 (5.0)

m5.3.5.1 TRA108062 CSR, Section 7.3.4.1

a. For subjects randomized to placebo in Part 2, baseline was defined as Part 2, Week 7 assessment. For subjects randomized to eltrombopag in Part 2, baseline was defined as Part 2 Day 1 assessment, if available, or the latest available screening assessment.

Analyses across trials, Pooled analyses and meta-analysis

The MAH has provided an analysis were data from PETIT2 and PETIT were pooled only from select efficacy endpoints given the differences in endpoints and treatment duration. PETIT2 rescue treatment and bleeding data for the first 6 weeks of the Randomized Period were analyzed for the purpose of pooling with PETIT data. With the exception of those noted as ad hoc, the endpoints and analysis strategy for the integrated data were defined prior to the unblinding of the two studies.

Comparison of Efficacy Results of all Studies

Platelet Response

-Pooled Data - Randomized Period:

Pooled data from the 2 pediatric studies showed that a significantly higher proportion of eltrombopag subjects achieved platelet counts ≥50 Gi/L at least once during the Randomized Period from Day 8 to 43 (Weeks 1 to 6) compared with placebo subjects (Table 25).

Table 25 Subjects (Responders) with Platelet counts ≥50Gi/L at least once between Days 8 and 43 (Weeks 1 to 6) of the Randomized Period (Logistic Regression Model, ITT Population, Pooled Data)

	Placebo N=51	Eltrombopag N=108
Responders; n (%)	12 (23.5)	67 (62.0)
Odds-ratio (Eltrombopag/Placebo)[a]	5.80	
95% CI	(2.69, 12.49)	
p-value (two-sided versus Placebo)	<0.001	

m5.3.5.3 ISE, Section 3.2.1.2

a. Logistic regression analysis adjusted for study, age cohort and treatment.

-Pooled Data - Eltrombopag-Only Period

The majority of subjects in both PETIT2 and PETIT achieved a platelet count response over the 24 week Eltrombopag-Only Period and the results were consistent across the 3 age cohorts in both studies. Pooled data showed that the majority of subjects had a platelet count response (≥50 Gi/L) at least once during the 24 weeks of the Eltrombopag-Only Period (Table 27).

Table 27 **Subjects with Platelet Counts >=50 Gi/L at Any Time during the 24 Weeks of Eltrombopag Dosing (Eltrombopag-Only, ITT Population, Pooled Data)**

	Eltrombopag N=154
Number evaluable	152
Responders, n (%)[a]	124 (80.5)
95% CI	(73.4, 86.5)

m5.3.5.3 ISE, Section 3.2.1.3

a. Proportion of responders within treatment group calculated by exact binomial method.

Durable Response

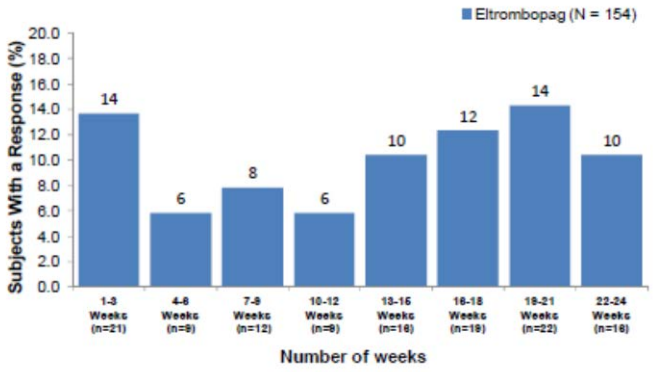
-Eltrombopag-Only Period

In the PETIT study 35.8% of subjects had sustained platelet counts ≥50 Gi/L for at least 60% of assessments between Week 2 and 24 of the Eltrombopag Only Period. Platelet response was also analyzed for the last 12 weeks of the Eltrombopag-Only Period to allow placebo-randomized subjects sufficient time to reach a stable eltrombopag dose. The proportion of subjects with a platelet count response for at least 50% of the assessments between Weeks 13 and 24 in the Eltrombopag-Only Period was 56.3% in the PETIT2 study and 46.3% in the PETIT study. The percentage of subjects with a platelet count response for at least 75% of assessments during the same time span was 43.7% in the PETIT2 study and 29.9% in the PETIT study.

In the pooled analysis, 51.9 % (80/154) subjects in the pediatric studies had a platelet count response for at least 50% of the assessments between Weeks 13 and 24 of the Eltrombopag-Only Period and 37.7% (58/154) subjects had a platelet count response for at least 75% of the assessments. This durable response was consistent across the age cohorts.

The total number of weeks that subjects achieved a response during the 24-week open-label phase was also assessed. Pooled data showed that nearly half (47%) of subjects had a response for 13 weeks or more, and 25% had response for at least 19 out of the 24 weeks (Table 28).

Table 28 **Total Number of Weeks Subjects Achieved a Response (Platelet Counts >=50 Gi/L without Rescue) during the Eltrombopag-Only Period (ITT Population, Pooled Data)**



Median duration of continuous response was 6 weeks (range: 0 to 24 weeks) during Weeks 1-24 of the Eltrombopag-Only period in PETIT2 and 4 weeks in PETIT (range: 0 to 24 weeks). Results of the pooled analysis showed a median of 6.1 weeks (Table 29).

Table 29 Maximum Duration of Response (Platelet Count Continuously >=50 Gi/L) during the 24 Weeks of Eltrombopag Dosing (Eltrombopag-Only Period, ITT Population, Pooled Data)

Weeks	Eltrombopag N=154
n	152
25th percentile	1.1
Median	6.1
75th percentile	13.1
Min.	0
Max.	24

m5.3.5.3 ISE, Section 3.2.2.2

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Evidence from two randomized, double-blind, placebo-controlled studies (PETIT2 and PETIT) is presented to support the efficacy of eltrombopag in the treatment of pediatric patients with chronic ITP. Study PETIT 2 is considered the pivotal study while PETIT is presented as dose-finding supportive study. It is noted that the PIP only discussed the PETIT Study.

Design of the clinical studies

Both studies investigated the efficacy, safety and tolerability of eltrombopag as an add-on therapy to standard treatment in paediatric patients (ages 1 to <18 years) with previously treated chronic ITP. As a precautionary measure, the PETIT2 study and the randomised portion of PETIT started after preliminary results from the Eltrombopag Dose Finding Phase of PETIT were available.

PETIT2 was a two part, double-blind, randomized, placebo-controlled and open-label Phase III study to investigate the efficacy, safety and tolerability of eltrombopag in paediatric subjects with previously treated chronic ITP. Part 1 included 92 subjects who were randomized 2:1 to receive eltrombopag (63 subjects) or placebo (29 subjects) in a 13-week period, with the randomization stratified by 3 age-defined cohorts. Part 2 included 87 subjects from the previous one who received eltrombopag in an open-label manner for 24 weeks. After completion of Part 2, subjects were to complete a 24 to 28 week Follow-up visit including an ophthalmic examination 24 weeks after the last dose of study treatment.

Subjects between 1 year and <18 years of age at Day 1 and confirmed diagnosis of chronic ITP for at least 1 year according to the guidelines published in the International Working Group Report were included if there were no evidence of other causes of thrombocytopenia, were refractory or relapsed after at least one prior ITP therapy, or unable for a medical reason to continue other ITP treatments. According to the MAH, information on the reasoning to consider a patient as non-responder to prior therapies (or intolerant) was not collected. The refractory/non-responder definitions used for the adult population are not valid for the paediatric population. However, it is agreed that the studied population in the PETIT and PETIT II is considered a heavily pretreated population with no-response to prior treatment options.

Concomitant ITP medication (e.g. corticosteroids or azathioprine) administered at a stable dose for at least 4 weeks prior to Day 1 was allowed. Subjects had to have platelet count <30 Gi/L to be eligible for enrolment. Rescue treatment was allowed at any time during the study at the discretion of the investigator.

The primary endpoint was the proportion of subjects on eltrombopag, compared to placebo, achieving platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 to 12 of Part 1 (randomized Period)

in the absence of rescue medication. Other efficacy endpoints were analysis of the need for rescue treatment, the frequency and severity of bleeding, analysis of bleeding AEs, the reduction or discontinuation of baseline concomitant ITP medications and safety.

The **PETIT trial** was presented as supportive evidence of efficacy. This was a Phase II, multicenter, 3 part, staggered cohort, open-label and double blind, randomized, placebo controlled study stratified by 3 age-cohorts. Part 1 was a 24-week open label dose finding phase were 5 subjects in each age cohort received treatment, with safety, PK and platelet count review after 12 weeks (3 months) of treatment. Part 2 was a 7-week randomized, double-blind, placebo-controlled period involving a total of sixty-seven subjects (45 on eltrombopag, 22 on placebo). This was followed by an open-label treatment period where subjects randomized to eltrombopag in Part 2 received an additional 17 weeks of eltrombopag in Part 3 and subjects randomized to placebo in Part 2 received 24 weeks of eltrombopag in Part 3.

Efficacy data and additional analyses

PETIT 2 pivotal Study results:

Ninety-two subjects were enrolled in the 13-week Randomized Period, 63 subjects randomized to the eltrombopag treatment group and 29 subjects randomized to placebo. Twenty-eight (97%) placebo subjects and 59 (94%) eltrombopag subjects entered Part 2 Eltrombopag-Only Period. Treatment was overall well tolerated during the randomised phase, with few patients discontinuing treatment due to AE: one placebo subject due to AE of abdominal hemorrhage, and 2 eltrombopag subjects due to AEs of increases in aminotransferases. Tolerability was also good in the eltrombopag-only period, a total of 7 (8%) subjects discontinued eltrombopag during the 24-week treatment period. The most common reason for discontinuation of treatment was for an AE (4 subjects, 5% (3 with hepatobiliary laboratory abnormalities and 1 with thrombocytopenia).

Overall the studied population was considered representative of the target population: median age was 9 (1-17), 52% were male, 60% caucasians vs 27% East Asian, baseline platelets was ≤15Gi/L in 60% of patients while splenectomy had only been undergone by 4 (6.3%) of patients. The majority of subjects (78%) received 2 or more prior therapies, with corticosteroids, IVIg, Anti-D and rituximab being the most common. Information on the reasoning to consider a patient as non-responder to prior therapies (or intolerant) was not collected.

Baseline demographics and disease characteristics were in general well balanced between the treatment groups, with the exception of baseline ITP medications which were higher in the eltrombopag group. While there was imbalance between the arms on ITP baseline medication, there is no impact on the study results. This was also confirmed by the logistic regression efficacy analysis adjusted for baseline treatment, which demonstrated no difference in results with and without the use of baseline ITP medications.

