European Medicines Agency

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CHMP ASSESSMENT REPORT

FOR

Revolade

International Nonproprietary Name: eltrombopag

Procedure No. EMEA/H/C/001110

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant GlaxoSmithKline Trading Services Ltd. submitted on 04 December 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Revolade, which was designated as an orphan medicinal product EU/3/07/467 on 03 August 2007. Revolade was designated as an orphan medicinal product in the following indication: treatment of idiopathic thrombocytopenic purpura. The calculated prevalence of this condition was between 1 and 4 in 10,000 persons in the European Union, which, at the time of designation, corresponded to between about 50,000 and 199,000 persons.

The applicant applied for the following indication: treatment of previously treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Information on Paediatric requirements
Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMEA Decision P/207/2009 for the following condition:

- *Idiopathic thrombocytopenic purpura (ITP)*

on the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

Information relating to Orphan Market Exclusivity

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

Protocol Assistance:
The applicant received Protocol Assistance from the CHMP on 24 March 2006. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status:
Revolade has been given a Marketing Authorisation in the United States of America on 20 November 2008 (US tradename Promacta).

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Gonzalo Calvo Rojas** Co-Rapporteur: **Ian Hudson**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 04 December 2008.
- The procedure started on 24 December 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 30 March 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2009.
- During the meeting on 20-23 April 2009 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 23 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 8 July 2009.
- During the CHMP meeting on 20-23 July 2009, the CHMP agreed on the first List of Outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the First CHMP List of Outstanding Issues on 24 August 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the first List of Outstanding Issues to all CHMP members on 10 September 2009.
- During the CHMP meeting on 21-24 September 2009, the CHMP agreed on the second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 02 October 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 07 October 2009.
- During the CHMP meeting on 19-22 October 2009, the CHMP agreed on the third list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP third List of Outstanding Issues on 16 November 2009.
- During a meeting of an Expert group on 01 December 2009, experts were convened to address questions raised by the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the third List of Outstanding Issues to all CHMP members on 02 December 2009.
- During the meeting on 14-17 December 2009, 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 on 17 December 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 15 December 2009.
- The CHMP adopted a report on similarity of Revolade with Nplate on 25 June 2009.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 11 March 2010.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Chronic idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to a low peripheral blood platelet count (<150,000/μL). The epidemiology of ITP shows an overall incidence of ITP among adults from 1.6 to 3.0 per 100,000 person years of observation. Prevalence estimates range from 2.1 to approximately 36.4 per 100,000 persons. The estimated adult prevalence is 24.6 per 100,000 persons.

The exact aetiology of ITP is unknown and the diagnosis of ITP remains one of exclusion. The clinical hallmark of the disease is an increased, pathological tendency to bleed, spontaneously or after minimal trauma. Routine diagnostic tools are blood count, peripheral blood film, patient history, physical examination and prompt response to high-dose corticosteroids

Disease management decisions in patients with chronic ITP are based primarily on platelet count and severity of bleeding. The goal of treatment is to elevate platelet counts to a safe range (≥50,000/μL to 250,000/μL) to minimise the risk of bleeding. Medical treatment to elevate platelet counts to a safe range is recommended if patients' platelet count is below 30,000/μL or if bleeding symptoms are present.

Currently immunoglobulins (anti-D and IVIg) are used for the treatment of ITP. Additional drugs to treat chronic ITP include corticosteroids, azathioprine, cyclophosphamide, or vincristine. Based on the literature, first-line treatment with intravenous immunoglobulins or corticosteroids results in normal or sufficient platelet counts in about 70% of patients with chronic ITP. IVIg typically provides a temporary elevation of platelet counts within up to 5 days and for an average duration of 3-4 weeks. Corticosteroids will induce a response within up to two weeks, although the effect is often not sustained upon dose reduction or cessation of treatment, and long-term administration of corticosteroids is limited by the development of side effects. Furthermore, corticosteroid-treated patients are at increased risk of infections. Second-line therapy typically involves splenectomy. Two-thirds of patients with ITP who undergo splenectomy will achieve a normal platelet count, which is often sustained with no additional therapy. Patients who do not have a complete response can still expect some improvement in platelet counts (e.g. partial response) or transient increases in platelet count. When adult patients fail to first and second line therapies, they are considered as chronic refractory ITP. The actual percentage of patients defined as having refractory ITP varies from 11% to 35%. Romiplostim (Nplate), a recombinant protein that increases platelet production through activation of the thrombopoietin receptor (TPO-R), was authorised in the EU in February 2009.

This application seeks marketing authorization for Revolade (eltrombopag) as a centralised procedure according to (EC) No 726/2004, Mandatory scope (Article 3(1)), Annex (4) Orphan designated medicinal product. Eltrombopag received an orphan medicinal product designation in the European Union on 03 August 2007 for the treatment of chronic ITP (Community Register of OMP´s EU/3/07/467).

The claimed therapeutic indication is:

'Revolade is indicated for the treatment of previously treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.'

The approved therapeutic indication is:

"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".

A Paediatric Investigation Plan (PIP) for the condition idiopathic thrombocytopenic purpura (ITP) has been agreed by the PDCO. The subset of the paediatric population concerned by the paediatric development included children from 1 year to less than 18 years. Newborns and infants from birth to less than 1 year have been waived on the grounds that ITP does not occur in this paediatric subset.

The paediatric plan included the development of new a powder formulation for oral suspension in fixed single-dose sachets and a clinical study to investigate the safety, tolerability and efficacy of eltrombopag in patients diagnosed with ITP from 1 year to less than 18 years old. A deferral has been granted for completion of the quality study and for the initiation and completion of the clinical study.

Revolade is a small molecule for oral administration that increases platelet production through activation of the TPO-R. The recommended initial dose for eltrombopag is 50 mg once daily administered orally. If after 2 to 3 weeks of initial therapy, the platelet counts are below the clinically indicated levels (e.g. 50,000/µL); the dose may be increased to a maximum of 75 mg once daily. A dose reduction is recommended for patients with platelet counts between 150,000 and 250,000/µL. Once the platelet count is <100,000/µL, therapy should be reinitiated at a reduced daily dose. Eltrombopag treatment should only be initiated by a physician experienced in the treatment of thrombocytopenia. The diagnosis of ITP in adults and elderly patients should have been confirmed by the exclusion of other clinical entities presenting 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.

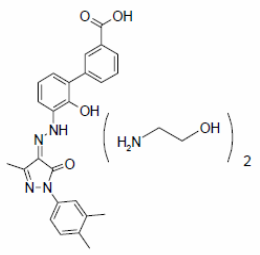
2.2 Quality aspects

Introduction

Revolade is presented in the form of film-coated tablets containing 31.9 mg or 63.8 mg of eltrombopag olamine equivalent to 25 mg or 50 mg of eltrombopag respectively. The tablets are packaged in blisters composed of polyamide / aluminium foil / polyvinyl chloride (PVC) laminate sealed with aluminium foil lidding with a vinyl acrylic seal coating.
Other excipients in the product are listed in Section 6.1 of the SPC.

Active Substance

Eltrombopag is an orally bioavailable, small molecule TPO-R agonist present in the form of the *bis*-monoethanolamine (olamine) salt.



It is a crystalline solid, red/brown, sparingly soluble in water. The molecule does not contain asymmetric centres although it exists as the

Z - conformer in the solid state. It is thermally stable up to about 125°C. One solid state form (Form 1), is consistently obtained by the synthetic process described, and this is the form that appears in the product. The active substance is milled to produce a consistent particle size distribution.

- Manufacture

The manufacturing process is correctly described, and specifications for reagents, solvents and auxiliary materials used in the process are satisfactory. All critical in-process controls parameters are well established and justified. The isolated intermediate is controlled by well described and validated methods. A single route of synthesis has been used throughout the chemical development of eltrombopag olamine. Based on knowledge gained during development of the process, together with tools such as a Parameter Attribute Matrix (PAM) and FMEA risk assessment, the process parameters most likely to have the greatest impact on API quality have been identified.

The chemical structure is well characterised by the usual range of spectroscopic and physicochemical studies. All relevant characteristics of this substance have been studied and established.

Concerning the impurities likely to arise during the synthesis, a reasoned discussion has been provided according to ICH Q3A (R2) Guideline, including their origin according to the manufacturing process described and the main degradation pathways.

- Specification

In general, the specification proposed is suitable to control the quality of the drug substance. In addition to the potential impurities, those impurities routinely found to arise during the synthesis of the active substance have been identified and controlled using validated methodology. Furthermore, the specified limits have been justified with reference to toxicology studies. Results of over 30 batches used in clinical, non-clinical and stability studies were provided during the evaluation phase and all recent batches at the intended commercial scale complied with the agreed specification.

- Stability

The drug substance is stored in HDPE containers lined with anti-static LDPE bags and sealed with plastic ties. The main degradation pathways of eltrombopag olamine have been defined.
The stability studies and conditions are in agreement with ICH Q1A Guideline and the tests performed are considered stability indicating. Based on the accumulated stability data so far, a suitable and practical retest period has been defined.

Medicinal Product

The tablets have been formulated to contain the following excipients: Microcrystalline cellulose, mannitol, povidone K-30, sodium starch glycolate, magnesium stearate and Opadry White YS-1-7706-G or Opadry Brown 03B26716. The Opadry White film coat consists of hypromellose, macrogol 400, polysorbate 80 and titanium dioxide (E171). The Opadry Brown film coat consists of hypromellose, macrogol 400, titanium dioxide (E171), Iron oxide Yellow (E-172) and Iron oxide Red (E-172). The excipients and packaging are usual for this type of dosage form.

- Pharmaceutical Development

The pharmaceutical development of the product has been adequately performed and the choice of excipients is justified and their functions explained. Appropriate multivariate experimental plans were designed based on the prior knowledge and the risk analysis. Based on the multivariate design of experiments, a design space for the manufacturing process parameters has been defined. The process inputs and the Critical Quality attributes are clearly defined in the design space. The choice of the packaging is justified. The composition of the batches used for clinical studies are similar to the final drug product.

- Manufacture of the Product

The manufacturing process covers dry mixing of ingredients, granulation, wet milling, drying, milling blending (pre-lubrication and lubrication), compression, coating and packaging. A manufacturing process flow diagram and a description of the manufacturing operations are provided. There is evidence of a significant level of manufacturing experience obtained during development, scale-up, and production of clinical supplies.

- Product Specification

The product specifications cover appropriate parameters for this dosage form and include specific references to PhEur where applicable. The analytical methods have been adequately described and validated. The analytical methods used are a combination of traditional methods and methods developed using Quality by Design (QbD) principles. Batch analytical data from the proposed production site have been provided, demonstrating compliance with the release specifications.

- Stability of the Product

Results of long-term and accelerated primary stability studies when stored at 30°C/65% RH or 40°C/75% RH, respectively, have been provided. At submission, twenty-four months' data were provided for these batches stored under long term condition, and 6 months' data provided for the batches stored under accelerated condition. All results from both primary stability and supportive stability batches comply with the limits and no significant changes and trend were observed in all the tested parameters. , generated from market image packs or supporting data from other presentations. Forced degradation studies and photostability studies have also been carried out.

Discussion on chemical, pharmaceutical and biological aspects

The pharmaceutical development of this sparingly-soluble drug product has been performed in a satisfactory way. Attention has focussed on the physical state of the active substance, in particular the particle size, in order to obtain consistent bioavailability. A risk-based approach is applied to the development of the active substance (in the synthesis process of eltrombopag free acid and the synthesis of eltrombopag olamine) in order to establish the design space and control strategy for the process parameters. Concerning pharmaceutical development of the product, the design intent was to develop an oral formulation, with a minimal number of tablets per dose. A risk based approach (FMEA and BRITEST) was utilised during development, to identify and mitigate risks by dosage form design, the manufacturing process and controls where appropriate.
Therefore the synthesis of the active substance and the manufacture of the product are under control and can deliver a consistently high quality active substance or product, controlled from batch to batch by relevant and validated test methodology and specification limits.

2.3 Non-clinical aspects

Introduction

A range of *in vitro* and *in vivo* studies have been conducted to investigate the primary and secondary pharmacology of eltrombopag, including a battery of safety pharmacology studies. Absorption, distribution, metabolism and excretion studies have been performed with eltrombopag to assess the suitability of the animal species used during toxicological evaluation.

As claimed by the applicant, all safety pharmacology studies, a number of pharmacokinetic studies and all pivotal toxicity studies (including the toxicokinetic investigations) were carried out in compliance with Good Laboratory Practice (GLP) regulations. All other studies were conducted in line with Company Divisional Standard Operating Procedures and Policies, and in general accordance with the principles of GLP.