No information has been provided on the adherence to the posology recommendation in relation to food intake and to what extent this might have been a problem in particular in the subset of youngest children.

A statistically greater proportion of eltrombopag subjects in the PETIT2 study achieved a sustained platelet response (>50 Gi/L in the absence of rescue) for at least 6 of 8 weeks (75% of study duration) between Weeks 5 to 12 of the Randomized Period (39.7%) compared with placebo subjects (3.4%). Consistent results were observed among the different cohorts of patients: cohort 1 (12-17 yrs): 10% placebo vs 39.1% eltrombopag; cohort 2 (6-11 yrs): 0.0% vs 42.3%; cohort 3 (1-5 yrs): 0.0% vs 35.7%. Subgroup analyses based on gender, race, use of ITP medication at baseline, baseline splenectomy status, and baseline platelet

counts (<15 Gi/L, >15 Gi/L) demonstrated that the response was consistent across the subgroups for each of these defined covariates. However, the magnitude of the effect appears somewhat lower to that seen in adults, the Applicant states that the efficacy results were consistent between adult (70% in 773A, 58.9% in 773B) and paediatric (62% and 61% in PETIT and PETIT II) population. This was also reflected in the overlapping confidence intervals across studies. Differences, thought, are still considered clinically relevant and supported by results in secondary endpoints based on platelets response. However, it is highlighted that a substantial proportion of patients will not reach a clinically relevant response and further, it is uncertain if a given response can be maintained in the long-term. Therefore, in order to provide adequate information to prescribers to avoid exposure to an ineffective treatment, a proposal to monitor response with adequate stopping rules if a relevant response is not observed during the initial 4 weeks is already included in the SmPC. This is agreed upon. The SmPC also contains recommendations for a continuous monitoring of the response over time and recommendations to stop treatment if the effect is no longer maintained. For the small proportion of paediatric patients with chronic ITP that do have spontaneous recovery, it is expected that the platelet counts would increase and the dose of eltrombopag would be reduced or interrupted. Restarting treatment with eltrombopag would be based upon the individual patient's platelet counts, and therefore the optimal duration of treatment with eltrombopag is dependent on each individual patient's clinical course

Increases in platelet counts in PETIT2 were associated with differences in the proportion of placebo subjects (7/29, 24.1%) compared with eltrombopag subjects (12/63, 19.0%) who received rescue treatment, defined as either a new ITP medication, an increase in dose of concomitant ITP medication from baseline, platelet transfusion or splenectomy (odds ratio = 0.44, 95% CI 0.21, 0.93, p=0.032). Thought statistically significant, the magnitude of the differences is rather modest. In fact, it is noteworthy the overall low use of rescue medication in both treatment arms, including placebo, despite the low platelet counts. However, it is noted that within subjects who received rescue therapy, the majority of eltrombopag subjects (9/12, 75%) were rescued once, whereas the majority of placebo subjects (5/7, 71%) were rescued 2 or more times. In addition, 8 of the 15 subjects taking baseline ITP medications at the start of the Eltrombopag-Only Period had a sustained reduction or permanent discontinuation of at least 1 baseline ITP medication (only permitted during the eltrombopag only period) without receiving on-therapy rescue: 7 subjects permanently discontinued all baseline ITP medications, and 1 subject had a sustained reduction of a baseline ITP medication for ≥18 weeks without requiring on-therapy rescue. A reduction in the concomitant medication speaks in favour of a relevant effect, although it should be noted that only a small portion of patients were on ITP concomitant medication at the start of eltrombopag only period.

Data show an overall reduction in the incidence of G1-4 bleeding events in both treatment arms, of a higher magnitude in eltrombopag treated arm. Concerning G2-4 bleeding events, an improvement was also seen in both treatment arms but differences between treatment groups were less evident. The magnitude of change from baseline to Week 12 was greater in the eltrombopag group (decreased by 20.6%) compared with the placebo group (decreased by 13.8%). The data are indicative of a trend for a lower incidence of bleeding events over time, which can be seen as supportive of efficacy.

In addition, the proportion of patients with bleeding and severe bleeding events during the study period, according to the platelet counts levels at baseline, i.e. <15Gi/L vs >15Gi/L and by the presence of recent history of bleeding, i.e. during previous 3 months has not been provided, because this was not collected during the study.

The main uncertainty concerning the relevance of the results is to what extent the effect is maintained in the long term.In PETIT2, of the 26 subjects who responded in the Randomized Period, 50% responded for 20 of

24 weeks in open-label eltrombopag period. 75% of the subjects responded for at least 18 of 24 weeks. Results were generally similar among the 3 age cohorts. In the pooled analysis, between Weeks 13 and 24 in the Eltrombopag-Only Period (the last 12 weeks of the study) 37.7% subjects had a platelet count response of $\geq$50 Gi/L for at least 75% of the assessments. The response was similar regardless of the previous treatment received during the Randomized Period; 40% of placebo-randomized and 36.5% of eltrombopag-randomized subjects achieved response for at least 75% of assessments in the last 12 weeks of the open label period. Similar results were observed for each individual age cohort. The overall incidence of bleeding events was decreased while on eltrombopag treatment, which may indicate that fluctuations do not pose patients at an increased risk for bleeding. Given that the target of platelets count will be decided in the clinical practice based on the individual patient´s bleeding risk and also considering the current SmPC recommendation for continuous monitoring and dose adjustments based on platelet counts, these are considered appropriate risk mitigation measures to avoid under or over-treatment.

With regard to the use of rescue medication during the eltrombopag only period.53 % (8/15) of subjects were able to reduce (n = 1) or discontinue (n = 7) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy An effect on bleeding events during the Eltrombopag-Only Period was observed, with less than 30% of subjects with an assessment reported any bleeding, all G2 or lower.

Dose-finding Study: Part 1 PETIT Study -Randomized plus OL eltrombopag only phases:
Sixty-seven subjects were enrolled in the Randomized Period and comprised the Double-Blind ITT Population. Subjects were evenly distributed across treatment groups with respect to age, gender, race, and baseline ITP medication use. All subjects with an ITP diagnosis <12 months had a diagnosis for at least 6 months. Median duration of ITP at screening was 28.4 months (range 6-171 months). The majority of subjects had platelet counts ≤ 15 Gi/L (50% placebo, 51.1% eltrombopag) at baseline. Prior splenectomy (0% placebo, 11% eltrombopag) was more prevalent on the eltrombopag arm. The largest proportion of subjects (38 subjects, 57%) was enrolled in US followed by the Spain (13 subjects, 19%). The studied population in PETIT represents a slightly less severe and heavily pre-treated population as compared to patients in the PETIT 2 trial, and a substantial proportion of patients had not previously received either CS or IVIG in the eltrombopag treated arm, i.e. around ¼ of patients in the eltrombopag arm.

Treatment with eltrombopag led to a statistically significant platelet response with 62.2% in the eltrombopag group compared with 31.8% in the placebo group achieving platelet counts ≥50 Gi/L at least once between Days 8 and 43 (Week 1 to 6) of the 6-week Randomized Period. Eltrombopag treatment was effective in producing a response rate of approximately 60% in each age cohort, which is consistent with the overall analysis.. In the PETIT study sustained platelet response was assessed by the proportion of subjects with platelet counts >50 Gi/L for at least 60% of assessments between Days 15 to 43 (Weeks 2 to 6) of the Randomized Period. The study demonstrated that a higher proportion of eltrombopag subjects than placebo subjects (35.6% vs. 0) had a sustained response during the Randomized Period. These results are supportive of an effect on platelet counts, but should be taken cautiously given the short duration of the randomised phase, the different period of assessment and the use of a purely pharmacodynamic measure, such that these data cannot be directly compared with those of the pivotal study. Sustained responses (15 out of 24 weeks) were seen in the 50% of the initial responders in PETIT Study. No apparent differences exist between age cohorts, but this information has not been provided. During the randomised period 90% of patients in placebo vs 73% patients in eltrombopag had any bleeding event (grade 1-4). Most bleeding during the Randomized Period was WHO Grade 1 or 2, while only two subjects (1 in each treatment group) had WHO Grade 3 and no subject had WHO Grade 4 bleeding. Therefore, differences between treatments in the incidence of bleedings are just due to G1 or 2 events.

The good results of the platelet count indirectly point out that children take the medications and the acceptability and the adherence to treatment are adequate, however as these aspects have not been directly measured, definite conclusions cannot be made.

2.5.4. Conclusions on the clinical efficacy

Overall, data provided are indicative of a clinical benefit for the paediatric population with cITP following treatment with eltrombopag. The data obtained support that the effect of eltrombopag is in line with that in the adult population, eltrombopag achieves to increase the platelet count up to a level considered enough to control the risk of bleeding.

2.6. Clinical safety

Patient exposure

The primary elements of this submission are the data from the 2 pediatric ITP studies, PETIT2 and PETIT. Data from PETIT2 and PETIT were pooled for the analysis of safety data because the patient population was somewhat similar between the two studies. This summary of safety presents data from the pooled analysis of these studies, including pooled safety data.

Patient exposure

There were a total of 174 subjects enrolled in both studies, and 171 subjects received at least 1 dose of eltrombopag at any time during the studies. There were 3 subjects who did not receive eltrombopag. In the ITT Population, 19 (11.9%) subjects withdrew prematurely from the studies with a higher proportion of subjects withdrawing in the eltrombopag group.

Table 7: Summary of End of Study Record (Intent to Treat Population)

	Overall		
	Placebo (N=51)	Eltrombopag (N=108)	Total (N=159)
Study Completion Status, n (%)			
Completed all parts [a]	45 (88.2)	83 (76.9)	128 (80.5)
Completed per-protocol [b]	46 (90.2)	91 (84.3)	137 (86.2)
Completed follow-up	**48 (94.1)**	**92 (85.2)**	**140 (88.1)**
Prematurely withdrawn	**3 (5.9)**	**16 (14.8)**	**19 (11.9)**
Reason for Premature Study Withdrawal, n (%)			
Lack of efficacy	0	2 (1.9)	2 (1.3)
Protocol deviation/violation	0	5 (4.6)	5 (3.1)
Lost to follow-up	0	6 (5.6)	6 (3.8)
Withdrew consent/Withdrawal by parent/guardian	3 (5.9)	3 (2.8)	6 (3.8)

Data Source: SDAP Table 6.1002

a. This represents subjects who completed the Randomized Period, Eltrombopag-Only Period and Follow-up Period.

b. Completed per-protocol represents subjects who completed the Randomized Period and Eltrombopag-Only Period.

Table 8: Summary of Study Treatment Discontinuation (Randomized Period – ITT Population)

	Overall		
	Placebo (N=51)	Eltrombopag (N=108)	Total (N=159)
Investigational product			
Completed double-blind period	50 (98.0)	103 (95.4)	153 (96.2)
Prematurely discontinued	1 (2.0)	3 (2.8)	4 (2.5)
Reason for premature discontinuation			
Adverse event	1 (2.0)	2 (1.9)	3 (1.9)
Lost to follow-up	0	1 (0.9)	1 (0.6)

Data Source: SDAP Table 6.1003

Table 9: Cumulative Exposure to Study Medication by Age Cohort and Overall (All Eltrombopag Treated Population)

	Eltrombopag			
	Cohort 1 (12-17 yrs) (N=61)	Cohort 2 (6-11 yrs) (N=70)	Cohort 3 (1-5 yrs) (N=40)	Overall (N=171)
Duration of Exposure - n (%)				
<6 weeks	0	1 (1.4)	2 (5.0)	3 (1.8)
≥6 weeks	61 (100.0)	69 (98.6)	38 (95.0)	168 (98.2)
≥12 weeks	60 (98.4)	66 (94.3)	36 (90.0)	162 (94.7)
≥24 weeks	46 (75.4)	53 (75.7)	29 (72.5)	128 (74.9)
≥36 weeks	19 (31.1)	23 (32.9)	10 (25.0)	52 (30.4)

Data Source: SDAP Table 8.1010

Table 10: Average Daily Dose (mg/kg) by Age Cohort (Randomized Period – Pooled Data)

Average Daily Dose (mg/kg)	Cohort 1 (12-17 yo)		Cohort 2 (6-11 yo)		Cohort 3 (1-5 yo)	
	Placebo N=18	Eltrombopag N=39	Placebo N=22	Eltrombopag N=43	Placebo N=10	Eltrombopag N=25
Median	1.00	1.00	1.65	1.40	1.80	1.70
Min	0.4	0.3	1.0	0.2	1.0	0.8
Max	1.4	2.1	3.0	2.8	2.4	2.4

Data Source: SDAP Table 8.1001

Overall, the demographics of subjects in the ITT Population were well balanced between treatment groups. The majority of the subjects were White and there were similar proportions of male and female subjects enrolled both within and between treatment groups. Overall, East Asian subjects (East/South East Asian/Japanese) made up 21.4% of the ITT Population and were enrolled in similar proportions between the treatment groups (20.4% eltrombopag; 23.5% placebo).

Adverse events

Overall, the number of subjects in the Safety Population who reported an AE was similar between the treatment groups. There were few serious adverse events (SAEs) and few AEs that led to discontinuation of study treatment (Table 11).

Table 11: Overall Summary of Subjects with Adverse Events Started On Therapy (Safety Population – Randomized Period)

	Overall			
	Placebo (N=50)		Eltrombopag (N=107)	
	n (%)	Events	n (%)	Events
Number of subjects with an AE	41 (82.0)	156	87 (81.3)	355
Number of subjects with a SAE	6 (12.0)	8	9 (8.4)	13
Number of subjects with a drug-related AE	13 (26.0)	25	28 (26.2)	69
Number of subjects with an AE leading to discontinuation of study treatment	1 (2.0)	1	3 (2.8)	6
Number of subjects with a SAE leading to discontinuation of study treatment	1 (2.0)	1	1 (0.9)	2

m5.3.5.3 ISS Section 2.1

In the All Eltrombopag Treated Population, the majority of subjects reported an AE on therapy. There were few SAEs and few events that led to discontinuation of study treatment.

In the Safety Population, the most common AEs (≥10% of subjects) reported in the eltrombopag group were headache, upper respiratory tract infection, and nasopharyngitis, with the latter 2 being reported in a higher proportion of subjects when compared to the placebo group (Table 12).

Table 12: Summary of Subjects with Adverse Events Started On Therapy by Decreasing Frequency – Incidence >=3% in the Eltrombopag Group (Safety Population – Randomized Period)

	Overall	
	Placebo (N=50)	Eltrombopag (N=107)
Subjects with any event, n (%)	**41 (82.0)**	**87 (81.3)**
Headache	12 (24.0)	19 (17.8)
Upper respiratory tract infection	3 (6.0)	18 (16.8)
Nasopharyngitis	2 (4.0)	13 (12.1)
Cough	0	10 (9.3)
Diarrhea	1 (2.0)	10 (9.3)
Pyrexia	4 (8.0)	10 (9.3)
Rhinitis	3 (6.0)	10 (9.3)
Abdominal pain	2 (4.0)	9 (8.4)
Epistaxis	10 (20.0)	9 (8.4)
Nausea	6 (12.0)	8 (7.5)
Oropharyngeal pain	1 (2.0)	8 (7.5)
Toothache	0	6 (5.6)
Vomiting	9 (18.0)	6 (5.6)
Abdominal pain upper	5 (10.0)	5 (4.7)
Rash	1 (2.0)	5 (4.7)
AST increased	0	4 (3.7)
Rhinorrhea	0	4 (3.7)

m5.3.5.3 ISS Section 2.1.1
Note: Terms are coded using the MedDRA dictionary version 16.1.
AST=Aspartate aminotransferase.

Table 13: Summary of Subjects with Treatment-Related Adverse Events Started On Therapy (Safety Population – Randomized Period)

	Overall	
	Placebo (N=50)	Eltrombopag (N=107)
Subjects with any event, n (%)	**13 (26.0)**	**28 (26.2)**
Nausea	5 (10.0)	6 (5.6)
Headache	6 (12.0)	5 (4.7)
Diarrhea	1 (2.0)	4 (3.7)
ALT increased	0	3 (2.8)
AST increased	0	3 (2.8)
Abdominal discomfort	0	2 (1.9)
Abdominal pain	1 (2.0)	2 (1.9)
Blood creatinine increased	1 (2.0)	2 (1.9)
Vomiting	3 (6.0)	2 (1.9)
Abdominal pain upper	1 (2.0)	1 (0.9)
Agitation	0	1 (0.9)
ALT abnormal	0	1 (0.9)
Anxiety	0	1 (0.9)
Arthralgia	0	1 (0.9)
AST abnormal	0	1 (0.9)
Dizziness	0	1 (0.9)
Epistaxis	0	1 (0.9)
Fatigue	1 (2.0)	1 (0.9)
Febrile neutropenia	0	1 (0.9)
Incision site pruritus	0	1 (0.9)
Leukopenia	0	1 (0.9)
Lymphopenia	0	1 (0.9)
Neutropenia	0	1 (0.9)
Nightmare	0	1 (0.9)
Platelet count increased	0	1 (0.9)
Pyrexia	0	1 (0.9)
Rash	0	1 (0.9)
Rash papular	0	1 (0.9)
Somnolence	0	1 (0.9)
Tic	0	1 (0.9)
Blood urea increased	1 (2.0)	0
Hyperbilirubinemia	1 (2.0)	0
Hypersomnia	1 (2.0)	0
Pain in extremity	1 (2.0)	0

m5.3.5.3 ISS Section 2.1.1.1
Note: Terms are coded using the MedDRA dictionary version 16.1.

Table 14: Summary of Subjects with Adverse Events with a Maximum Toxicity Grade of 3 or 4 Started On Therapy (Safety Population – Randomized Period)

	Overall					
	Placebo (N=50)			Eltrombopag (N=107)		
	n	Grade 3	Grade 4	n	Grade 3	Grade 4
Subjects with any event, n (%)	**7**	**5 (10.0)**	**2 (4.0)**	**13**	**11 (10.3)**	**2 (1.9)**
ALT increased	0	0	0	2	2 (1.9)	0
Anaemia	0	0	0	2	2 (1.9)	0
ALT abnormal	0	0	0	1	1 (0.9)	0
Febrile neutropenia	0	0	0	1	0	1 (0.9)
Gingivitis	0	0	0	1	1 (0.9)	0
Influenza	0	0	0	1	1 (0.9)	0
Leukopenia	0	0	0	1	1 (0.9)	0
Lobar pneumonia	0	0	0	1	1 (0.9)	0
Lymphopenia	0	0	0	1	1 (0.9)	0
Meningitis aseptic	0	0	0	1	1 (0.9)	0
Pneumonia	0	0	0	1	1 (0.9)	0
Pneumonia fungal	0	0	0	1	1 (0.9)	0
Pyrexia	0	0	0	1	1 (0.9)	0
Urinary tract infection	0	0	0	1	1 (0.9)	0
Epistaxis	3	3 (6.0)	0	0	0	0
Abdominal pain	1	0	1 (2.0)	0	0	0
Arthralgia	1	1 (2.0)	0	0	0	0
Hemorrhage	1	0	1 (2.0)	0	0	0
Hypertensive crisis	1	1 (2.0)	0	0	0	0
Impetigo	1	1 (2.0)	0	0	0	0
Menorrhagia	1	1 (2.0)	0	0	0	0
Neutropenia	1	1 (2.0)	0	2	1 (0.9)	1 (0.9)
Skin hemorrhage	1	1 (2.0)	0	0	0	0
Varicella	1	1 (2.0)	0	0	0	0

m5.3.5.3 ISS Section 2.1.1.2
Note: Terms are coded using the MedDRA dictionary version 16.1.

Serious adverse events and deaths

There were no fatal AEs reported in the Safety Population or in the All Eltrombopag Treated Population at any time during the studies.

Table 15: Summary of Subjects with Serious Adverse Events Started On-Therapy by Decreasing Frequency (Safety Population – Randomized Period)

	Overall	
	Placebo (N=50)	Eltrombopag (N=107)
Subjects with any event, n (%)	**6 (12.0)**	**9 (8.4)**
ALT abnormal	0	1 (0.9)
Anemia	0	1 (0.9)
AST abnormal	0	1 (0.9)
Febrile neutropenia	0	1 (0.9)
Gingivitis	0	1 (0.9)
Influenza	0	1 (0.9)
Meningitis aseptic	0	1 (0.9)
Neutropenia	0	1 (0.9)
Pneumonia	0	1 (0.9)
Pneumonia fungal	0	1 (0.9)
Pyrexia	0	1 (0.9)
Urinary tract infection	0	1 (0.9)
Conjunctivitis	1 (2.0)	0
Epistaxis	2 (4.0)	0
Hemorrhage	1 (2.0)	0
Hypertensive crisis	1 (2.0)	0
Impetigo	1 (2.0)	0
Petechiae	1 (2.0)	0
Varicella	1 (2.0)	0

m5.3.5.3 ISS Section 2.1.3

Note: Terms are coded using the MedDRA dictionary version 16.1.