Pharmacology

- Primary pharmacodynamics

In vitro studies

In murine lymphocytic leukaemia (BAF3)-TPO cells stably transfected with human TPO-R eltrombopag half maximal effective concentration (EC_{50}) was 0.27 μM, and in 32D-mpl cells (murine cells transfected with human TPO-R and gpIIb promoter linked to luciferase) the EC_{50} was 0.1μM.

Activation of the STAT and MAPK pathways by eltrombopag was observed using phospho-specific antibodies in western blots. Eltrombopag (10 μM) stimulated STAT 3 and STAT5 (STAT-based transduction pathways) and activated p42/44 MAPK, with a similar kinetics to that observed for TPO. However, eltrombopag was only able to induce minimal phosphorylation of STAT 1 and no phosphorylation of AKT. In addition to activation of the STAT and MAPK signal transduction paths, the expression of certain early response genes associated with proliferation and TPO activation, i.e., Fos, EGR-1 and thyroid-like receptor 3 was upregulated following treatment with eltrombopag (30 μM).

Eltrombopag induced proliferation of a megakaryocyte cell line (N2C-TPO, also named UT7/TPO) with an EC_{50} of 0.03 μM. Eltrombopag also showed to be able to increase differentiation of human CD 34+ marrow progenitor cells into CD41+ megakaryocytic cells in a dose dependent manner with an EC_{50} of 0.1 μM. Megakaryocyte differentiation equivalent to that observed following treatment with TPO (0.1 μg/mL) was observed at an eltrombopag concentration of 3 μM. Comparison of eltrombopag potency with TPO potency in terms of EC_{50} (μM) showed that TPO is between 7 to 9 orders of magnitude more potent than eltrombopag in the CD34+ megakaryocyte differentiation assay, as well as in the N2C-TPO proliferation assay. When comparing the maximum effect achieved by TPO and eltrombopag in these two assays, maximum eltrombopag effect is between 95 and 155% the maximum effect achieved by TPO.

Eltrombopag showed an additive effect with TPO on STAT activation, and in a proliferation assay in N2C-TPO cells. In an apoptosis assay, both eltrombopag and TPO were additive in their ability to prevent cell death; the level of maximal activity was demonstrated at 0.1 μg/mL TPO and at 0.3 μM eltrombopag.

There was no activity of eltrombopag (over a 3 log concentration range) in the BAF3 parental line and in additional proliferation, reporter gene or STAT activation assays in cells that did not express TPO-R but that utilize STAT signalling pathways (UT7-EPO, BAF3/GCSFR, HepG2 and BAF parental).

Eltrombopag inhibited the proliferation of fifteen out of seventeen leukaemia and lymphoma cell lines (IC_{50} = 0.56 to 15.4 μg/mL) and of liver cancer cell line HepG2 (IC_{50}= 5.61 μg/mL). The cell lines NOMO-1 and OCI-M1 (AML) were resistant to eltrombopag with IC_{50} > 40 μg/mL, the maximum tested dose. Other two cell lines N2C-TPO and HEL 92.1.7, demonstrated increased proliferation at eltrombopag concentrations from 0.006 to 1.7 μg/mL, and 0.1 to 0.4 μg/mL, respectively. Additional studies were performed in other tumour cell lines which included 4 different lung carcinoma cell lines, 2 prostate tumour cell lines and 3 ovarian tumour cell lines. There was no increase in proliferation of any of the additional cell lines tested.

TPO-R mRNA expression was low in the majority of the 376 tumour cell lines tested, as measured by qRT-PCR. Nevertheless, two AML cell lines, HEL 92.1.7 and KG-1, and the lung carcinoma cell line NCI-H510 had greater than 9500 normalized abundance for TPO-R mRNA.

In contrast to TPO, eltrombopag (1 to 10 μM) has no direct effect on *in vitro* platelet aggregation or activation, nor does it influence the ability of ADP (3 μM), collagen (2 μg/mL) or the thrombin receptor activating peptide (TRAP) (20 μM) to induce platelet aggregation.

Eltrombopag showed a marked specificity for human and chimpanzee TPO-R. The transmembrane domain and amino acid residue His499 in particular, was demonstrated to be necessary for eltrombopag/TPO-R interaction. Threonine 492 and zinc also contribute to the *in vitro* activity of eltrombopag in transient transfection models as well.

In vivo studies

Primary pharmacodynamics *in vivo* studies were performed in chimpanzees. Five daily doses of 10 mg/kg/day produced increases between 1.3- to 2.4- fold in platelet counts approximately 1 week after the last dose and returned to baseline values within 2 weeks. A similar trend was observed in reticulated platelet counts.

- Secondary pharmacodynamics

The selectivity of eltrombopag was assessed in a panel of standard *in vitro* radio-ligand binding and enzyme activity assays against 41 physiologically relevant receptors, enzymes and ion channels. Eltrombopag showed activity (defined as > 25% inhibition) on 4 targets: α_{2B}-receptor (38%, IC_{50}= 15.5 μM), I_2-receptor (88%, IC_{50}= 1.7 μM), oestrogen-α-receptor (85%, IC_{50}= 0.3 μM) and oestrogen-β-receptor (33%, IC_{50}= 1.9 μM).

- Safety pharmacology programme

- *In vitro* studies on the effect on cardiac ion channels:

The effects of eltrombopag (10 or 25 μM) on action potential duration at 30%, 60% and 90% repolarisation, maximum rate of depolarization (MRD), upstroke amplitude (UA) and resting membrane potential (RMP) were investigated in isolated dog Purkinje fibres paced at stimulation frequencies of 1 and 0.5 Hz. In fibres paced at 3 Hz (control and 25 μM), only MRD was measured.

In fibres stimulated at frequencies of 0.5 and 1 Hz, exposure to eltrombopag at concentrations of 10 and 25 μM had no effects on resting membrane potential and action potential duration at 30% repolarisation. In the presence of 10 μM (4.4 μg/mL) and 25 μM (11.1 μg/mL) eltrombopag induced decreases in maximum rate of depolarization, upstroke amplitude and action potential duration at 60% and 90% repolarisation. The effects on MRD at 1 and 0.5 Hz suggested that eltrombopag may produce a tonic inhibition of cardiac sodium channels.

A study was conducted to measure the effect of eltrombopag on hERG currents recorded from HEK293 cells stably transfected with hERG-1 cDNA. A series of concentrations up to the maximum soluble concentration of eltrombopag (21.7 μM) were tested. E-4031 (0.1 μM), a known inhibitor of the I_{Kr} , current was used as a reference substance. Eltrombopag was found to inhibit hERG channel tail current in a concentration- dependent manner. The nominal IC_{25}, IC_{50} and IC_{75} values were estimated to be 0.09, 0.69 and 5.13 μM, respectively.

In vivo studies

- Overt Central and Peripheral Effects:

Male Sprague Dawley rats (10 per group) were administered eltrombopag as single oral doses at 0, 3, 10 or 40 mg/kg. Eltrombopag did not affect any of the measures of the functional observational battery (FOB). The no-observed-adverse-effect-level (NOAEL) for this study is 40 mg/kg (6-fold the maximum proposed human Cmax of eltrombopag when administered at 75 mg/day (12.7 μg/mL).

- Actions on Cardiovascular and Respiratory Systems:

Conscious male Sprague Dawley rats (n=4) were administered eltrombopag as single oral doses at 0, 3, 10 and 40 mg/kg on separate days in a crossover study design with 7 days between treatments.

Ventilatory parameters (tidal volume, respiratory rate and minute volume) and airway resistance (total pulmonary resistance) were recorded before dosing, around the times of C_{max} (1 and 4 hours post dose) and at approximately 24 and 48 hours post dose. Eltrombopag did not produce any adverse effect on respiratory function in the male rat. The no-observed-adverse-effect-level (NOAEL) for this study is 40 mg/kg.

Conscious male Beagle Dogs (n=4) were administered eltrombopag as single oral doses at 0, 3, 10 and 30 mg/kg on separate days in a crossover study design with 7 days between treatments.

Eltrombopag had no effect on arterial blood pressures, heart rate or ECG intervals during the 48 hours post dose. There was no evidence of ECG waveform abnormalities or arrhythmias in ECG tracings at t_{max} (1 hour post dose), and at approximately 4, 24 and 48 hours post dose. Additionally no evidence of cardiac abnormalities was observed in dogs in the 52 week repeat dose study at doses up to 30 mg/kg/day (3-fold higher exposure than expected at maximum human dose).

- Pharmacodynamic drug interactions

No studies have been submitted.

Pharmacokinetics

For pharmacokinetic and toxicokinetic investigations, plasma samples were analyzed for eltrombopag (parent compound) by high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) analysis, preceded by protein precipitation. The lower limit of quantification for eltrombopag was 10 ng/mL and the higher limit of quantification was 2500 ng/mL using a 50 μL plasma sample.

Determination of the radioactivity in biological samples following the administration of 14C-labelled eltrombopag was carried out by either direct liquid scintillation counting (LSC) or by LSC following combustion of the sample. For radioactivity levels in tissues, whole body autoradiographic technique with quantitative imaging was used. The profiling and identification of metabolites of eltrombopag was performed using a variety of techniques including HPLC with radiochemical and ultraviolet (UV) detection, liquid chromatography with mass spectrometry (LC-MS), liquid chromatography with tandem mass spectrometry (LC-MS/MS) and/or NMR analysis.

- Absorption

Following single intravenous administration, plasma clearance of eltrombopag (parent compound) was 0.45 mL/min/kg in rats, 0.44 mL/min/kg in dogs and 3.3 mL/min/kg in monkeys, with half-lives of 12, 14 and 7.7 hours, respectively. Volume of distribution corresponded to 2 times the total body water in the monkey (1.39 L/kg), but less than one-half total body water in rats and dogs (0.196 L/kg and 0.47 L/kg, respectively).

Following a single oral administration in solution, eltrombopag was more quickly absorbed in rats, dogs, or humans (t_{max} of 1.35 to 2.5 hours) than in the monkey (t_{max} of 4.25 hours). In mice, t_{max} values ranged from 1 to 4 hours.

Oral bioavailability of eltrombopag (parent compound) when administered in solution was between 12 to 34% in rats, 83% in dogs and 89% in monkeys. In dogs, when administered in a capsule, the oral bioavailability of eltrombopag was higher when given as the bis-monoethanolamine salt (48%) than that following administration of the parent compound (21%). When comparing oral bioavailability of eltrombopag (parent compound) administered in solution, suspension or in a capsule, the highest bioavailability was for the solution, being F values of 83%, 15.8% and 7.09%, respectively.

Repeat administration of the salting agent, monoethanolamine, at 32.4 mg/kg/day to mice for 7 days (equivalent to eltrombopag bis-monoethanolamine salt at 150 mg/kg/day) did not increase monoethanolamine above normal endogenous levels in plasma.

In repeat dose toxicity studies conducted with eltrombopag in mice, rats and dogs, systemic exposures of eltrombopag increased with dose (approximately proportionally in mice and dogs, but greater than proportionally in rats). In juvenile rats systemic exposures of eltrombopag decreased with dose. There were no marked differences in systemic exposure between males and females and no consistent indication of accumulation upon repeat administration in any species. In general there were no differences in exposure between pigmented and non-pigmented animals. In embryofoetal development studies in rabbits, systemic exposures of eltrombopag increased above dose-proportionally.

- Distribution

Eltrombopag-related material was widely distributed into peripheral tissues in mice and rats, although higher levels were generally associated with tissues involved in absorption and/or elimination (gastrointestinal tract, liver and renal cortex); 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, although the levels of the radioactivity in the tissues after repeated administration in rats were slightly higher and declined slower than those observed following a single dose.

Eltrombopag was highly bound to plasma proteins in mouse (93.7%-99.8%), and very highly bound (99.0%-99.8%) in rats, dogs, monkeys and humans; with low association to blood cells.

- Metabolism

Following incubation of [^{14}C]eltrombopag with human liver microsomes and supersomes resulted in the formation of metabolite J (a mono-oxygenation product of eltrombopag). CYP1A2 and CYP2C8 were the primary enzymes involved in the *in vitro* oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 metabolized eltrombopag to form metabolite K (glucuronide conjugate). Following incubation of [^{14}C]eltrombopag with human hepatocytes, the major metabolic pathways observed were conjugation with glucuronic acid (metabolite K) or cysteine (metabolite G). Other minor pathways were conjugation with glutathione (metabolite F) and oxidation that led to formation of an M+14 metabolite. Additional metabolites detected included metabolite J (mono-oxygenated) and metabolite O (oxidation of a methyl to a carboxylic acid). Human kidney microsomes exhibited minimal capacity to metabolize eltrombopag *in vitro*.