Laboratory findings

Hematological findings

Table 16: Summary of Subjects with Hematology Toxicity Grade Increases from Baseline to Worst Post-Baseline Assessment (Safety Population – Randomized Period)

Parameter	Category	Overall		
		Placebo (N=50)	Eltrombopag (N=107)	Total (N=157)
White Blood Cell count (Gi/L) (Leukopenia)	**n (%)**	**50**	**107**	**157**
	Any increase	9 (18.0)	17 (15.9)	26 (16.6)
	Increase to Grade 1	8 (16.0)	11 (10.3)	19 (12.1)
	Increase to Grade 2	1 (2.0)	2 (1.9)	3 (1.9)
	Increase to Grade 3	0	3 (2.8)	3 (1.9)
	Increase to Grade 4	0	1 (0.9)	1 (0.6)
Total Neutrophils (Gi/L) (Neutropenia)	**n (%)**	**50**	**107**	**157**
	Any increase	5 (10.0)	17 (15.9)	22 (14.0)
	Increase to Grade 1	3 (6.0)	3 (2.8)	6 (3.8)
	Increase to Grade 2	0	9 (8.4)	9 (5.7)
	Increase to Grade 3	2 (4.0)	2 (1.9)	4 (2.5)
	Increase to Grade 4	0	3 (2.8)	3 (1.9)
Hemoglobin (g/L) (Anemia)	**n (%)**	**50**	**107**	**157**
	Any increase	10 (20.0)	26 (24.3)	36 (22.9)
	Increase to Grade 1	7 (14.0)	21 (19.6)	28 (17.8)
	Increase to Grade 2	0	4 (3.7)	4 (2.5)
	Increase to Grade 3	3 (6.0)	1 (0.9)	4 (2.5)
	Increase to Grade 4	0	0	0
Lymphocyte count (Gi/L) (Lymphocytopenia)	**n (%)**	**50**	**107**	**157**
	Any increase	9 (18.0)	24 (22.4)	33 (21.0)
	Increase to Grade 1	9 (18.0)	20 (18.7)	29 (18.5)
	Increase to Grade 2	0	2 (1.9)	2 (1.3)
	Increase to Grade 3	0	2 (1.9)	2 (1.3)
	Increase to Grade 4	0	0	0

m5.3.5.3 ISS Section 3.2

n = number of subjects with values at the specified planned time.

Adverse Events of special interest

Bleeding Events

Table 17: Summary of Subjects with Adverse Events of Special Interest (Bleeding) Started On-Therapy (Safety Population – Randomized Period)

	Overall	
	Placebo (N=50)	Eltrombopag (N=107)
Subjects with any event, n (%)	**18 (36.0)**	**18 (16.8)**
95% CI[a]	**(22.9, 50.8)**	**(10.3, 25.3)**
Epistaxis	10 (20.0)	9 (8.4)
Gingival bleeding	3 (6.0)	2 (1.9)
Menorrhagia	2 (4.0)	2 (1.9)
Petechiae	2 (4.0)	2 (1.9)
Mouth hemorrhage	1 (2.0)	2 (1.9)
Tongue hemorrhage	1 (2.0)	1 (0.9)
Mucosal hemorrhage	0	1 (0.9)
Periorbital contusion	0	1 (0.9)
Wound hemorrhage	0	1 (0.9)
Lip hemorrhage	0	1 (0.9)
Hematochezia	1 (2.0)	0
Ecchymosis	1 (2.0)	0
Skin hemorrhage	1 (2.0)	0
Hematotympanum	1 (2.0)	0
Urethral hemorrhage	1 (2.0)	0
Hemorrhage	1 (2.0)	0

m5.3.5.3 ISS Section 2.1.5.1

Note: Terms are coded using the MedDRA dictionary version 16.1.

a. 95% CI for proportion of subjects with an Event within treatment group and cohort calculated by exact binomial method.

Hepatobiliary events

Table 18: Summary of Subjects Meeting Hepatobiliary Laboratory Abnormality Criteria at Any Post-Baseline Visit (Safety Population – Randomized Period)

	Overall	
	Placebo (N=50)	Eltrombopag (N=107)
Subjects with events meeting at least one criterion, n (%)	**1 (2.0)**	**8 (7.5)**
ALT and/or AST ≥3xULN and Total Bili. ≥1.5xULN	0	0
Direct Bilirubin >35% Total Bilirubin [a]	0	0
ALT+AST ≥5xULN	0	0
ALT+AST ≥3xULN	0	1 (0.9)
ALT ≥10xULN	0	0
ALT ≥5xULN	0	2 (1.9)
ALT ≥3xULN	0	5 (4.7)
AST ≥5xULN	0	0
AST ≥3xULN	0	1 (0.9)
Total Bilirubin ≥2xULN	1 (2.0)	0
Direct Bilirubin >35% Total Bilirubin [b]	0	0
Total Bili. ≥1.5xULN	1 (2.0)	1 (0.9)
Direct Bilirubin >35% Total Bilirubin [c]	0	0
Alk. Phos. ≥1.5xULN	0	2 (1.9)

m5.3.5.3 ISS Section 2.1.5.2

Note: Based on Guidance for Drug-Induced Liver Injury: Premarketing Clinical Evaluation [FDA, 2009]. Abnormality criteria applied on lab value/ULN calculated to 1 decimal place where criteria are multiple of ULN, otherwise direct comparison of lab value to ULN is performed.

a. Denominator is number of subjects with ALT and/or AST ≥3xULN and Total Bili. ≥1.5xULN.
b. Denominator is number of subjects with Total Bili. ≥2xULN.
c. Denominator is number of subjects with Total Bili. ≥1.5xULN.

Table 19: Summary of Characteristics for Adverse Events of Special Interest (Hepatobiliary) Started On-Therapy (Safety Population – Randomized Period)

	Overall		
	Placebo (N=50)	Eltrombopag (N=107)	Total (N=157)
Number of subjects with events	0	7	7
Number of subjects with toxicity grade 3 or 4 events	0	3 (2.8)	3 (1.9)
95% CI[a]	(0.0, 7.1)	(0.6, 8.0)	(0.4, 5.5)
Number of events	0	14	14
Event Characteristics, n (%)			
Serious	0	2 (14.3)	2 (14.3)
Drug-related	0	9 (64.3)	9 (64.3)
Leading to discontinuation of study treatment	0	5 (35.7)	5 (35.7)
Toxicity Grade 3 or 4	0	3 (21.4)	3 (21.4)

m5.3.5.3 ISS Section 2.1.5.2

a. 95% CI for the proportion of subjects with a toxicity grade of 3 or 4 within treatment group calculated by exact binomial method.

Thromboembolic Events

There were no reports of thromboembolic events in either population at any time during the studies

Renal Adverse Events

There was no notable difference in the incidence of renal AEs between treatment groups (Table 32).

Cataract

In the Safety Population, one subject in the eltrombopag group (PETIT2, Cohort 1; East Asian) was determined to have a cataract event. This subject had bilateral visually significant cataracts at baseline, and cataract risk factor of chronic corticosteroid use. The CEC members were discordant in their adjudication of the case: only one of three CEC members considered the case a bilateral, progressive event which occurred during the Randomized Period.

In the All Eltrombopag Treated Population, there was one additional subject (PETIT2; Cohort 2; East Asian) who was determined to have a cataract event; this subject, who had cataract risk factor of chronic corticosteroid use, experienced a bilateral, incident cataract event at the 24-week ocular follow-up visit.

Overall Ocular Assessment

Based on the CEC review of ocular data, 2 subjects who had received eltrombopag were determined to have 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.

Malignancy

No hematologic malignancies were reported. There was one report of malignancy 20 months after the discontinuation of eltrombopag treatment. A subject was diagnosed with thyroid papillary carcinoma and underwent total thyroidectomy with left neck dissection. The investigator considered the event unrelated to study treatment.

Bone Marrow

There were no events indicative of bone marrow fibrosis in either population at any time

Safety in special populations

AE by age in the paediatric population

Table 21: Overall Summary of Subjects with Adverse Events Started On-Therapy by Age Cohort (Safety Population – Randomized Period)

	Cohort 1 (12-17 yrs)				Cohort 2 (6-11 yrs)				Cohort 3 (1-5 yrs)			
	Placebo (N=18)		Eltrombopag (N=39)		Placebo (N=22)		Eltrombopag (N=43)		Placebo (N=10)		Eltrombopag (N=25)	
Number of subjects with:	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Adverse event	15 (83.3)	51	30 (76.9)	131	18 (81.8)	82	38 (88.4)	160	8 (80.0)	23	19 (76.0)	64
Serious adverse event	2 (11.1)	2	3 (7.7)	5	3 (13.6)	5	6 (14.0)	8	1 (10.0)	1		0
Drug-related AE	3 (16.7)	5	7 (17.9)	12	7 (31.8)	16	16 (37.2)	51	3 (30.0)	4	5 (20.0)	6
AE leading to discontinuation of study treatment	1 (5.6)	1	0	0	0	0	3 (7.0)	6	0	0	0	0
SAE leading to discontinuation of study treatment	1 (5.6)	1	0	0	0	0	1 (2.3)	2	0	0	0	0

m5.3.5.3 ISS Section 5.1.1

Table 22: Summary of Subjects with Events of Special Interest by Age (Safety Population – Randomized Period)

Subjects with event, n (%)	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)	
	Placebo (N=18)	Eltrombopag (N=39)	Placebo (N=22)	Eltrombopag (N=43)	Placebo (N=10)	Eltrombopag (N=25)
Bleeding AEs	6 (33.3)	9 (23.1)	8 (36.4)	4 (9.3)	4 (40.0)	5 (20.0)
Hepatobiliary AEs	0	2 (5.1)	0	5 (11.6)	0	0
ALT >= 3xULN	0	0	0	4 (9.3)	0	1 (4.0)
Renal AEs	1 (5.6)	2 (5.1)	2 (9.1)	1 (2.3)	0	0
CEC Adjudicated Cataract Events	0	1 (2.6)	0	0	0	0

m5.3.5.3 ISS Section 5.1.1, TRA115450 CSR, Section 7.4.5.4.

Table 23: Subjects with Adverse Events by Age Cohort (Randomized Period – Pooled Data)

	Cohort 1 (12-17 yo)		Cohort 2 (6-11 yo)		Cohort 3 (1-5 yo)	
	Placebo N=18	Eltrombopag N=39	Placebo N=22	Eltrombopag N=43	Placebo N=10	Eltrombopag N=25
Subjects with an AE, n (%)	15 (83.3)	30 (76.9)	18 (81.1)	38 (88.4)	8 (80.0)	19 (76.0)
Subjects with an SAE, n (%)	2 (11.1)	3 (7.7)	3 (13.6)	6 (14.0)	1 (10.0)	0
Subjects with a drug-related AE, n (%)	3 (16.7)	7 (17.9)	7 (31.8)	16 (37.2)	3 (30.0)	5 (20.0)
Subjects with maximum toxicity Grade 3 or 4	3 (16.7)	4 (10.3)	3 (13.6)	9 (20.9)	1 (10.0)	0
Subjects with ALT≥ 3x ULN, n (%)	0	0	0	4 (9.3)	0	1 (4.0)

Data Source: SDAP Table 8.2001, Table 8.2084, Table 8.6003, Table 8.12001

Table 24: Number of subjects who experienced AE of Diarrhoea by Cohort in TRA108062: Randomized Period

Attributes	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)		Overall	
	PTM (N=8) n (%)	Epag (N=16) n (%)	PTM (N=9) n (%)	Epag (N=17) n (%)	PTM (N=4) n (%)	Epag (N=11) n (%)	PTM (N=21) n (%)	Epag (N=44) n (%)
Any event; n (%)	8 (100)	13 (81.3)	9 (100.0)	14 (82.4)	3 (75.0)	9 (81.8)	20 20 (95.2)	36 (81.8)
Diarrhoea	1 (12.5)	0	0	3 (17.6)	0	4 (36.4)	1 (4.8)	7 (15.9)

Table 25: Number of subjects who experienced AE of Diarrhoea by Cohort in TRA115450: Randomized Period

Attributes	Cohort 1 (12-17 yrs)		Cohort 2 (6-11 yrs)		Cohort 3 (1-5 yrs)		Overall	
	PTM (N=10) n (%)	Epag (N=23) n (%)	PTM (N=13) n (%)	Epag (N=26) n (%)	PTM (N=6) n (%)	Epag (N=14) n (%)	PTM (N=29) n (%)	Epag (N=63) n (%)
Any event	7 (70.0)	17 (73.9)	9 (69.2)	24 (92.3)	5 (83.3)	10 (71.4)	21 (72.4)	51 (81.0)
Diarrhoea	0	1 (4.3)	0	0	0	2 (14.3)	0	3 (4.8)

AE by race

Table 26: Overall Summary of Subjects with Adverse Events Started On Therapy by Race (Safety Population – Randomized Period)

	East Asian Subjects				Non East Asian Subjects			
	Placebo (N=12)		Eltrombopag (N=22)		Placebo (N=38)		Eltrombopag (N=85)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
AE	7 (58.3)	12	16 (72.7)	55	34 (89.5)	144	71 (83.5)	300
SAE	0	0	3 (13.6)	5	6 (15.8)	8	6 (7.1)	8
Drug-related AE	0	0	3 (13.6)	7	13 (34.2)	25	25 (29.4)	62
AE leading to discontinuation of study treatment	0	0	2 (9.1)	4	1 (2.6)	1	1 (1.2)	2
SAE leading to discontinuation of study treatment	0	0	0	0	1 (2.6)	1	1 (1.2)	2

m5.3.5.3 ISS Section 5.1.2

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to AEs

Table 27 Summary of Subjects with Adverse Events Leading to Discontinuation of Study Treatment Started On-Therapy (Safety Population – Randomized Period)

	Overall	
	Placebo (N=50)	Eltrombopag (N=107)
Subjects with any event, n (%)	**1 (2.0)**	**3 (2.8)**
ALT increased	0	2 (1.9) [a]
ALT abnormal	0	1 (0.9)
AST abnormal	0	1 (0.9)
AST increased	0	1 (0.9)
Blood creatinine increased	0	1 (0.9)
Hemorrhage	1 (2.0)	0

Data Source: SDAP Table 8.2023

Note: Terms are coded using the MedDRA dictionary version 16.1.

a. Subject 775 in PETIT2 reported an AE of increased ALT which began in the Randomized Period. The event met liver stopping criteria in the Eltrombopag Only Period and the subject discontinued study treatment.

2.6.1. Discussion on clinical safety

Overall 171 paediatric patients have been treated with eltrombopag, 128 (74.9%) had at least 24 weeks exposure. Although limited, data may be sufficient to characterize the safety profile of eltrombopag in children given the extensive experience of use in adults. It is important to keep in mind that the majority of ITP cases in the childhood are acute, following a viral infection and that around 15%-30% become chronic ITP forms. Moreover a substantial proportion of children recover with the current first line treatment options (corticosteroids and inmunoglobulins). Therefore, the use of eltrombopag for the treatment of cITP in clinical practice is expected to limited.

In general, children of all ages have been recruited in the clinical studies; 61 children aged 12-17 years (cohort 1), 70 children aged 6-11 years (cohort 2) and 40 children aged 1-5 years (cohort 3). There were no children below 1 year, but they are excluded from the claimed indication (and also a waiver was granted). Exposure time was rather consistent across age cohorts and the safety profile is properly studied in each group. In this sense, it is noted that some adverse events like diarrhea (24.0%, 7.0% and 2.6% in cohort 3, 2 and 1) and pyrexia (20.0%, 7% and 5.1% in cohort 3, 2 and 1) occurred more commonly in the youngest age group (1-5 yrs). It is uncertain if this is truly related to age, given that this subgroup also received the highest doses (per kg of body weight). On the other hand 12.8% of adolescents experienced nausea (as opposite 7% in cohort 2, and 0 in the cohort 3) and 9.3% vomiting in cohort 2 (2.6% in the cohort 1 and 4.0% in cohort 3). The amount of mannitol used in the PfOS 25 mg formulation is (1196.75 mg), higher than the amount used in the 25 mg tablet formulation 29.7 mg (40:1 ratio). However it does not seem to be associated with the occurrence of diarrhoea in the eltrombopag-treated patients, because no cases were reported in placebo treated subjects despite that they received a similar (slightly higher) mannitol amount in the clinical trials PETIT and PETIT1.

Although the Applicant has not discussed how the high incidence of diarrhoea in the youngest patients can affect to the efficacy of the product, it is assumed that given that all the cases were graded as mild the impact in the efficacy will be minor.

However, the high incidence of diarrhoea is a known effect for the paediatric population, which is adequately reflected in the SmPC. Data show an incidence between 14%-36.4%, therefore the frequency appears as "very common" in paediatric population. To study safety the Applicant planned two different analyses, one based on the comparative phase with placebo (randomized period) and the analysis of all patients who received eltrombopag during completed paediatric clinical program, this approach is supported, although the difficulty in the interpretation of the second analysis are fully acknowledged. So, the main analysis relies on the randomized period where safety of patients treated with eltrombopag is compared to that of the placebo arm. Overall 50 patients were treated with placebo and 107 subjects with eltrombopag.

According to the analysis of the safety population, the median (min-max) daily dose in mg was 53.30 (20.3-71.4) in cohort 1, 50 (4.7-71.2) in cohort 2 and 27.10 (12.3-47.5) in cohort 3. The Applicant has submitted information of the incidence of adverse events by age cohort, assuming that the oldest cohort received the lowest dose by Kg of body weight (BW) and the youngest received the highest dose by BW, there was no relationship between the dose and the safety profile.

In cohort 2 (6-11 years) there is an imbalance between the investigational product and placebo in the percentage of subjects with AE grade 3/4 (20.9% vs 13.6%) and the subjects with ALT values above 3x ULN (9.3% vs no cases). Given the small number of patients enrolled it is nonetheless impossible to firmly conclude that a worse safety profile can be expected in the youngest age group.

The adverse events profile in children is consistent with that in adults and the majority of adverse events had been described previously. The MAH has identified a number of AEs that have only been observed in children or at a frequency different to that described for the adult population: nasopharyngitis, upper respiratory tract infections, rhinitis, cough, oropharyngeal pain, rhinorrhoea, toothache and pyrexia, all of them commonly observed in the paediatric population and that are to be reflected in section 4.8 of the SmPC.

AEs at the nervous system have been described for eltrombopag, but the relevance for the paediatric population may be different and data available is not considered of particular concern. In addition, the occurrence of febrile neutropenia was a matter of concern. However the Applicant has provided additional information to consider this event as not eltrombopag-related. Nevertheless, it is acknowledged that no deaths and a rather low incidence of SAEs have been reported, which is reassuring. The Applicant has submitted an analysis of hepatobiliary events, thromboembolic events, post-therapy reoccurrence of thrombocytopenia, haematological malignancies, bone marrow reticulin fibrosis, cataracts, renal tubular toxicity, haematological changes, and malignancies. Although the number of patients studied is small and thus, some uncertainties remain, it is noted that in the paediatric population no particular trend has been identified in frequency and/or the severity of AEs as compared to the adult population.

There were no cases of thromboembolic events, haematological abnormalities or increased bone marrow reticulin formation. Overall 8 subjects (7.5%) in the randomized analysis had hepatic laboratory abnormalities and 21 (12.3%) in “all eltrombopag treated population”. Seven patients suffered 14 events of hepatobiliary AE (5 discontinued the treatment) in the randomized treatment and 18 patients had 35 episodes of hepatobiliary events from the analysis of “all eltrombopag treated population” (9 discontinued the treatment); in all cases followed by complete resolution after stopping treatment.

From “all eltrombopag treated population” two subjects had cataracts according to CEC assessment, but both subjects had reported previous corticosteroid use, so it is difficult to attribute them to eltrombopag

treatment. The recommendation stated in the SmPC about routine ophthalmologic monitoring is appropriate and no further information is required.