The metabolic profiles of eltrombopag *in vitro* were qualitatively similar in rats, dogs and monkeys. There has been no evidence for the formation of any human specific metabolites. *In vivo* eltrombopag was the predominant circulating component in all species. In rats there was adequate coverage for the circulating metabolites in humans. M14 which accounts for a 20% in human urine excretion was present up to 9.2% in mice urine but was not detected in rats and information is not available in dogs.

- Excretion

Eltrombopag was primarily eliminated as unchanged drug in the faeces with renal elimination of cleavage products contributing as a minor route. Gut microbes readily cleaved eltrombopag based on *in vitro* incubation of eltrombopag with human faeces and mouse and rat cecal contents in anaerobic conditions. Qualitatively, all of the major metabolites of eltrombopag observed in humans were observed in the non-clinical species.

- Pharmacokinetic drug interactions

In *vitro* studies show that eltrombopag was an inhibitor of CYP2C8 and CYP2C9 with IC_{50} values of 24.8 and 20.2 μM, respectively, but was not an inhibitor of CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11 at concentrations up to 100 μM.

Eltrombopag was only a weak activator of human Pregnane X receptor (PXR) with low efficacy and was not an activator of rat PXR. Furthermore, in conjunction with oral toxicity studies, repeat administration of eltrombopag for up to 14 days did not result in notable changes in activities of CYP1A, CYP2B, CYP2E, CYP3A and CYP4A in rat or dog. Eltrombopag did not cause induction of CYP1A2, CYP2B6 and CYP3A4 in cultured human hepatocytes.

Eltrombopag was found to be an *in vitro* inhibitor of several uridine diphosphate glucuronosyl transferases (UGTs) with IC_{50}s ranging from 3 to 30 µM (UGT1A9, UGT1A3, UGT1A1, UGT2B15, UGT1A6, UGT2B7 and UGT1A4).

In vitro eltrombopag is a substrate of CYP1A2 and CYP2C8. According to the Applicant, only 21% of the dose could be subjected to hepatic conversion mediated by CYP1A2 and CYP2C8.

Eltrombopag was neither an inhibitor nor a substrate of human Pgp and was not a substrate of human OATP1B1, although it was an inhibitor of this transporter and the potential for such an interaction was confirmed clinically following co-administration of eltrombopag with rosuvastatin (a substrate of OATP1B1 and BCRP). Eltrombopag inhibited OATP1B1-mediated uptake of [^{3}H]estradiol 17β-D-glucuronide with and IC_{50} of 2.71 µM. In addition, eltrombopag was an *in vitro* inhibitor and a substrate of human BCRP. Eltrombopag inhibited also BCRP-mediated transport of cimetidine *in vitro* with an IC_{50} of 2.7 µM.

Toxicology

The toxicity profile of eltrombopag has been investigated in a battery of studies including a single dose study in dogs, repeat dose toxicity studies of up to 13 weeks in mice, 28 weeks in rats and 52 weeks in dogs, genotoxicity and carcinogenicity studies, reproductive toxicity studies and local tolerance studies. Pivotal studies were conducted in accordance with GLP regulations.

- Single dose toxicity

Beagle dogs (n= 1 male and 1 female) were administered a single oral dose of eltrombopag at 100 or 300 mg/kg, 7 days apart, to determine the maximum tolerated dose (MTD) in dogs by the oral route. A dose of 100 mg/kg was tolerated with clinical signs limited to slight reductions in food consumption and body weight (4 to 7%). A dose of 300 mg/kg was poorly-tolerated and was associated with emesis, abnormal stool consistency, decreased activity, inappetence and moderate body weight reduction.

Toxicokinetic data were determined on Days 1 and 8 – pre-dose, and approximately 1, 2, 4, 8, 24, 48 and 72 hours post-dose. A 3-fold increase in dose supposed a more than dose proportional increase in exposure in the male dog (~ 5-fold), and a 3-fold decrease in exposure in the female dog. Exposures ranged from 12.6-fold to 86-fold the maximum proposed clinical exposure (exposure margins are presented based upon comparison of the animal systemic exposure with that reported for ITP patients receiving the maximum proposed oral therapeutic dose of 75 mg/day eltrombopag: AUC= 168 µg.h/mL, C_{max}= 12.7 µg/mL).

- Repeat dose toxicity (with toxicokinetics)

The toxicity of repeated oral doses of eltrombopag has been assessed in mice (5 studies), rats (6 studies), rabbits (2 studies) and dogs (4 studies) in studies of up to 13, 28, 1 and 52 weeks, respectively. In addition, repeat dose toxicity was assessed in 2 year carcinogenicity studies in mice. The major findings are summarised in Table 2.

Table 2. Summary of the most relevant findings in the pivotal repeat toxicity studies.

Species/Sex/ Number/Group	Dose (mg/kg/day)/ Route Duration	NOEL/ NOAEL	Major findings
Mouse (Crl:CD-1(ICR)BR), 12/sex/group. Toxicokinetics: additional 21/sex/group	0, 10, 60, 100/ p.o.(gavage) once daily 13 weeks	100 mg/kg/day (C_{max}= 105 µg/mL, AUC_{0-24}=652 µg.h/mL)	Clinical observations, organ findings and histopathology: One of 24 mice (100 mg/kg/day): minimal tubular epithelial degeneration/ necrosis in the kidney (not considered treatment related) Toxicokinetics: For a 10-fold increase in dose, AUC_{0-24} and C_{max} values increased 32- and 36-fold, with no marked difference between sexes.
Rat (Sprague-Dawley) 10/sex/group Toxicokinetics: additional 3/sex/group	0, 3, 10, 40/ p.o.(gavage) once daily 14 days	10 mg/kg/day (C_{max}= 79.9 µg/mL, AUC_{0-24}=650 µg.h/mL (on Day 14))	Body weight and food consumption: ↓ food consumption and body weight gain at 40 mg/kg/day (M) during the first week Clinical observations, organ findings and histopathology: ↑ absolute and relative testis weight at 40 mg/kg/day (M). No microscopic correlate for these changes. Midzonal hepatocellular vacuolation (liver) at 40 mg/kg/day. Minimal (M) and minimal to moderate (F). Positive for neutral lipid (Oil Red O staining). Toxicokinetics: Maximum plasma concentrations of eltrombopag increased with increasing dose. T_{max} ~ 1-4 h. There was no difference in systemic exposure between males and females. AUC_{0-24} increased on average, 44.5- and 24.4-fold for a 13.3-fold increase in dose between 3 and 40 mg/kg/day on Days 1 and 14, respectively. There was a trend toward a higher AUC_{0-24} on Day 14 versus Day 1 for the 3 and 10 mg/kg/day dose groups.
Rat (Sprague-Dawley) 10/group (F) Reversibility: additional 10/F/group at 0 and 40 mg/kg/day Toxicokinetics: additional 3/sex/group	0, 20, 40/ p.o.(gavage) once daily 14 days + 4 weeks recovery period	not determined	Biochemistry: ↓ TGs, total bile acids and cholesterol at ≥ 20 mg/kg/day (F) on Day 15. ↑ total bilirubin at ≥ 20 mg/kg/day (F) on Day 15. Clinical observations, organ findings and histopathology: ↑ mean liver weights at 40 mg/kg/day (F) on Day 15. Pale and/or friable livers at 40 mg/kg/day (F). Dose-related midzonal hepatocellular vacuolation at ≥ 20 mg/kg/day (F). All hepatic findings were reversible. Toxicokinetics: Mean systemic exposure increased approximately dose proportionally. T_{max} ~ 1-4 h. There was no marked change in mean systemic exposure between Days 1 and 14.
Rat (Sprague-Dawley) 12/sex/group	0, 3, 10, 30, 60/ p.o.(gavage) once daily 28 weeks	30 mg/kg/day (C_{max}= 75.0 µg/mL, AUC_{0-24}=661 µg.h/mL)	Deaths: 11/12 (M) and 4/12 (F) died or were sacrified in moribund condition at 60 mg/kg/day. Body weight and food consumption: ↓ at 60 mg/kg/day M & F. Haematology: ↓ (slight to moderate) red cell parameters ↑ reticulocyte counts (M) at 60 mg/kg/day at Week 4, and (F) at 60 mg/kg/day at Weeks 4 and 28. Urianalysis: ↑ urinary protein excretion and protein/creatinin ratios (M) at 30 or 60 mg/kg/day. No histologic correlate. Clinical observations, organ findings and histopathology: Hypoactivity, audible, laboured and/or irregular respiration, hunched posture, thin appearance, paleness, and cold to the touch at 60 mg/kg/day. Treatment-related microscopic findings in liver, adrenal cortex, pituitary and eye of M & F at 60 mg/kg/day, and in liver of F given 30 mg/kg/day. Liver: centrilobular degeneration and necrosis, and periportal and

Species/Sex/ Number/Group	Dose (mg/kg/day)/ Route Duration	NOEL/ NOAEL	Major findings
			midzonal hepatocellular vacuolation. Adrenal cortex: vacuolation and necrosis. Pituitary: vacuolation in the par distalis. Eye: cataracts. Endosteal hyperostosis in the femur (2 M) and tibia (1 M) at 60 mg/kg/day. Depletion on lymphoid cells in the spleen, lymph nodes and thymus at 60 mg/kg/day. Toxicokinetics: Plasma concentrations increased with increasing dose. T_{max} ~ 1-4 h post dose. There was no marked difference in systemic exposure between M and F. Systemic exposure increased 37-fold for a 20-fold increase in dose between 3 and 60 mg/kg/day in females and 31-fold for a 10-fold increase in dose between 3 and 30 mg/kg/day in males.
Beagle dog 3/sex/group	0, 3, 10, 30/ p.o.(gelatine capsule) once daily 14 days	10 mg/kg/day (C_{max}= 51.3 µg/mL, AUC_{0-24}=782 µg.h/mL (on Day 14))	Biochemistry: ↑ ALT and AST (2.4- to 2.7- fold) at 30 mg/kg/day on Day 14. Haematology: ↓ reticulocyte counts at 30 mg/kg/day on Days 4 and/or 14. Toxicokinetics: There were no marked differences in systemic exposure between M and F. There was a trend for higher AUC_{0-24} values on Day 14 when compared to Day 1. On average, systemic exposure ↑ 18.3- fold (Day 1) and 13.6-fold (Day 14) for a 10-fold increase in dose.
Beagle dog 4/sex/group	0, 3, 10, 30/ p.o.(gelatine capsule) once daily 52 weeks	30 mg/kg/day (AUC_{0-24}=418 µg.h/mL)	Biochemistry: ↑ ALP (M) at 10 or 30 mg/kg/day, and (F) at 30 mg/kg/day, Week 52, from 1.8- to 4.3-fold higher than control). Generally bone specific ALP. Considered a mild stimulation of bone formation. Toxicokinetics: T_{max} occurred between 1 and 12 hours post dose. In general, there was no marked (> 2-fold) difference in systemic exposure between males and females or among sampling periods for each dose. Exposure increased approximately dose-proportionally. There was a trend for Day 1 systemic exposures at 10 and 30 mg/kg/day dose to be 2- to 3-fold lower than the other sampling periods.

In addition in a safety, pharmacology and pharmacokinetics study in chimpanzees it was reported that there were no treatment-related effects on clinical signs or body weight and no adverse clinical pathology findings following single eltrombopag doses of 0.1, 1, 3 or 10 mg/kg or repeated doses of 10 mg/kg.

- Genotoxicity

The genotoxicity testing program performed for Revolade is presented in Table 3:

Table 3. Genotoxicity assays/studies.