Analysis based on race highlight the difference with regard to SAEs (16% in East Asian population vs 7.1% in non- East Asian Population), and hepatobiliary laboratory abnormalities (23.5% East Asian Subjects vs 6.6% non-East Asian). Given the small number of patients studied, it is difficult to firmly conclude but this goes in line with the findings in the adult population and thus caution should be exercised when treating this EA population. Also, for patients with baseline platelet count < 15 Gi/L (11.5% vs 4.4%) and in subjects taking baseline ITP medication (29.4 % vs 4.4%), a higher incidence of SAEs was reported. It does not seem to be related to the eltrombopag. The post-commercialization experience in adult patients with 4458 spontaneous reports from post-marketing surveillance is reassuring.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been assessed and relevant information included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Based on the information provided, the safety profile of eltrombopag in the paediatric population appears similar to that seen in adults, with no relevant new trends or changes identified. Safety findings of special interest in the adult population, including hepatotoxicity, cataracts, potential haematological changes (leukocytosis and anaemia, cases of thrombocytosis), recurrence of thrombocytopenia, malignancies (haematological) and renal tubular toxicity/renal failure have been investigated in the paediatric population and data are reassuring, but given the low number of patients and the overall short-term of follow up, all the measures stated in the PhV program and the RMP should be followed.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 34.1 is acceptable. The endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 34.1 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	**Adult ITP, <u>Paediatric ITP,</u> HCV-associated thrombocytopenia and Severe Aplastic Anaemia** Hepatotoxicity Thromboembolic events Post Therapy occurrence of thrombocytopenia

Summary of safety concerns	
	Cataract **HCV-associated thrombocytopenia** Hepatic decompensation Thromboembolic events - Portal vein thrombosis Retinal Haemorrhage
Important potential risks	**Adult ITP, <u>Paediatric ITP</u>, HCV-associated thrombocytopenia and Severe Aplastic Anaemia** Thrombotic Microangiopathy with Acute Renal Failure Potential for Increased Bone Marrow Reticulin Formation Haematological Malignancies Renal Tubular Toxicity Phototoxicity Potential for Haematological changes Potential for Endosteal Hyperostosis **HCV-associated thrombocytopenia** QT/QTc interval prolongation **Severe Aplastic Anaemia** Cytogenetic abnormalities
Missing information	**Adult ITP, <u>Paediatric ITP,</u> HCV-associated thrombocytopenia and Severe Aplastic Anaemia** Pregnant or lactating females Asian population Black Race population Patients with hepatic impairment Patients with renal impairment Off-label use **Adult ITP** Very elderly patients **HCV-associated thrombocytopenia** Paediatric patients Elderly patients Very elderly patients HCV patients with FibroSURE score of F0, F1, F2 HCV patients infected with genotype other than 1, 2 or 3 HCV patients with Child Pugh score B (7-9) Safety and efficacy of eltrombopag in combination with new direct acting agents (telaprivir/boceprevir) **Severe Aplastic Anaemia**

Summary of safety concerns	
	Cyclosporine

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
TRA105325/ EXTEND Clinical Category 3	Extension study in adults with ITP long term safety including collection of bone marrow reticulin	Bone Marrow Reticulin Formation	Ongoing	Final study report September 2015
TRA112940/ Bone Marrow Study Clinical Category 3	Safety in adults with ITP long term safety including collection of bone marrow reticulin	Bone Marrow Reticulin Formation	Ongoing	Final study report September 2015
US Pregnancy Registry Pharmacoepidemiology Category 3	Safety data on pregnant females	Pregnant and Lactating Females	Terminated	Released from FDA requirement
TRA113101/Lactation Study Clinical Category 3	Safety data on lactating females	Pregnant and Lactating Females	Terminated	Released from FDA requirement
WWE116951: Prospective observational study of ENABLE clinical trial patients to understand later outcome patterns among patients with and without a Thromboembolic event. Pharmacoepidemiology Category 3	TEE in patients with HCV associated thrombocytopenia	TEE	Ongoing	Final study report December 2017
Drug utilization study Pharmacoepidemiology Category 3	Collect data of 'real-world' use of Eltrombopag post approval	Off label use	Ongoing	Final report December 2016
GSK PASS Study: Proposed Post Authorization Safety Study of HCV patients treated with Eltrombopag: Multicenter, Prospective Observational Cohort Study of Thrombocytopenic HCV Patients Receiving Eltrombopag	Assess occurrence of safety events among HCV patients who receive Eltrombopag in the post approval, real world setting	TEE and Hepatic decompensation	Ongoing	6 months interim analysis, December 2016 12 months interim analysis, June 2017 18 months

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Pharmacoepidemiology Category 3				interim analysis, December 2017 Final report, November 2019
HCV-TARGET: Proposed Post Authorization Safety Study of HCV patients treated with Eltrombopag: Hepatitis C Therapeutic Registry and Research Network Pharmacoepidemiology Category 3	Assess occurrence of safety events among HCV patients who receive Eltrombopag in the post approval, real world setting	TEE and Hepatic decompensation	Ongoing	First interim, October 2016 Final report, October 2019
Effectiveness of Eltrombopag Educational Materials for Hepatitis C associated thrombocytopenia Category 3	Measurement of the effectiveness of the Eltrombopag Risk Minimisation education materials	Key elements within the educational materials including hepatic decompensation, TEEs and fatal adverse events	Ongoing	Interim report, April 2015 Final report, September 2015
ELT116826 Clinical Category 3	Safety of eltrombopag in SAA patients unresponsive to IST	Safety in SAA patients unresponsive to IST and potential risk of cytogenetic abnormalities	Ongoing	August 2018
ELT116643 Clinical Category 3	Safety of eltrombopag in SAA patients receiving front-line treatment	Safety in front-line SAA patients receiving treatment with IST and potential risk of cytogenetic abnormalities	Ongoing	May 2016
RAD201583 Clinical Category 3	Determine effect of cyclosporine on PK of eltrombopag	DDI – cyclosporine and eltrombopag	Planned	Sep 2015
RAD200936 Clinical Category 3	Safety of eltrombopag in paediatric SAA	Paediatrics	Planned	Dec 2020
Gem-Platinum/TRC112765 Clinical	Safety of eltrombopag in subjects with solid	May provide additional safety data regarding	Ongoing	April 2016

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Category 3	tumors receiving gemcitabine monotherapy or gemcitabine plus cisplatin or carboplatin	potential risk of Haematological changes		
ASPIRE/TRC114968 Clinical Category 3	Safety of eltrombopag in subjects with advanced MDS or AML	May provide additional safety data regarding potential risk of Haematological changes	Ongoing	April 2016

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional pharmacovigilance activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatotoxicity	Adult ITP - Current text in SmPC • Statement in Section 4.4. Warning and Precaution of the SmPC advising to monitor and manage patient with hepatotoxicity. Specify liver testing before initiation, every 2 weeks during the first 3 months, thereafter every 4-6 weeks • Liver stopping criteria: Specific instructions for discontinuation of eltrombopag to avoid further elevations of hepatobiliary laboratory values • Increased ALT, AST and indirect bilirubin have been added in Section 4.8 (Undesirable effects). <u>Paediatric ITP – See above</u> HCV-Associated Thrombocytopenia - Current text in SmPC text • In the SmPC, a warning regarding the potential for Hepatobiliary laboratory abnormalities (ALT, AST, bilirubin, and alkaline phosphatase) in Section 4.4 (Special warnings and precautions for use). • Also, preferred terms related to hepatotoxicity in Section 4.8 Undesirable effects).	Educational materials
Thromboembolic events Portal Vein Thrombosis	Adult ITP - Current text in SmPC • Section 4.2 (Posology and method of administration), section 4.4 (Special warnings	Educational materials

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and precautions for use), and section 5.2 (Pharmacokinetic properties) of the SmPC state that eltrombopag should not be used in patients with moderate to severe hepatic impairment unless the expected benefit outweighs the identified risk of portal venous thrombosis. • Section 4.2 of the SmPC further states that if the use of eltrombopag is deemed necessary [in patients with moderate to severe hepatic impairment] the starting dose must be 25mg once daily. • A statement in Section 4.4 (Special warnings and precautions) regarding the potential for thromboembolic events is included including caution for patient with known risk factors for TEE. The PIL also reflects this information • Thromboembolic events are included in Section 4.8 (Undesirable effects). • Information regarding patients with chronic liver disease and the risk of thromboembolic events is included in Sections 4.4 and 4.8 of the SmPC. Thromboembolic events <u>Paediatric ITP – See above</u> HCV-Associated Thrombocytopenia - Current text in SmPC • In the SmPC, a warning regarding the potential for thromboembolic events including portal vein thrombosis in Section 4.4 (Special warnings and precautions for use). Also, thromboembolic events in Section 4.8 (Undesirable effects).	
Post Therapy occurrence of thrombocytopenia	Current text in SmPC • A statement in Section 4.4 (Special Warnings and precautions) regarding the potential for decrease in platelet counts post discontinuation of therapy. The PIL also reflects this information. • A warning has been added to Section 4.4 (Special warnings and precautions) of the SmPC stating that in HCV clinical trials, gastrointestinal bleeding was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding. The PIL also reflects this information. • Thrombocytopenia following discontinuation of treatment is included in Section 4.8 (Undesirable effects).	Educational materials
Cataract	Current text in SmPC	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• A statement in Section 4.4 (Special Warnings and precautions) regarding the routine monitoring for cataracts is included. The PIL also reflects this information.	
Hepatic decompensation	HCV-Associated Thrombocytopenia - Current text in SmPC • In the SmPC, a warning regarding the potential for hepatic decompensation will be proposed for addition to Section 4.4 (Special warnings and precautions for use). • Also, preferred terms related to hepatic decompensation in Section 4.8 (Undesirable effects). Also, preferred terms related to hepatic decompensation in Section 4.8 (Undesirable effects)	Educational materials
Retinal Haemorrhage	Current text in SmPC • A warning in Section 4.4. (Special warnings and precautions) is proposed that states retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2 % of the eltrombopag group and 2 % of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended. • The PIL also reflects this information.	None
Thrombotic Microangiopathy with Acute Renal Failure	The current SmPC includes a warning in Section 4.4 regarding the risk of thrombotic/thromboembolic complications in both study populations, ITP and HCV (in combination with anti-viral interferon and ribavirin therapy). In Section 4.8, deep vein thrombosis, and renal failure are included as adverse reactions in the ITP study population.	None
Potential for Increased Bone Marrow Reticulin Formation	Current text in SmPC • A statement in Section 4.4 (Special Warnings and precautions) of the SmPC informing prescribers to monitor for immature or dysplastic cells and the potential for increase in bone marrow reticulin fibres is included, the PIL also reflects this information.	Educational materials
Haematological Malignancies	Current text in SmPC • Section 4.4 of the SmPC (Special Warnings and precautions) states that the diagnosis of ITP in adults and elderly patients should have been confirmed by the exclusion of other clinical	Educational materials

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	entities with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs. • An update to Section 4.4 (Special warning and precautions) of the SmPC informing prescriber of a concern that thrombopoietin receptor (TPO-R) agonists may stimulate the progression of existing haematopoietic malignancies such as MDS • Section 4.8 of the SmPC (Undesirable effects) in the single-arm, open label trial in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) subject has been diagnosed with MDS or AML in each study.	
Renal Tubular Toxicity	Current text in SmPC • A statement in Section 5.3 (Pre-clinical safety data) that the clinical relevance of the renal tubular toxicity finding in rodents is unknown.	None
Phototoxicity	Current text in SmPC • A statement in Section 5.3 (Pre-clinical safety data) that there is a potential risk of photoallergy and that the clinical relevance of the in-vitro finding is unknown.	None
Potential for Haematological changes	Current text in SmPC • A warning is in Section 4.4. (Special warnings and precautions) of the SmPC informing prescribers to monitor for immature or dysplastic cells. • A statement in Section 5.3 (Pre-clinical safety data) of the haematological changes findings in rats and dogs and that the clinical relevance of the finding is unknown.	None
Potential for Endosteal Hyperostosis	Current text in SmPC • A statement in Section 5.3 (Pre-clinical safety data) of the endosteal hyperostosis findings in rodents and that the clinical relevance of the finding is unknown.	None
QT/QTc interval prolongation	Current text in SmPC • A statement in Section 4.4 (Special warning and precautions) of the SmPC stating a QTc study indicates that eltrombopag will not have a clinically significant effect on cardiac repolarisation at therapeutic or supra-therapeutic	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	doses. QTc interval prolongation has been reported in clinical trials of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.	
Cytogenetic abnormalities	Proposed text in SmPC A statement in Section 4.8 (Undesirable effects) of the SmPC informing prescribers of the following: In the single-arm, open-label trial in SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight (19%) patients had a new cytogenetic abnormality reported, including 5 patients who had changes in chromosome 7. In the two ongoing studies (ELT116826 and ELT116643), cytogenetic abnormalities have been detected in 4/28 (14%) and 4/62 (6%) subjects in each study. Additionally, Section 4.2 states: • If new cytogenetic abnormalities are detected, evaluate whether continuation of eltrombopag is appropriate.	None
Paediatric patients	Current text in SmPC • Section 4.2 (Posology and method of administration) of the SmPC, states that ~~the safety and efficacy of eltrombopag in paediatric patients (< 18 years of age) has not been established~~ Revolade is not recommended for use in children under the age of 1 with chronic ITP due to insufficient data on safety and efficacy.	None
Pregnant or lactating females	Current text in SmPC • The SmPC (Section 4.6) and package leaflet states that the risk to pregnant or lactating women is unknown.	None
Asian population	Adult ITP and HCV - Current text in SmPC • A statement the SmPC (Section 4.2 Posology) states the following: *East Asian patients* Initiation of eltrombopag at a reduced dose of 25 mg once daily may be considered for ITP patients of East Asian ancestry (such as Chinese, Japanese,	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Taiwanese, Thai or Korean) (see section 5.2). Initiate eltrombopag at a dose of 25 mg once daily in HCV patients of East Asian ancestry. Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed. For ITP or HCV patients of East Asian ancestry with hepatic impairment initiate eltrombopag at a dose of 25 mg once daily. Paediatric ITP Current text in SmPC: *Adults and paediatric population aged 6 to 17 years* For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). *Paediatric population aged 1 to 5 years* For paediatric ITP patients aged 1 to 5 years of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean, or Thai), eltrombopag should be initiated at a dose of 25 mg once every other day (see section 5.2). **SAA** Proposed text in SmPC: A lower starting dose of 25 mg is recommended for patients of East Asian ancestry and patients with hepatic impairment.	
Black Race population	None	None
Elderly patients Very elderly patients	Current text in SmPC • The SmPC (Section 4.2 Posology) states that there are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	There are limited data on the use of eltrombopag in HCV patients aged over 75 years. Caution should be exercised in these patients.	
Patients with hepatic impairment	Adult ITP and HCV - The SmPC (Section 4.2 Posology) states the following: *Hepatic impairment* Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment wait 3 weeks before increasing the dose. No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Thrombocytopenic patients with chronic HCV should initiate eltrombopag at a dose of 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment wait 2 weeks before increasing the dose. There is an increased risk for adverse events, including thromboembolic events, in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedures or in HCV patients undergoing antiviral therapy. <u>Paediatric ITP - See above</u> **SAA** Proposed text in SmPC: A lower starting dose of 25 mg is recommended for patients of East Asian ancestry and patients with hepatic impairment.	None
Patients with renal impairment	The SmPC (Section 4.2 Posology) states the following: *Renal impairment:* No dose adjustment is necessary in patients with renal impairment. Patients with	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis.	
HCV patients with a FibroSURE score of F0/F1/F2	The SmPC (Section 5.1 Pharmacodynamic properties) states the following: The majority of patients were HCV genotype 1 (64 %), had mild hepatic impairment (Child-Pugh Score 5-6), and had a FibroSURE score equivalent to Metavir F3 or F4, indicative of bridging fibrosis and cirrhosis.	None
HCV patients infected with genotype other than 1, 2 or 3	The SmPC (Section 5.1 Pharmacodynamic properties) states the following: The majority of patients were HCV genotype 1 (64 %), had mild hepatic impairment (Child-Pugh Score 5-6), and had a FibroSURE score equivalent to Metavir F3 or F4, indicative of bridging fibrosis and cirrhosis.	None
HCV patients with Child Pugh score B (7-9)	The SmPC (Section 4.4) states the following: Eltrombopag should not be used in patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, exercise caution when administering eltrombopag to patients with hepatic impairment.	None
Off label use	Adult ITP The SmPC (Section 4.1) states the following: Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated. Paediatric ITP ~~Revolade is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.~~ Revolade is indicated for paediatric (age 1 year and above) chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who had an insufficient response to other treatments (e.g. corticosteroids, immunoglobulins). Section 4.2 of the SmPC states the following:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Paediatric population Revolade is not recommended for use in children under the age of 1 with chronic ITP due to insufficient data on safety and efficacy. HCV Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia prevents the initiation or limits the ability to maintain optimal interferon-based therapy (see section 5.1). The safety and efficacy of eltrombopag has not been established in children and adolescents (< 18 years) with chronic HCV related thrombocytopenia or SAA. No data are available.	
Safety and efficacy of eltrombopag in combination with new direct acting agents (telaprevir/boceprevir)	Current text in SmPC A statement in Section 4.4 that Safety and efficacy have not been established for eltrombopag in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection. The SmPC (Section 4.5) states that dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir	None
Safety of eltrombopag in cyclosporine	None	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the

applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the PETIT2 study 39.7% of eltrombopag subjects achieved a sustained platelet response (>50 Gi/L in the absence of rescue) for at least 6 of 8 weeks (75% of study duration) between Weeks 5 to 12 of the Randomized Period compared with 3.4% of placebo subjects. Consistent results were observed among the different cohorts of patients: cohort 1 (12-17 yrs): 10% placebo vs 39.1% eltrombopag; cohort 2 (6-11 yrs): 0.0% vs 42.3%; cohort 3 (1-5 yrs): 0.0% vs 35.7%. Subgroup analyses based on gender and race were consistent. Increases in platelet counts in PETIT2 were associated with a decrease in the proportion of subjects who received rescue treatment; 12/63, 19.0% in eltrombopag subjects compared with 7/29, 24.1% in placebo (odds ratio = 0.44, 95% CI 0.21, 0.93, p=0.032). Consistent results favouring eltrombopag treatment over placebo were observed for the other secondary endpoints based on platelet counts, bleeding events, or the ability to reduce or withdrawn ITP concomitant medication. During the eltrombopag only phase, platelet count ≥50 Gi/L for at least 75% of assessments between weeks 13 and 24 was seen in 43.7% of patients included in this phase. Again, consistent results favouring eltrombopag over placebo were seen for concomitant medication use, bleeding events and use of rescue medication during the 24 week period.

Results from the PETIT supportive study, double blind randomised phase, showed that treatment with eltrombopag led to a statistically significant platelet response with 62.2% in the eltrombopag group compared with 31.8% in the placebo group achieving platelet counts ≥50 Gi/L at least once between Days 8 and 43 (Week 1 to 6) of the 6-week Randomized Period. Responses were similar among the 3 age cohorts. In the PETIT study sustained platelet response was assessed by the proportion of subjects with platelet counts >50 Gi/L for at least 60% of assessments between Days 15 to 43 (Weeks 2 to 6) of the randomized Period. The study demonstrated that a higher proportion of eltrombopag subjects than placebo subjects (35.6% vs. 0) had a sustained response during the Randomized Period, which was statistically significant and consistent to those of the pivotal study. Results of the secondary endpoints were supportive of the primary analysis. Seemingly, during the O-L eltrombopag only phase, sustained platelet response (percentage of subjects with platelet counts >50 Gi/L for at least 60% of assessments between Week 2 and 24) was observed in twenty-four subjects (35.8%). Consistent results favouring eltrombopag treatment were also seen for the secondary endpoints.

The effect appears to be maintained in the long-term such that sustained responses (20 out of 24 weeks) were seen in 50% of the initial responders in PETIT 2 and less durable (15 out of 24 weeks) in PETIT Study. This means that fluctuations in platelet counts are to be expected while on treatment, which reinforces the importance of close monitoring as already stated in the SmPC.

Uncertainty in the knowledge about the beneficial effects

The studied population was a mixed of refractory and intolerant patients; the proportion of each subset is unknown as this was not collected during clinical trials. However the clinical effect is robust and consistent which is reassuring. In order to reflect the real target population which is candidate to eltrompopag and, the agreed indication is in line with the one of agreed for the adult population.

The recommendation to administer eltrombopag tablets at least 2 hours prior or 4 hours after polyvalent metal caution-containing products is considered well justified from a PK point of view, but it might be difficult to be followed in the clinical practice, in particular for the youngest age group of patients, and issues with adherence to treatment might be anticipated. The good results of the platelet count indirectly point out that children take the medications and the acceptability and the adherence to treatment are adequate, which provides some reassurance.

Risks

Unfavourable effects

The safety database is limited to 171 paediatric patients. Overall, the safety profile appears consistent to that seen in adults although there seems to be some differences in the incidence of some AEs like upper respiratory tract infections and neutropenia. Other AEs of particular interest like liver enzyme elevations have been commonly seen, with a pattern similar between adults and paediatrics.

There have been 2 cases of reported cataracts.

Uncertainty in the knowledge about the unfavourable effects

The main uncertainties relate to the overall limited number of patients and, in particular, limited long term safety data.

Thrombopoietin receptor (TPO-R) agonists may stimulate the progression of existing haematopoietic malignancies such as MDS – this is of particular concern in the paediatric population and is currently under monitoring (see RMP) by routine pharmacovigilance and educational material.

Considering that this is expected to be a chronic treatment, some safety findings like hepatotoxicity, cataracts, potential haematological changes (leukocytosis and anaemia, cases of thrombocytosis), recurrence of thrombocytopenia and renal tubular toxicity/renal failure require further follow up.