Method of administration	Type of test	Test system	Dose or Concentrations/ Metabolising system	Results Positive/negative/equivocal	
				+ S9	- S9
In vitro	Gene mutations in bacteria (Ames test) 2 independent tests	Salmonella strains (TA98, TA100, TA1535, TA1537) and *E. coli* WP2 pKM101 and WP2 uvrA pKM101	62.5-2500 µg/plate (72 hr treatment): +/- S9	negative	negative
In vitro	Gene mutations in mammalian cells (L5178Y mouse	Mouse lymphoma L5178Y cells	3.125 to 70 µg/mL (3 hour treatment, +S9) 3.125 to 37.5 µg/mL (3 hour	positive (at ≥ 10 µg/mL)	positive at ≥ 6.25 µg/mL (3 hour treatment)

	lymphoma assay)		treatment - S9) 0.5 to 8 µg/mL (24 hour treatment - S9)		
In vitro	Gene mutations in mammalian cells (L5178Y mouse lymphoma assay)	Mouse lymphoma L5178Y cells	1 to 10 µg/mL (3 hour treatment + S9) 0.5 to 14 µg/mL (3 hour treatment - S9) 2 to 10 µg/mL (24 hour treatment –S9)	negative	positive at 9 and 10 µg/mL (24 hour treatment)
In vitro	Gene mutations in mammalian cells (L5178Y mouse lymphoma assay)	Mouse lymphoma L5178Y cells	20 to 43 µg/mL (2-aminoethanol only)(3 hours treatment +/- S9) (24 hours treatment – S9)	negative	positive (24 hour treatment)
Oral (gavage)	Chromosomal aberrations in vivo (rat, micronulei in bone marrow)	Sprague-Dawley rats (7 males/group)	120, 240, 500 mg/kg/day for 2 days	negative (+/- S9 not applicable)	
Oral (gavage), 1 day (animals were dosed twice)	Primary DNA damage (unscheduled DNA synthesis)	Sprague-Dawley rats (4 males/group)	120, 240, 500 mg/kg/day at 12 to 14 hours and 2 to 4 hours prior to necropsy.	negative (+/- S9 not applicable)	

- Carcinogenicity

The carcinogenicity studies are shown in Table 4:

Table 4. Overview of carcinogenicity studies performed for eltrombopag.

Dose/Route Duration	**Exposure (AUC)**	**Species/No. of animals**	**Major findings**
0, 25, 75, 150/115, 300[a]mg/kg/day Oral (gavage) 2 years	$AUC_{(0-24)}$= 591 µg.h/mL and C_{max}=70.4 µg/mL at Week 67. (Gender-averaged mean; at a dose of 75 mg/kg/day).	Mouse (CD-1)/ 60/sex/group + 48/sex/group	<u>Survival and neoplastic findings:</u> Doses ≥150/115 mg/kg/day were associated with high mortality and early termination. No increased incidence of any rare or commonly-observed tumour type at doses up to 75 mg/kg/day. <u>Non-neoplastic findings:</u> Dose-dependent ↑ in **cataracts**, noted at Week 8 at 150 mg/kg/day, and Week 13 at75 mg/kg/day. **Renal effects** (slight to severe degeneration and necrosis of proximal convoluted tubules, regenerative changes) at all dose levels. <u>Toxicokinetics:</u> Quantifiable for the 24 hour interval during all different sample periods. No marked difference in AUC_{0-24} between M & F. AUC_{0-24} increased proportionally with dose during Weeks 4 and 67.
0, 10, 20, 40 mg/kg/day Oral (gavage) 2 years	$AUC_{(0-24)}$= 677µg.h/mL and C_{max}=76.8 µg/mL at Week 26. (Gender-averaged mean; at a dose of 40 mg/kg/day).	Rat (Sprague-Dawley)/ 60/sex/group + 6/sex/group	<u>Survival and neoplastic findings:</u> No effect on survival. No increased incidence of any rare or commonly-observed tumour type at doses up to 40 mg/kg/day. <u>Non-neoplastic findings:</u> **Cataracts** in M at 40 mg/kg/day from Week 36 (low incidence in F). Slight ↓ in **Hb** and **Hct** in M at 40 mg/kg/day. Basophilic and eosinophilic cellular alteration in the **liver** in M at 40 mg/kg/day. **Chronic progressive nephropathy** in M and F at 40 mg/kg/day. <u>Toxicokinetics:</u> No marked difference in AUC_{0-24} between M & F. For a 4-fold increase in dose between 10 and 40 mg/kg/day, AUC_{0-24} values increased 5.5-, 5.9- and 5.3- fold and C_{max} values increased 4.7, 4.8- and 3.4-fold during Weeks 4, 11 and 26, respectively. In general there were no marked changes in AUC_{0-24} and C_{max} values between Weeks 4 and 26 for any dose level.

a: Due to mortality, 300 mg/kg/day was discontinued at Week 3. In females, 150 mg/kg/day was lowered to 115 mg/kg/day at Week 21 due to clinical signs. Dosing in both males at 150 mg/kg/day and females at 150/115 mg/kg/day was discontinued at Week 43 and the animals were euthanized at Week 64.

- Reproduction Toxicity

The effects of eltrombopag on fertility and general reproductive performance, peri- and post-natal development and juvenile toxicity have been investigated in Sprague-Dawley rats, while the effects on embryofoetal development have been investigated in Sprague Dawley rats and New Zealand white rabbits.

In a male fertility study in Sprague-Dawley rats testicular weights were slightly increased at 40 mg/kg/day, but there were no effects of eltrombopag on mating and fertility of the treated males, nor any effects on survival, growth or external morphology of the foetuses sired by the treated males. The no observed adverse effect dose for male fertility in this study was 40 mg/kg/day. In a rat repeat dose oral toxicity study for up to 10 days vacuolar changes in the testes were noted at 40 and 120 mg/kg/day, as well as spermatid retention/ degeneration at 120 mg/kg/day eltrombopag (2.3- to 5.1-fold greater than the maximum proposed clinical exposure). These were not associated with systemic toxicity.

In a female fertility and early embryonic development study in Sprague-Dawley rats, decreases in maternal body weight gain and food consumption were noted at 60 mg/kg/day (6.2-fold the maximum proposed clinical exposure). Embryotoxicity was observed at 60 mg/kg/day in the form of increased pre- and post-implantation loss (leading to a 27% decrease in live litter size) and a 20% to 21% decrease in foetal weight. Under the conditions of this study, the No Observed Adverse Effect Level (NOAEL) for fertility and early embryonic development was 20 mg/kg/day (2-fold the maximum proposed clinical exposure).

In one embryofoetal development study in rat, animals given eltrombopag orally at 60 mg/kg/day for 11 days, showed decreased maternal body weight (9%) and food consumption (8%-11%), as well as decreased foetal weights in males and females (6%-7%), and increased incidence of cervical ribs. No test article-related changes were observed for any caesarean section parameters (corpora lutea, implants, pre- and post- implantation loss and number of live foetuses). These studies were performed at 60 mg/kg/day eltrombopag, 6.2-fold the maximum proposed clinical exposure.

One embryofoetal development study was performed in New Zealand rabbits. Eltrombopag did not produce effects on uterine or teratogenicity parameters.

In a pre- and post-natal development study in rats, there were no adverse effects on pregnancy, parturition or lactation of female rats and no effects on the growth, development, neurobehavioral or reproductive function of the offspring at doses up to 20 mg/kg/day.

Two juvenile toxicity studies were conducted in rat pups dosed eltrombopag from Days 4 to 32 pp. At doses ≥ 30 mg/kg/day (2274 μg.h/mL, 13.5-fold the maximum proposed clinical exposure) some deaths occurred, as well as evident toxicity clinical signs (decreased activity, weakness, thinness and cold to touch). Pale yellow discoloration of the fur/skin, 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 were noted grossly in five animals in the middle dose group (30 mg/kg/day). There were no treatment related findings at 10 mg/kg/day (977 μg.h/mL; 5.8- fold the maximum proposed clinical exposure).

In one of the studies there was a slight decrease in red blood cell count, haemoglobin, and mean cell haemoglobin concentration values for males, a slight increase in absolute reticulocyte counts for females, and slight increases in red cell distribution width for males and females at 15 mg/kg/day.

Due to age-dependent development of hepatic excretory pathways, and additional juvenile toxicity study was conducted at higher doses in slightly older rats. Pups were dosed eltrombopag orally once daily from Day 32 to 63 post partum. There were no 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), effects on red blood cell parameters to the same extent than observed in the previous study in younger pups were also noted. In this case, these findings were not considered adverse.

At 40 mg/kg/day dose group, increased urinary protein was noted in males, It 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. Immunohistochemical staining indicated that the hyaline droplets contained alpha-2 microglobulin, a male-rat specific protein. Changes were only accompanied by slight proteinuria and were not accompanied by histologic evidence of renal damage.

As a conclusion from these three studies, toxicity was observed at lower eltrombopag doses in the youngest animals dosed from Day 4 to 32 pp (NOAEL: 10-15 mg/kg/day), when compared to older animals, administered from Day 32 to 63 pp (NOAEL: 40 mg/kg/day).

- Local tolerance

Local tolerance studies included *in vitro* ocular and dermal irritancy studies and an *ex vivo* ocular irritancy assay. Eltrombopag was considered not to be skin irritant but a severe ocular irritant.

- Other toxicity studies

Antigenicity
An *in vivo* study on skin sensitisation potential in the mouse local lymph node assay was submitted. Eltrombopag was considered to be a non-sensitizer under the conditions of this assay.

Immunotoxicity
A study was performed to investigate the effects of eltrombopag on the primary antibody response to T-cell dependent antigen, keyhole limpet hemocyanin (KLH). There was no treatment-related effect on immunology parameters in females. Male rats in the highest dose group showed a decrease in group geometric mean anti-KLH IgM antibody concentration, compared to the male control group (3 versus 19 µg/mL; $p \leq 0.01$). The decrease in anti-KLH IgM response in the 40 mg/kg/day male group is considered related to drug treatment; however, whether it is a direct drug effect or secondary to the slight decrease (12 and 15%) in body weight gain at the time of immunization and IgM measurement, is uncertain. The finding is considered non-adverse based on nominal differences in anti-KLH IgG response which were neither statistically nor biologically significant in the 40 mg/kg/day male group, compared to controls. In conclusion, eltrombopag at doses up to 40 mg/kg/day does not adversely affect immune function.

Phototoxicity

Eltrombopag was demonstrated to be phototoxic in vitro (3T3 NRU phototoxicity test).

There was no evidence of cutaneous phototoxicity in SKH1-hr mice at ~1 hour, 4 hours (tmax) and 3 days post UVR exposure (dose equivalent to ~ 0.5 MED) at doses up to 150 mg/kg/day for 14 days (Cmax of 167 µg/mL and AUC of 1607 µg.h/mL, corresponding to 13.1- and 9.5- fold maximum proposed clinical exposure, respectively).

Studies were performed to investigate the phototoxic potential of eltrombopag on the eyes of pigmented and non-pigmented (albino) mice and rats. The overall incidence and progression of cataracts was generally increased in pigmented female mice (B6C3F1) versus albino female mice (CD-1) given eltrombopag (100 or 150 mg/kg/day) for 12 weeks, with or without UVR exposure (0.6 MED/day or 3 MED/week). There were 6 deaths (6 out of 35) in albino mice given 150 mg/kg/day eltrombopag (3 exposed and 3 no exposed). No adverse clinical observations or deaths related to treatment were noted in pigmented mice

No adverse ophthalmological or histological findings were noted in eyes of male Long Evans (pigmented) and Sprague Dawley (albino) rats given 40 mg/kg/day eltrombopag orally for 14 days followed by a single UVR exposure (~0.5 MED).

Renal effects

A four-week investigative study on potential eltrombopag-induced renal toxicity was performed in female CD-1 mice (n=12/group; ~ 11 weeks of age at the start of dosing). Eltrombopag dose: 150 mg/kg/day, p.o., for 4 weeks; or 250 mg/kg/day, p.o., for 11 days. Toxicokinetics: additional 20 animals/group.

Mortality and deteriorating clinical condition at 250 mg/kg/day between Days 9 and 11 resulted in the early termination (Day 11) of the remainder of that group. Renal findings associated with the spontaneous syndrome of chronic nephropathy in mice, tubular basophilia and interstitial inflammatory infiltrates were present in eltrombopag-treated mice at an increased incidence (0 control vs. 6 mice given 150 mg/kg/day, Day 28) and tubular casts were present at 250 mg/kg/day at an increased number and localization (cortex and medulla vs. confined to the medulla in controls or mice given 150 mg/kg/day). Eltrombopag-related tubular degeneration, tubular dilation and/or regenerative changes were observed at low incidence (approximately 20%) and minimal to mild severity at doses of 150 or 250 mg/kg/day. Systemic exposure was similar (AUC ≈ 2300 µg.h/mL) at doses of 150 mg/kg/day on Day 28 or 250 mg/kg/day on Day 11. tmax occurred at 8 or 2 hours post dose at 150 or 250 mg/kg/day, respectively.