Effects Table

Table 28. Effects Table for [insert product name and indication]

Effect	Short Description	Unit	Eltrombopag	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Sustained platelet response at Week 12 (PETIT II)	proportion of patients with platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 to 12, in the absence of rescue medication	%	39.7%	3.4%	ORR (eltromb/placebo) 17.96 (2.29, 140.23) P<0.001 Consistent results among the three cohorts of patients Uncertainties on the maintenance of the effect over time	

Effect	Short Description	Unit	Eltrombopag	Placebo	Uncertainties/ Strength of evidence	References
Bleeding events G1-4 (G2-4)	Incidence of any bleeding events and severe bleeding events	%	36.5% (4.8%)	55.2% (6.9%)		
Rescue medication use			19.0%	24.1%	Statistically significant results (odds ratio: 0.44; 95% CI: 0.21, 0.93; p=0.032)	
Unfavourable Effects						
URTI	Subjects with AE started On-Therapy	%	16.8	6		Safety Population (Randomized period)
Diarrhoea	Safety Population (Randomized period)	%	9.3	2		Safety Population (Randomized period)
Abdominal pain	Safety Population (Randomized period)	%	8.2	4		Safety Population (Randomized period)
Oropharyngeal pain	Safety Population (Randomized period)	%	7.5	2		Safety Population (Randomized period)
Toothache	Safety Population (Randomized period)	%	5.6	0		Safety Population (Randomized period)
Increase Neutropenia	Hematology toxicity grade increase from BS to worst post BL exam	%	15.9	10.0		Safety Population (Randomized period)
Increase Anemia	Hematology toxicity grade increase from BS to worst post BL exam	%	24.3	20		Safety Population (Randomized period)
Increase Lymphocytopenia	Hematology toxicity grade increase from BS to worst post BL exam	%	22.4	18.0		Safety Population (Randomized period)
Hepatobiliary AE	Subjects with any events	%	6.5	0		Safety Population (Randomized period)
Hepatobiliary Laboratory disorders	Subjects with events meeting at least one criterion	%	7.5 (1)	2.0		Safety Population (Randomized period)
Renal AE		%	2.8	6.0		Safety Population (Randomized period)
Visually significant cataract		Nº Patients	1(2)	0		Safety Population (Randomized period) (2)

(1) Five patients discontinued of study treatment due to hepatobiliary laboratory abnormalities.

(2) In the eltrombopag OL; one additional case of cataract

Benefit-risk balance

Importance of favourable and unfavourable effects

A statistically significant difference in the proportion of patients who reach a sustained platelet response was seen in patients treated with eltrombopag compared to those on placebo. Differences in platelet counts could be considered clinically relevant if these are maintained in the long term, such that may allow patients to live normal lives by minimising the risk of bleeding events. The safety profile in the pediatric population appears similar to that in adults. However, due to the limited number of patients and the lack of long-term follow up data, all measured listed in the RMP and in the PhcV programme should be followed. .

Benefit-risk balance

The benefit–risk balance in the revised indication

> "Revolade is indicated for ~~adult~~ chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients **aged 1 year and above** who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1)"

is therefore positive.

Discussion on the benefit-risk balance

The expected place for eltrombopag would be limited to patients after failure to prior ITP treatments or when these cannot be maintained due to medical reasons.

Based on the data provided, a relevant effect has been observed achieving a sustained platelet response in the short term, consistent among the three age cohorts of patients and supported by results in secondary endpoints which systematically favour eltrombopag over placebo. The effect appears to be clinically relevant, although the effect on the use of rescue medication, need for concomitant treatments and bleeding events, is of limited value given the limited number of patients who required rescue medication, including those on placebo or that were on concomitant ITP medication. Given that the study allow the inclusion of a mixed population, i.e. refractory patients and those unable to continue on current ITP medication due to medical reasons, however the robust effect and in view of consistency with the adult population, the indication was worded as originally was but targeting the population aged 1 year and above.

Treatment appears well tolerated, with very few patients discontinuing from study treatment, with no differences among the three age cohorts. However, there are doubts on the actual adherence to treatment, in particular for the youngest age group, given the strict recommendations in relation to food intake which might be difficult to follow in the clinical practice and the high volume included in the PfOS.

Overall, the safety profile appears similar to that seen in adults and is considered acceptable in front of the expected benefits. The safety database is limited with regard to number of patients and the time of follow up, but is considered enough given the low incidence of the disease and the consistent efficacy and safety results thus far compared to the adult population.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Revolade (eltrombopag) is not similar to Nplate (romiplostim) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See Appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Revolade in the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) is favourable and therefore recommends the variation to the marketing authorisation and granting of the marketing authorisation for the new pharmaceutical forms.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall agree the details of an educational programme with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing all physicians are provided with a healthcare professional information pack containing the following:

- Educational material
- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling

Key elements to be included in the educational material

Hepatotoxicity

• Educate patients about the potential for hepatic enzyme elevations, importance of monthly laboratory monitoring of ALT and AST, as well as the signs and symptoms associated with liver injury (e.g. jaundice).
• Measure serum ALT, AST and bilirubin prior to initiation of Revolade, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose.
• Discontinue Revolade if ALT levels increase (≥ 3X the upper limit of normal [ULN]) and are:
- progressive, or
- persistent for > 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.
• Exercise caution when administering eltrombopag to patients with hepatic disease. Use a lower starting dose of eltrombopag and monitor closely when administering eltrombopag to patients with hepatic impairment.

Thromboembolic events
ITP patients

• Eltrombopag should not be used in patients with hepatic impairment (Child Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If use of eltrombopag is deemed necessary, the starting dose must be 25 mg once daily.
• Educate patients about the potential for thromboembolic events (TEE) in patients with chronic ITP and those known risk factors for thromboembolic events (e.g. Factor V Leiden, ATIII deficiency, antiphospholipid syndrome).
• Educate patients about chronic liver disease and the risk of thromboembolic events.
• In patients with chronic liver disease treated with eltrombopag there was an association between TEE and platelet counts ≥ 200,000µl.
• A dose reduction is recommended for ITP patients with platelet counts between 150,000-250,000/µl.
• Revolade should be interrupted if platelet counts increase to > 250,000/µl. Once the platelet count is < 100,000/µl, reinitiate therapy at a reduced daily dose.

HCV patients

- Thrombocytopenic patients with HCV should initiate eltrombopag at a dose of 25 mg once daily.
- Educate thrombocytopenic patients with chronic HCV about the risk of thromboembolic events, particularly the increased incidence of portal vein thrombosis and known risk factors for thromboembolic events (e.g. Factor V Leiden, ATIII deficiency, antiphospholipid syndrome).
- In thrombocytopenic patients with chronic HCV there was no specific temporal relationship between start of treatment and event of TEE. TEEs were more common in patients > 60 years old and in patients with albumin below 35 g/L.
- A dose reduction is recommended for thrombocytopenic chronic HCV patients with platelet counts between 100,000-150,000/µl.
- Revolade should be interrupted if platelet counts increase to > 150,000/µl. Once the platelet count is < 100,000/µl, reinitiate therapy at a reduced daily dose.

Posology

• Educate patients on the appropriate administration of Revolade (e.g. titration of Revolade, food-medicinal product interaction, dose recommendations for special populations [e.g. East Asians]).

Food Interactions

• Educate patients about the potential food-medicinal product interaction (i.e. chelation with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four

hours before or two hours after Revolade dosing to avoid significant reduction in Revolade absorption due to chelation.
• Assist patient in developing a plan to administer Revolade at a time each day that fits into the patient's own daily schedule.

Reoccurrence of Thrombocytopenia

• Educate patients about the potential risk of bleeding after treatment has stopped (include incidence in clinical trials and likelihood of reoccurrence of thrombocytopenia after cessation of treatment).
• Following discontinuation of Revolade, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding.
• Monitor platelet count weekly for 4 weeks following discontinuation of Revolade.

Increased Bone Marrow Reticulin Fibres

• Educate patients about the potential for bone marrow reticulin fibre formation.
• Background information on reticulin in the bone marrow (i.e. background rates of reticulin in bone marrow in ITP patients and the observed incidence and potential mechanism of action of reticulin deposition in response to Revolade).
• Prior to initiation of Revolade, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities.
• Following identification of a stable dose of Revolade, perform full blood count (FBC) with white blood cell count (WBC) differential monthly.
• If immature or dysplastic cells are observed, examine peripheral blood smears for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s).
• If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with Revolade and consider a bone marrow biopsy, including staining for fibrosis.

Haematological malignancies

• The diagnosis of ITP in adults and elderly patients should have been confirmed by excluding other clinical entities with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs.
• Educate patients about the theoretical risk of haematological malignancies with thrombopoietin receptor agonists.
• Importance of not using Revolade outside the context of its license unless in a clinical trial setting.

Potential for Off-label Use

• The risk-benefit for the treatment of thrombocytopenia outside of the registered indication has not been established.
• The risk-benefit of Revolade in paediatric HCV-associated thrombocytopenia and SAA has not been established. The paediatric population is defined as those persons aged between 0 and 18 years.
• Awareness to prescribers of the labelled indication and warnings associated with non-indicated populations (e.g. not recommended for use in children, pregnant or breast-feeding women, other off label uses).

Hepatic Decompensation (use with interferon)

- Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa-interferon therapy
- Educate thrombocytopenic patients with chronic HCV that safety findings suggestive of hepatic decompensation were reported more frequently in patients treated with eltrombopag/interferon/ribavirin.
- Thrombocytopenic patients with chronic HCV with low albumin (≤ 35 g/L) or Model for End-Stage Liver Disease (MELD) score ≥ 10 at baseline had a greater risk of hepatic decompensation when treated with eltrombopag/interferon/ribavirin. Patients with these signs should be closely monitored for signs and symptoms of hepatic decompensation.

Fatal Adverse Reactions in thrombocytopenic patients with HCV

- In thrombocytopenic patients with chronic HCV, patients who receive anti viral therapy in combination with eltrombopag may be at greater risk of fatal adverse reactions, particularly those with the poorest prognosis, i.e.:
  - MELD score ≥10,
  - Albumin ≤ 35 g/L
- Educate patients with the poorest prognosis about the increased risk of fatal adverse reactions, particularly hepatic decompensation (hepatic failure, ascites, encephalopathy and bleeding varices), infective and ischemic complications.
- Treatment with eltrombopag should be stopped if signs and symptoms suggestive of thrombotic events and hepatic decompensation occur (see TEE and hepatic decompensation above).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0307/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.