A second investigative study on potential eltrombopag-induced renal toxicity was performed in female CD-1 mice (n=40/group; ~ 6 weeks of age at the start of dosing). Eltrombopag dose: 150 mg/kg/day p.o., for up to 28 or 32 weeks. Mice given 150 mg/kg/day had decreased body weight gain and 4 of 40 mice died or were euthanized in moribund condition (following 81 to 193 doses of eltrombopag; Weeks 12 to 28). Degeneration and necrosis noted in cortical and medullar tubules of 3 of these mice were considered secondary changes associated with moribundity and vascular compromise. Increases in urine protein-to-urine creatinine ratios (up to 3.9X control) were observed in mice given 150 mg/kg/day following 87 to 196 days of dosing (Weeks 13 to 28). Tubular basophilia, inflammatory infiltrates within interstitial and tubular casts, associated with the spontaneous syndrome of chronic nephropathy in mice, were found in both the treated and control group with no differences in the incidence and severity, which increased with age. There were no test article-related microscopic renal findings following up to 193 days of dosing.

Studies on impurities

A review of the synthetic route for eltrombopag and possible degradation chemistry of reagents used therein highlighted a number of synthetic intermediates and degradation products as potential genotoxins: SB-611855-AAB, SB-601205, SB-564758, GSK560666A and SB-710620-A.

SB-611855-AAB and SB-601205 were negative in Ames bacterial mutation assays in the presence and absence of a metabolic activation system (S9-mix) when tested up to 5000 µg/plate. SB-564758, an isolated intermediate, was not mutagenic in an Ames assay in the presence and absence of S9-mix at up to 5000 µg/plate but was clastogenic in an *in vitro* chromosomal aberration assay in human lymphocytes in the presence and absence of S9-mix. SB-564758 was negative in a rat oral micronucleus assay at doses up to 600 mg/kg/day. Based on these findings, SB-611855-AAB, SB-601205 and SB-564758 are considered non-genotoxic impurities.

SB-710620-A and GSK560666A were positive in an *in vitro* bacterial mutation HTFT (high throughput fluctuation test) mutagenicity screen.

Ecotoxicity/environmental risk assessment

Using the Phase I calculation without marketing penetration factor (Fpen) refinement for prediction of Predicted Environmental Concentration (PEC), the calculated PEC for eltrombopag (0.35 µg/l) was above the trigger value of 0.01 µg/l. According to published epidemiological data

(Abrahamson *et al*. 2009), an incidence of 0.39 in 10,000 is equivalent to 0.0039% of the population and use of this refined figure in the standard Phase I calculation of worst case PEC would give a PEC value of 0.0015 µg/L which is significantly below the nominal trigger value of 0.01 µg/L.

The study OECD 107 for the determination of logK_{ow} showed a log K_{ow} above 4.5 at pH7.

Discussion on the non-clinical aspects

The *in vitro* inhibitory effects on $\alpha_{2B,}$ I_2-, oestrogen-α- and oestrogen-β-receptors were not correlated with *in vivo* findings in clinical trials or in non-clinical species at exposures approximately 3- to 6-fold maximum clinical exposure (based on AUC and C_{max}). The potential for secondary pharmacodynamic effects on these receptors in patients receiving eltrombopag is unlikely and thus, potential interactions associated with a particular medical condition or with concomitant medications are not expected.

According to Guideline 3BS1a on Single dose Toxicity, single-dose toxicity studies must be conducted on at least two mammalian species. For eltrombopag only one study in dogs was performed. According to the same Guideline, two different routes of administration should be used. In the only study provided, eltrombopag was just administered orally, the intended route for man. However, this approach has been considered acceptable based on the battery of repeat dose toxicity studies provided.

The principal toxicological findings associated with eltrombopag administration include cataracts (mice and rats), renal toxicity (mice) and hepatotoxicity (mice, rats and dogs). *In vitro* phototoxicity (3T3 and CHO cells) has also been observed. This information has been addressed in section 5.3 of the SPC.

Observed effects on red blood cells including decreased reticulocyte counts (in rats and dogs) and regenerative bone marrow erythroid hyperplasia (rats only) observed in short term studies and endosteal hyperostosis (rats only) have been addressed in section 5.3 of the SPC.

Studies in animals have shown reproductive toxicity (included in section 5.3 of the SPC). Studies in animals have shown that eltrombopag is likely secreted into milk, therefore a risk to the suckling child cannot be excluded and a warning has been included in section 4.6 of the SPC.

Study OECD 107 for the determination of logK_{ow} presented in the ERA showed a log K_{ow} above 4.5 at pH7; therefore a PBT-assessment is necessary. The substance should be screened in a step-wise procedure for persistence (OECD 308), toxicity (OECD 210, OECD 211) and bioaccumulation (OECD 305) and the Applicant has committed to submit these studies as a follow up measure.

2.4 Clinical aspects

Introduction

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

The therapeutic indication for Revolade claimed by the Applicant was: Revolade is indicated for the treatment of previously treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

The approved therapeutic indication is: 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.

The Applicant received Protocol Assistance from the CHMP on clinical aspects of the dossier focusing on the study design for the pivotal trials.

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.

Pharmacokinetics

The following studies have been submitted:

SB497115/001	Single dose PK 3 to 9 mg qd
SB497115/002	Single and repeat dose escalation (5 to 75 mg qd) CYP450 drug interaction
SB487115/005	Bioavailability and food effect
TRA102860	Repeat dose PK 50 to 200 mg qd QTc
TRA106914	Measure of phototoxic index
TRA102861	Absorption and excretion of 75 mg single dose of eltrombopag (radiolabelled drug)
TRA104412	Renal Impairment
TRA103453	Hepatic impairment
TRA105120	Drug interactions – rosuvastatin
TRA102863	Bioavailability
TRA104603	Single dose PK in healthy Japanese
TRA105580	Single and repeat dose PK in healthy Japanese)
TRA104631	Food effect of low-calcium meals and antacid interaction
TRA105122	Bioequivalence
TPL111716	Drug interactions - lopinavir/ritonavir
RM2007/00685/00	Genetic polymorphism
RM2007/00768/02 Study	Population PK analysis
RM2008/00711/00 Study	Population PK/PD analysis

- Methods

Analytical methods

Plasma samples were analysed for eltrombopag using a method based on protein precipitation, followed by high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) analysis. Data on BQL, within and between-run precision, accuracy and sample stability show values within the accepted range of suitability for a human plasma analysis.

Pharmacokinetic data analysis

Pharmacokinetic data were firstly explored on the basis of an individual approach by using non-compartmental PK analysis (WinNonlin software). Population pharmacokinetic methods, using the program NONMEM VI, have also been used to analyse PK data from 5 studies: 3 Phase I studies (TRA102860, TRA105580, SB-487115/002), 1 Phase II study (TRA100773A) and 1 Phase III study (TRA100773B).
Statistical analyses conducted with PK data were standard and appropriate in each case.

- Absorption

The plasma eltrombopag concentration-time data was collected in 88 subjects with ITP in Studies TRA100773A and TRA100773B (see Table 5). Plasma eltrombopag concentrations were quantifiable within approximately 1 h, with peak concentrations occurring 2 to 6h after oral administration of single and repeat doses of eltrombopag. The plasma elimination half life of eltrombopag is approximately 21 to 32 h.

Table 5: Plasma Eltrombopag AUC(0-tau) and Cmax Estimates for Subjects with ITP in Studies TRA100773A and TRA100773B

Eltrombopag Dose, QD	N	AUC(0-τ)[a], μg.h/mL	Cmax[a], μg/mL
30mg	**28**	**47 (39, 58)**	**3.78 (3.18, 4.49)**
50mg	**34**	**108 (88, 134)**	**8.01 (6.73, 9.53)**
75mg	**26**	**168 (143, 198)**	**12.7 (11.0, 14.5)**

Data presented as geometric mean (95% CI). AUC(0-τ) and Cmax based on population PK post-hoc estimates.

Plasma eltrombopag AUC and Cmax increased with increasing dose and the evaluation of proportionality was dose dependent. Plasma eltrombopag AUC(0-τ) increased in a dose proportional manner between 50 mg and 200 mg; Cmax increased in a dose proportional manner between 50 mg and 150 mg. At doses below 50 mg, plasma eltrombopag AUC(0-∞) and Cmax increased in a greater than dose-proportional manner. Between-subject variability (%CVb) in AUC and Cmax was generally between 30 and 40%.

A population PK analysis was performed using the data from 111 healthy subjects from three Phase I studies (TRA102860, TRA105580, SB-497115/002) and 88 ITP patients from one Phase II study (TRA100773A) and one Phase III study (TRA100773B). The PK of eltrombopag following single- and repeat-oral administration were adequately described by a linear 2-compartment model with absorption lag time, dual sequential first order absorption, inter-occasion variability on absorption and first order elimination. The absorption rate constant at 1.9 hours post dose increased from 0.5 hr-1 to 10.4 hr-1, indicating that eltrombopag absorption rate is much faster in the small intestine than in the stomach. The estimated mean (95% confidence interval (CI)) parameter values for an ITP male Caucasian patient that weighed 70 kg and did not take corticosteroids are shown in Table 6.

Table 6: Final estimates of the population PK model

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	
CL/F [L/hr]	0.668	8.19	0.561-0.775	
Vc/F [L]	8.76	3.61	8.14-9.38	
Vp/F [L]	11.3	5.63	10.1-12.5	
Q/F [L/hr]	0.399	4.81	0.361-0.437	
Ka1 [hr^{-1}]	0.503	7.38	0.43-0.576	
Ka2 [hr^{-1}]	10.4	18.8	6.58-14.2	
ALAG1 [hr]	0.457	1.82	0.441-0.473	
MTIME [hr]	1.94	1.22	1.89-1.99	
σProp ~ITP	1.42	8.66	1.18-1.66	
σProp ~TAD<4hr	1.4	5.40	1.25-1.55	
CL/F ~WT, Q/F~WT	0.616	13.9	0.449-0.783	
Vc/F ~WT, Vp/F~WT	0.617	30.0	0.254-0.98	
CL/F ~DOSE<20 mg	1.68	6.67	1.46-1.9	
Vc/F ~DOSE<20 mg	1.55	6.00	1.37-1.73	
CL/F ~Healthy	1.17	7.6	0.996-1.34	
CL/F ~Asian	0.665	5.74	0.59-0.74	
CL/F ~Female	0.808	7.54	0.689-0.927	
CL/F ~CORT	0.742	13.0	0.553-0.931	
Inter-individual or inter-occasion variability				**CV% or R [b]**
ω^2_{CL}	0.165	17.3	0.109-0.221	CV= 40.6%
Covar $\omega_{CL,}\omega_{Vc}$	0.113	22.7	0.0628-0.163	R= 0.743
ω^2_{Vc}	0.14	22.4	0.0787-0.201	CV= 37.4%
$\omega^2_{IOV\ Ka}$	1.62	11.0	1.27-1.97	CV= 127%
Residual variability				**CV% or SD**
σ^2_{prop}	0.0433	10.5	0.0344-0.0522	CV= 20.8%
σ^2_{add}	899	42.5	148-1630	SD=29.8

In healthy subjects receiving eltrombopag once daily for 10 days, the accumulation ratio (90% CI) was 1.44 (1.20,1.63) for 50 mg once daily and 1.56 (1.23,1.97) for 75 mg once daily. Eltrombopag demonstrated time-invariant PK over the dose range of 5 mg to 75 mg administered once daily for 10 days. Based on a population PK analysis, the apparent oral clearance for eltrombopag was, on average, 17% higher in healthy subjects as compared to patients with chronic ITP.

Influence of food

The absorption of eltrombopag was significantly reduced when administered with the standard high-fat breakfast with milk (corresponding to 427mg calcium); whereas, low-calcium meals (<50mg calcium), regardless of fat content, had minimal impact on plasma eltrombopag exposure. In addition, the absorption of eltrombopag was significantly reduced when co-administered with a polyvalent cation-containing antacid.

- Distribution

Distribution was well characterized in the final population PK model by assuming a 2-compartment PK model. Thus, two volumes of distribution have to be estimated as fixed parameters: volume of central compartment (Vc/F) and volume of the peripheral compartment (Vp/F). Interindividual random effects (IIV) on both were firstly included using exponential models with a diagonal variance –covariance matrix. The apparent volumes of distribution for the Vc/F and Vp/F compartments were estimated to be low (8.76L and 11.3L, respectively). IIV on Vp/F resulted to be quite high: 45%. Correlation between CL/F and Vc/F was also included in the final popPK model (0.81). Weight and low dose (< 20 mg) were the most significant determinants on apparent volume of the central compartment. The effects of weight on Vp/F were fixed to the same as for Vc/F.

In vitro data showed that eltrombopag is highly bound to human plasma proteins (> 99.9 %), predominantly to albumin.

- Elimination

In a human radiolabel study (Study TRA102861), 75 mg eltrombopag were administered by single dose. Eltrombopag accounted for approximately 64% of plasma radiocarbon AUC_{0-t} suggesting the presence of metabolites. On average, 59% of the dose was recovered in faeces, 20% as unchanged eltrombopag and 21% as three co-eluting metabolites including a glutathione, glutamyl-cysteine, and cysteine adduct. On average, 31% of the dose was recovered in urine, none as unchanged eltrombopag, and 20% as a glucuronide of the phenylpyrazole moiety resulting from hydrazine cleavage. Hydrazine cleavage products identified in human urine suggested that eltrombopag might be metabolized by bacteria in the gastrointestinal tract. The remaining unaccounted dose in the excreta was comprised of multiple metabolites that could not be identified because their levels were close to or below background radioactivity (19% of dose overall, 8% in faeces and 11% in urine), and losses incurred during sample processing and analysis (10% of dose in faeces).

Plasma eltrombopag half-life in humans following a single oral administration ranged from 21 to 32 hours. Data from the mass balance study show that the mean total recovery of radioactivity was 89.6% (range of 83.8 to 93.2%) of the dose. Faecal elimination was the predominant route of elimination with a mean of 58.9% (range of 40.9 to 69.8%) of the total radiocarbon dose. Urinary excretion accounted for a mean recovery of 30.7% (range of 23.4 to 45.4%) of the administered dose. Urinary elimination was essentially complete in the first 48 hours post dose while faecal elimination continued for several more days. Most of the dose was recovered by 144 hours after dosing.

The *in vivo* metabolism of eltrombopag was investigated in six healthy male subjects (CD 2006/01628/00) following a single oral administration of [14C]eltrombopag at dose of 75 mg. Eltrombopag was the predominant radiocomponent in plasma extracts. Minor metabolites, each accounting for approximate 10% or less of plasma radioactivity were also detected and were products of glucuronidation or oxidation. Parent eltrombopag was not detected in urine. The predominant radiometabolite present in the human urine (accounting for about 20% of the dose) was a glucuronide of the phenylpyrazole moiety (lower portion) of the molecule following the cleavage of the hydrazine linkage. NMR analysis confirmed that a glucuronide conjugate of the biphenyl moiety (unlabelled top portion after cleavage) of eltrombopag was also present in urine. In faeces, unchanged eltrombopag and three co-eluting glutathione-related conjugates were the predominant radio-components. Eltrombopag accounted for approximately 20% of the administered dose and the co-eluting metabolites (a glutathione, a glutamyl-cysteine, and a cysteine adduct of eltrombopag) together accounted for approximately 21% of the dose.

Based on the metabolic profile characterized in the human mass balance study, it is estimated that approximately 21% of a dose could be metabolised through the CYP system and CYP1A2 and CYP2C8 were identified *in vitro* as enzymes responsible for the oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 were identified as the enzymes responsible for glucuronidation. Eltrombopag, administered as 75 mg QD for 7 days, did not inhibit or induce the metabolism of probe substrates for CYP 1A2, 2C9, 2C19, and 3A4 in healthy male subjects. In addition, there has been no evidence for the formation of any human specific metabolites.

Eltrombopag is not a substrate or inhibitor of P-glycoprotein. Eltrombopag is not a substrate for OATP1B1, but is an inhibitor of this transporter with an IC50 value of 2.7μg/mL). Eltrombopag is a substrate and inhibitor of breast cancer resistance protein (BCRP with an IC50 value of 2.7 μg/mL), and has been shown to increase plasma concentrations of the OATP1B1 and BCRP substrate rosuvastatin (Study TRA105120).

Elimination was well characterized in the final population PK model by assuming a 2-compartment PK model with first order absorption and first order elimination. The final covariate model included the influence of body weight on CL/F, Vc/F, Q/F, and Vp/F, and influence of the disease (ITP versus healthy), race, gender, and concomitant corticosteroids on CL/F. Mean (95% CI) apparent clearance was 33% (26%, 41%) lower in Asians compared to all other races, 26% (7%, 45%) lower in patients

taking corticosteroids concomitantly, and 19% (7%, 31%) lower in females compared to males. Healthy subjects had 17% (0%, 34%) higher CL/F than ITP patients.

Eight polymorphisms were identified as significantly associated with PK variability using the tiered approach in Asian or White HVT subjects. None of these polymorphisms was associated with PK variability in both Asian and White HVT samples.

- Dose proportionality and time dependencies

Following administration of single oral doses of eltrombopag as granules in a capsule, plasma eltrombopag exposure increased more than proportionally with dose over the range of 3 mg to 9 mg; the slope (95% CI) estimate was 1.59 (1.21, 1.97) for AUC(0-t), 1.51 (1.14, 1.88) for AUC(0-∞), and 1.68 (1.39, 1.97) for Cmax. Plasma eltrombopag AUC and Cmax increased in a greater than dose proportional manner between 3mg and 9mg because the lower limit of the 95% CI for the slope estimate was greater than one.

No accumulation of plasma eltrombopag AUC(0-τ) was observed after QD dosing at 5 mg and 10 mg; however, 37–56% accumulation was observed after QD dosing of 20 mg, 30 mg, 50 mg, and 75 mg for 10 days (49115/002). Single dose plasma eltrombopag AUC(0-∞) and Cmax values increased with increasing dose in a slightly greater than dose proportional manner where the slope estimate (90%) CI) 1.13 (1.04, 1.22) for AUC(0-∞) and 1.15 (1.07, 1.24) for Cmax over a range of 5 mg to 75 mg. Steady-state plasma eltrombopag AUC(0-τ) and Cmax increased with increasing dose in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.19 (1.11, 1.26) for AUC(0-τ) and 1.20 (1.12, 1.27) for Cmax over a range of 5 mg to 75 mg QD.

No time dependent changes in plasma eltrombopag pharmacokinetics were observed across the dose levels (49115/002). After receiving a dose of 75 mg qd of eltrombopag, AUC, Cmax and half-live values at the first and the tenth day were quite similar with no statistically significant differences (72 vs.79 mg*h/L; 6 vs.7 mg/L; 16 vs.14h, respectively).

- Special populations

Impaired renal function
An open-label, non-randomized pharmacokinetic and safety study of a single oral dose of 50 mg eltrombopag was performed in healthy subjects and in subjects with renal impairment. Plasma eltrombopag AUC(0-∞) was on average 32%, 36% and 60% lower in subjects with mild, moderate and severe renal impairment, respectively, compared with healthy subjects. Moderate to high between-subject variability (CVb%) was observed in the PK parameters and variability increased with increasing severity of renal impairment. The impact on half-life was not so evident but CL/F showed a significant increase from healthy subjects to severe renal impairment subjects.

Impaired hepatic function
An open-label, non-randomized pharmacokinetic and safety study of a single oral dose of 50 mg eltrombopag was performed in healthy subjects and in volunteers with mild, moderate or severe hepatic impairment. $AUC_{0-\infty}$ of eltrombopag was 41 % higher in subjects with mild hepatic impairment and 80 % to 93 % higher in subjects with moderate to severe hepatic impairment compared with healthy volunteers.

Gender
The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 50 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). East Asian ITP subjects had approximately 87% higher plasma eltrombopag AUC(0-τ) values compared to non-East Asian ITP subjects who were predominantly Caucasian, without adjustment for body weight differences. Similar differences in plasma eltrombopag PK were observed between East Asian and non-Asian healthy subjects. Evaluation of platelet response across the ITP studies suggests that East Asian ITP subjects were more likely to achieve platelet counts >400 ,000/μL. In addition, there was a trend to a higher incidence of hepatobiliary laboratory abnormalities in East Asian ITP subjects.

Weight
Apparent clearance and volume were influenced by body weight. For the range of weights in the population pharmacokinetic analysis (43 kg to 122 kg), predicted typical (for ITP male Caucasian patient without corticosteroids) CL/F and Vc/F and are 0.495 to 0.941 L/h and 6.49 to 12.3 L, respectively.

Elderly
The studies included patients over a wide range of age. The median (range) age across the 199 subjects included in the population pharmacokinetic analysis was 30 (18-85) years. Age did not influence the pharmacokinetics of eltrombopag.

Children
No studies have been submitted.

Weight, gender, race (Asian vs. Non-Asian) and corticosteroid use were predictors of drug exposure in ITP patients; following the same dosing regimen lighter subjects, women, subjects of Asian origin and corticosteroid users would have greater eltrombopag exposures.

- Pharmacokinetic interaction studies

A clinical drug interaction study was conducted to determine the potential impact of co-administering eltrombopag on the PK of rosuvastatin, an HMG-CoA reductase inhibitor used to reduce total cholesterol and triglycerides, and an OATP1B1 and BCRP substrate. Eltrombopag 75 mg once daily for 5 days with a single dose of rosuvastatin 10 mg increased plasma rosuvastatin Cmax 103 % (90 % CI: 82 %, 126 %) and $AUC_{0-\infty}$ 55 % (90 % CI: 42 %, 69 %).

A clinical drug interaction study was conducted to determine the potential impact of co-administering eltrombopag with a polyvalent metal cation-containing antacid. Administration of a single 75 mg dose of eltrombopag with an antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag AUC(0-∞) and Cmax by 70%.

A clinical drug interaction study was conducted to evaluate the potential impact of co-administering eltrombopag on the PK of CYP substrates. Administration of eltrombopag 75 mg once daily for 7 days with single doses of CYP substrates did not inhibit or induce CYP1A2 (caffeine), CYP2C9 (flurbiprofen), CYP2C19 (omeprazole), or CYP3A4 (midazolam) as evidenced by no change in probe substrate PK.

Study TPL 111716 in 40 healthy volunteers was a phase I, open-label, single sequence study was aimed at providing information on the potential drug-drug interaction between eltrombopag and lopinavir/ritonavir (LPV/RTV). The primary objectives of the study were to evaluate the impact of LPV/RTV on plasma eltrombopag PK following administration of LPV/RTV 400/100 mg BID for 14 days with a single dose of eltrombopag 100 mg in healthy adult subjects. In addition the impact of eltrombopag on plasma LPV/RTV following administration of LPV/RTV 400/100 mg BID for 14 days with a single dose of eltrombopag 100 mg in healthy adult subjects was evaluated.

The results obtained show that this inhibitor of HIV protease accelerates the metabolism/elimination of eltrombopag, decreasing the AUC(0-∞) of eltrombopag approximately 17%, (90% CI 6.6%,

26.6%). No information was provided for eltrombopag used in a dose repeating scheme, which is the one used in clinical practise.

With regard to safety, the adverse events and laboratory findings of LPV/RTV observed in the study are those already covered in the SPC of Kaletra, and were consistent with the safety profile of this medicinal product. Similarly, the adverse events observed with eltrombopag, are in line with ones recorded during the clinical program of the product.

Pharmacodynamics

- Mechanism of action

No studies have been submitted.

- Primary and secondary pharmacology

Dose dependent increases in platelet counts were observed in three clinical studies following repeat dose administration of eltrombopag to healthy adult subjects:
Study 497115/002- The mean maximum change from baseline in platelet counts were 104,000 platelets/μL for 30 mg QD, 156,100 platelets/μL for 50 mg QD, and 163,000 platelets/μL for 75mg QD after a 10-day repeat dose administration in 26 healthy male subjects. Platelet function, as measured by platelet aggregation and activation, was not affected by the administration of eltrombopag.
Study TRA105580- Platelet count increases of 10,700 platelets/μL for placebo, 128,500 platelets/μL for 25 mg QD, 195,000 platelets/μL for 50 mg QD and 202,200 platelets/μL for 75 mg QD were observed after a 10-day repeat dose administration in 42 healthy Japanese male subjects. Platelet counts reached peak level on Day 14 post-dose, and returned to baseline values during follow-up periods.
Study TRA102860- Platelet count increases of 14, 200 platelets/μL for placebo, 67,400 platelets/μL for 100 mg QD, 107,300 platelets/μL for 150 mg QD, and 149,600 platelets/μL for 200 mg QD were observed after a 5-day repeat dose administration in 33 healthy subjects (18 males/15 females). Platelet counts reached peak level on Day 14 post-dose, and returned to baseline values during follow-up periods.

Pharmacodynamic response was not observed following single dose administration of eltrombopag in the following studies:
Study 497115/001-Following single oral administration of 3, 6, and 9 mg of eltrombopag to 24 healthy male subjects.
Study 497115/002- Following single oral administration of 5, 10, 20, 50 and 75 mg of eltrombopag to 97 healthy male subjects.
Study TRA105580- Following single oral administration of 25, 50 and 75 mg of eltrombopag to 42 healthy male subjects.
Study TRA104603- Following single oral administration of 30, 50, 75 and 100 mg of eltrombopag to 16 healthy male Japanese subjects.

A conventional sequential PK/PD approach was used to build the population PK/PD model. The PD data were fitted alone using the individual *maximum a posteriori* Bayesian PK parameter estimates (obtained from the population PK model) to predict the eltrombopag concentrations. The population PK/PD model assumes that platelet precursor production is the same in healthy volunteers and ITP patients, but that platelets are degraded much faster in ITP patients (larger KP), which is consistent with an increased rate of platelet destruction in ITP disease well described in the literature. Despite the higher platelet count variability and fixing KIN and KOUT to the estimates from the healthy volunteer model, the ITP patient PK/PD model predictions were consistent with the observed platelet count versus time data. The population PK/PD model was validated (internal validation: visual predictive check (VPC) and non-parametric bootstrap analysis) to confirm the internal robustness of the model.

The final model was used to simulate platelet counts for ITP patients following 10 weeks of once daily dosing of 50 mg eltrombopag. The results of the simulations indicated that steady-state platelet counts were achieved by week 3 and that 90% of steady-state was achieved by week 2. Thus, biweekly dose adjustments are a reasonable approach to titrate each patient. Doubling the eltrombopag dose from 25 to 50 mg once daily would increase median steady-state platelet count 45%, and a 50% increase in dose from 50 to 75 mg once daily would increase steady-state median platelet count 31%.

In healthy subjects, baseline platelet counts, gender and race (Asian versus non-Asian) were tested as covariates on the parameters KIN, KOUT, and SLOP, and gender was also tested on the parameter BASE. Finally, the only significant covariate-parameter relationship was gender on SLOP indicating females had a 36% lower slope compared to males. In the ITP patients population PK/PD model, gender and age were the only covariates which could be included in the model on KIN suggesting that female and older ITP patients (≥65 years) appear to be more sensitive to eltrombopag than men and younger patients.
In healthy subjects, concomitant drugs were not included in the final population PK/PD model since no significant covariate-parameter relationship was found. Concurrent and prior ITP medications of interest included: corticosteroids, intravenous immunoglobulins (IVIg), vincristine/vinblastine, cyclophosamide, danazol, rituximab, azathioprine, cyclosporine, dapsone and mycophenolate. Corticosteroids were the only concomitant ITP medication group used by more than 10% of population. The use of concurrent corticosteroids has been identified as a predictive factor of higher platelet counts following administration of eltrombopag to ITP patients, either due to higher plasma eltrombopag exposure (PK) or greater PD response.

According to submitted data, samples from more than 200 patients with 8 different sorts of solid and non-solid tumours demonstrated levels of Mpl below the levels of accurate detection by microarray or qRT-PCR. No single non-megakaryocytic cell line tested has demonstrated increased proliferation when treated with eltrombopag up to 100 µg/mL, and last submitted data show low or non quantifiable levels of Mpl expression in all the different tumours tested ex-vivo.

Discussion on clinical pharmacology

The gene encoding for TPO-R is a proto-oncogen, also known as c-Mpl, the increased expression of which has been linked to poor prognosis in myelodysplastic syndrome and in acute myeloid leukaemia. According to the submitted data the concern on the potential stimulatory effect of eltrombopag on the proliferation of some malignant cell lines is minimal, although it cannot be completely discarded. A warning has been included in section 4.4 of the SPC reflecting this risk and the Applicant will study long term effects in a post-marketing study included in the risk management plan.

Data of concentration over time and platelet counts used in the population PK/PD analysis are rich enough and well distributed across time to support the estimation of the population PK/PD parameters with fairly good precision.

Based on estimates from the population pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 87 % higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were predominantly Caucasian, without adjustment for body weight differences. Initiation of eltrombopag at a reduced dose of 25 mg once daily may be considered for patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese or Korean) and this information has been included in sections 4.2 and 5.2 of the SPC. The Applicant has committed to further investigate the ethnic differences observed in eltrombopag exposure in a post-authorisation commitment.

In order to avoid clinically significant reductions in plasma eltrombopag exposure, eltrombopag should be administered at least 4 hours apart from antacids and other products containing polyvalent cations such as mineral supplements and dairy products. Administration of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag

$AUC_{0-\infty}$ by 59 % and C_{max} by 65 %. This information has been included in the SPC in sections 4.2 and 4.5.

Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP (corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin) in order to avoid platelet counts outside of the recommended range (relevant information included in section 4.2 of the SPC).

Interactions of eltrombopag and rosuvastatin have been demonstrated in healthy adults. Interactions are also expected with other HMG-CoA reductase inhibitors, including pravastatin, simvastatin and lovastatin, however, clinically significant interactions are not expected between eltrombopag and atorvastatin or fluvastatin. Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should also be undertaken with caution. This information has been included in section 4.5 of the SPC.

Co-administration of eltrombopag with lopinavir/ritonavir may cause a decrease in the concentration of eltrombopag. Therefore, caution should be used when co-administration of eltrombopag with lopinavir/ritonavir takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued. This interaction has been included in section 4.5 of the SPC for information. In addition the Applicant has committed to provide further information on the co-administration of eltrombopag with lopinavir/ritonavir as a post-authorisation commitment.

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with hepatic impairment. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentration for this highly protein bound medicinal product were not measured. Therefore, eltrombopag should not be used in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) unless the expected benefit outweighs the identified risk of portal venous thrombosis.. Information on patients with moderate to severe hepatic impairment has been included in sections 4.2, 4.4 and 5.2 of the SPC.

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis. This information has been included in sections 4.2 and 5.2 of the SPC.

Clinical efficacy

The primary evidence for the efficacy of eltrombopag comes from 3 double-blind, placebo-controlled studies (TRA100773A, TRA100773B, and RAISE, see Table 7). TRA 100773 consisted of two independent, sequentially conducted studies: the phase II dose-finding TRA 100773A study and the phase III TRA 100773B study, both with treatment periods for up to 6 weeks. RAISE was phase III study of 6 months treatment duration.

Additional efficacy data from 2 single-arm, open-label studies (REPEAT and EXTEND, see Table 7) are ongoing. The REPEAT study was designed to determine the efficacy and safety of eltrombopag following up to 3 intermittent treatment cycles of up to 6 weeks of eltrombopag administration. The EXTEND study was designed to determine the long-term safety and efficacy of eltrombopag in subject who has been previously participated in an eltrombopag study.

Table 7. Eltrombopag ITP Clinical Studies

Study	Phase	Study Design/ Primary Objective	Dosing and Administration	Randomised
Double-blind Studies				
TRA100773A	II	G, R, DB, PC Dose finding	PBO, 30mg, 50mg or 75mg qd for up to 6 weeks; No dose adjustments allowed	PBO: 29 Eltr: 89
TRA100773B	III	G, R, DB, PC Efficacy	PBO or 50mg qd for up to 6 weeks; Dose increase allowed after Day 21	PBO: 38 Eltr: 76
RAISE	III	G, R, DB, PC Efficacy	PBO or 50mg qd for up to 6 months; Dose adjustments allowed	PBO: 62 Eltr: 135
Open-label Studies				
REPEAT	II	G, OL Repeat treatment	50mg qd for up to 6 weeks for 3 cycles; Dose increase allowed	Eltr: 66
EXTEND	III	G, OL Safety	50mg qd; Dose adjustments allowed	Eltr: 207 (ongoing)

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

- Dose response study

TRA100773A Study
The first part of study TRA100773 (TRA100773A) was a double-blind, randomized, placebo-controlled, parallel group study comparing 30, 50 and 75 mg and placebo as oral tablets once-daily for 6 weeks to adult male and female subjects with chronic immune thrombocytopenic purpura. This phase II/III investigated the efficacy of eltrombopag as short-term therapy (six weeks) for patients with chronic ITP. The study was expected to determine an optimal dose (part A), whose efficacy and safety in the short-term treatment of patients with ITP were to be established in part B.

Dose levels to be tested were chosen based upon the results obtained in previous PD and PK studies. Dose dependent increases in platelet counts, of at least 1.3-fold above baseline, were observed in healthy male subjects who received 20, 30, 50 and 75mg once-daily for 10 days. In addition, there was an acceptable safety and tolerability of repeat oral doses of up to 75mg eltrombopag once-daily for 10 days in healthy male subjects.

Patients with chronic ITP that had failed at least one previous therapy were included. As an inclusion criterion, a baseline platelet count below 30,000/μL was required. Both splenectomised and non-splenectomised patients were allowed to enter the study.

Stratification was done by use of ITP medication at randomization, splenectomy status and baseline platelet count ≤15,000/μL. The treatment phase included a daily dose of randomised medication for up to 6 weeks. Subjects who achieved a platelet count >200,000/μL discontinued treatment with study medication. Platelet counts were scheduled every week during the on-therapy period, and after 2, 4 and 6 weeks post therapy.

The primary endpoint was the proportion of responders at day 43 (week 6 visit). Responders were defined as subjects whose platelet count reached ≥ 50,000/μL at the day 43 visit from a baseline count of <30,000/μL. Patients were also classified as responders if they achieved a platelet count of >200,000/μL prior to day 43. The final on-treatment value was carried forward for such patients for Intent-to-Treat (ITT) analyses. Patients were classified as non-responders if they discontinued study medication prior to the day 43 visit for any other reason, irrespective of their last on treatment platelet count. The baseline score was carried forward for these patients in ITT analyses. The proportion of responders was compared between treatments using a logistic regression model adjusted by the stratification factors used in the randomisation.

The primary analysis was conducted on the efficacy population (subjects randomized and treated with at least one dose of study medication and with a baseline platelet count of <30,000/μL).

Additional supportive analyses were performed using the ITT Population (all randomized subjects who received at least one dose of study medication and had at least one platelet count post-dosing) and the Per-Protocol (PP) Population, which excluded major protocol violators.

Two interim analyses were scheduled. The first analysis was to be done when on-therapy platelet count data were available for approximately one-third (~90) of subjects and the second interim analysis when data were available from two-thirds (~180) of the subjects. At each interim analysis, a dose could be stopped for either efficacy using a step-down procedure or for futility using a step-up procedure or for safety concerns. The critical value for stopping the study early for efficacy was $p \leq 0.0113$ (1-sided) for the first interim and would have been $p \leq 0.0112$ (1-sided) for the second interim. The final analysis was to be conducted using $p \leq 0.0147$ as the critical value. In order to protect the overall Type I error at 2.5% (1-sided), a closed testing procedure was applied.

Patients' baseline characteristics were properly balanced between groups (considering the relatively small sample size).

The study was stopped at the first interim analysis. The primary efficacy endpoint showed that there was a dose-dependent effect as assessed by the rate of responders (27.6%, 70.4% and 80.8% in the groups of treatment 30 mg, 50 mg, and 75 mg respectively) being the results of the 2 higher doses statistically significantly different from placebo ($p<0.001$) (see results in Table 8 and Figure 1).

The logistic regression analysis (primary analysis defined in the protocol) showed a consistent effect regardless the population considered. An interaction between treatment and background therapy and baseline platelet count was found, especially for the 50 mg dose.

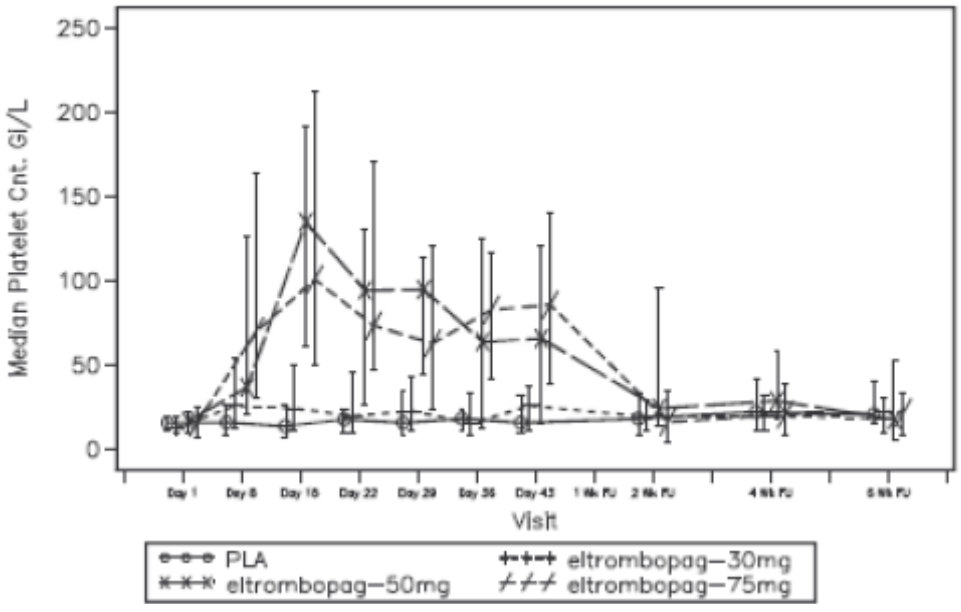
Table 8. Analysis of Responders (Efficacy Population)

	Treatment Group		
	30mg N=29	50mg N=27	75mg N=26
Odds ratio[a]	3.09	21.96	38.82
95% CI	(0.69,13.75)	(4.72,102.23)	(7.62,197.73)
p-value (one-sided)	0.070	<0.001	<0.001

Data Source: Table 7.4

a. An odds ratio >1 indicates a greater odds of responding in the eltrombopag-treated group relative to PBO.

Figure 1. Median Platelet Counts (Efficacy Population, Observed Dataset)



In a post-hoc analysis the durability of the response was assessed. The number of patients who showed a sustained response during >4 weeks was 10%, 27% and 18 % in the groups of treatment 30 mg, 50 mg, and 75 mg respectively. Due to the small sample size and the nature of the analysis these results should be interpreted with caution.

In conclusion, study TRA100773A showed a dose dependent increase in the number of patients whose platelet counts increased form a pre-dosing level of <30,000/µL to >50,000/µL/ (primary endpoint) over the six weeks duration of the study. This effect was supported by the analysis of secondary endpoints (mean platelet count, bleeding events). On the basis of these results the Applicant selected 50 mg/d as the starting dose for phase III studies.

- Main studies

TRA100773B
A double-blind, randomized, placebo-controlled, parallel group study to investigate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of eltrombopag-GR, a thrombopoietin receptor agonist, administered at 30, 50 and 75 mg as oral tablets once-daily for 6 weeks to adult male and female subjects with refractory, chronic immune thrombocytopenic purpura.

METHODS

Study Participants

Sixty-three study centres were located in a total of 23 countries in North America, Europe, Asia, Africa, South America and Australia.

Inclusion Criteria
Subjects were required to meet all the following inclusion criteria:
1. were diagnosed with chronic ITP at least 6 months prior to screening, and had a platelet count of <30,000/μL on Day 1 (or within 24 hours [h] prior to dosing on Day 1);
2. were previously treated subjects who had either not responded to 1 or more prior therapies, or who had relapsed within 3 months of prior therapy. Previous therapy with immunoglobulins, immunomodulators and cyclophosphamide must have been completed at least 2 weeks prior to randomization;
3. were allowed to receive ITP medications (corticosteroids, azathioprine, danazol, cyclosporin A or mycophenolate mofetil) during the study, provided the dose had been stable for at least 1 month;
4. had a normal prothrombin time (PT/INR) and activated partial thromboplastin time (aPTT), and no history of clotting disorder, other than ITP;
5. had a complete blood count (CBC), reticulocyte count, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin and alkaline phosphatase (AP) within the reference range, with the following exceptions:
• platelet count <30,000/μL was required;
• hemoglobin ≥10.0g/dL were eligible for inclusion;
• total neutrophils (ANC) ≥1500/μL (1.5 x 109/L) was required (elevated white blood cell [WBC]/ANC due to steroid treatment was acceptable);
6. were practicing an acceptable method of contraception, or female subjects (or female partners of male subjects) who were of non-childbearing potential;
7. were ≥18 years old;
8. had signed and dated written informed consent; and
9. were able to understand and comply with protocol requirements and instructions and intended to complete the study as planned.

Exclusion criteria
A subject was excluded from the study if the subject:
1. had any clinically relevant abnormality, other than ITP, or any other medical condition or circumstance, which in the opinion of the Investigator, made the subject unsuitable for participation in the study;
2. had a history of thrombosis within the last year;
3. had pre-existing cardiac disease, myocardial infarction in the last 3 months, or clinically significant findings on resting 12-lead electrocardiogram (ECG) at screening;
4. was nursing or pregnant at screening or pre-dose on Day 1;
5. had a history of alcohol/drug abuse or dependence within 12 months of the study;
6. was treated with an investigational drug within 30 days or five half-lives (whichever is longer) preceding the first dose of study medication;
7. had consumed aspirin, aspirin-containing compounds, salicylates, anti-coagulants, quinine or non-steroidal anti-inflammatories (NSAIDs) for >3 consecutive days within 2 weeks of the study start and until the end of the study;
8. had consumed liquid antacids, chewable antacids or calcium supplements within 48h of the first dose of study medication, and/or required these medications during the
6-week dosing period;
9. had consumed any herbal or dietary supplements, excluding vitamin or mineral supplements, within 1 week of the study start or consumed rosuvastatin or pravastatin within 1 week of the first dose of study medication and/or required these medications during the 6-week dosing period;
10. had a history of platelet aggregation that prevented reliable measurement of platelet counts; or
11. had any laboratory or clinical evidence for human immunodeficiency virus (HIV) infection, any clinical history or laboratory evidence for hepatitis C infection, any clinical history or laboratory

evidence for chronic hepatitis B infection, or any evidence for active hepatitis at the time of subject screening.
12. previous participation in a clinical study with eltrombopag.

Treatments
The doses for this study were eltrombopag 50mg or matching placebo once daily for up to 6 weeks. Subjects with platelet counts <50,000/μL on Day ≥22 may have had their dose increased to eltrombopag 75mg (or matching placebo). Subjects reaching a platelet count above 200,000/μL were withdrawn from the study medication, but continued to attend follow-up visits.

Subjects were permitted to use stable, maintenance ITP medications (corticosteroids, azathioprine, danazol, cyclosporin A and mycophenolate mofetil) during the treatment period of the trial. Dose and duration of treatment were recorded during the on-therapy and follow-up periods. If the dose of concomitant maintenance ITP medication was modified, the subject was to be withdrawn from study medication.

Objectives
The primary objective of the study was to determine the efficacy of eltrombopag as a thrombopoietic agent, when administered once daily for up to 6 weeks to previously treated adult subjects with chronic ITP.

Secondary objectives of the study were:
• To assess the safety and tolerability of eltrombopag when administered once daily for up to 6 weeks to previously treated adult subjects with chronic ITP;
• To characterize the population pharmacokinetic profile of oral eltrombopag using a serial pharmacokinetic sampling strategy when administered once daily for up to 6 weeks to previously treated adult subjects with chronic ITP;
• To assess the impact of eltrombopag on the incidence and severity of symptoms of thrombocytopenia when administered once daily for up to 6 weeks to previously treated adult subjects with chronic ITP; and
• To assess the impact of eltrombopag on the health-related quality of life when administered once daily for up to 6 weeks to previously treated adult subjects with chronic ITP.

Outcomes/endpoints
The primary efficacy endpoint was a shift from a baseline platelet count of <30,000/μL to ≥50,000/μL after up to 42 days of dosing with study medication. The primary analysis of this endpoint was performed on a dataset which classified subjects as either responders or non-responders (primary dataset).

Criteria to determine response in the primary dataset:
- Subjects were classified as responders if they achieved a platelet count of ≥50,000/μL at the Day 43 Visit;
- Subjects were also classified as responders if they responded strongly with a platelet count >200,000/μL and discontinued study medication prior to Day 43; their last on treatment platelet count was used to determine response; and
- Subjects were classified as non-responders if they discontinued treatment with study medication prior to the Day 43 Visit for any other reason, irrespective of their last on treatment platelet count.

Other secondary endpoints include:
• Platelet counts;
• Proportion of subjects responding to treatment during Weeks 2 to 6 of the study
• Proportion of subjects with platelet counts ≥50,000/μL and at least twice their baseline
• Incidence and severity of symptoms associated with chronic ITP, including bleeding, bruising, and petechiae, were measured using the WHO Bleeding Scale and the ITP Bleeding Score; and
• Physical and mental health status using the Short Form-36, version 2 (SF-36v2) health-related quality of life (HR-QoL) tool and Patient Preference Assessment.

Sample size
The sample size was calculated to compare the differences between eltrombopag 50mg versus placebo in the proportion of responders 42 days after initiation of dosing (Day 43 measurement). Assuming 25% and 60% responses on placebo and eltrombopag 50mg, respectively, 87 evaluable subjects (58 on eltrombopag, 29 on placebo) were needed in order to provide 90% power at the 5% level of significance (two-sided). However, in order to provide additional safety data, 66 subjects were to be recruited to the eltrombopag treatment group and 33 subjects to the placebo treatment group.

Randomisation
Subjects were randomized to treatment (eltrombopag 50mg or placebo) in a 2:1 ratio. Randomization was stratified based upon use or non-use of ITP medications at randomization, splenectomy status (refractory following splenectomy or non-splenectomised) and baseline platelet count (≤15,000/μL or >15,000/μL).

Blinding (masking)
This was a double-blind study and treatment allocation was blinded to the subjects, the site staff and sponsor personnel. Treatment blinding was maintained by use of matching placebo tablets.

Statistical methods

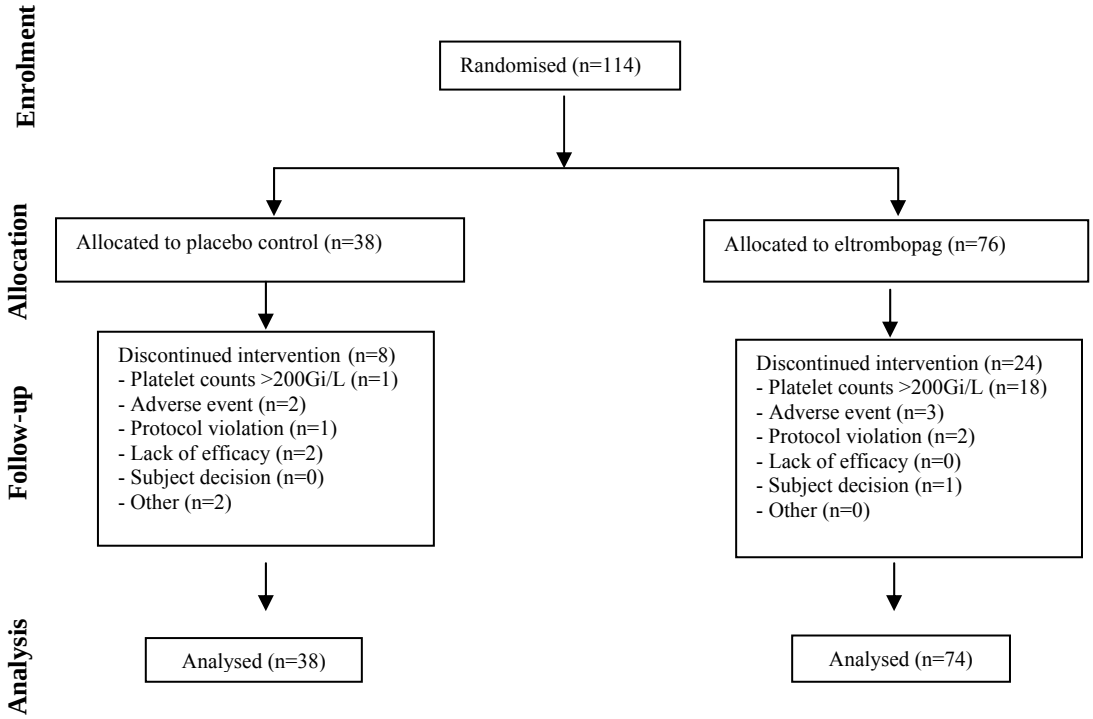
All programming was performed using SAS version 8, or a later release, in a UNIX environment. All confidence intervals were calculated at the 95% confidence levels. Any analyses requiring significance testing were performed using a two-sided test at the 0.05 significance level, unless otherwise specified.
The proportion of responders was compared between treatments using a logistic regression model adjusted for ITP medication use at randomization, splenectomy status and baseline platelet count.

Summary statistics for the primary endpoint were presented for each stratum. Similar summaries for other subgroups, such as gender, race and age, were also provided. The level of significance for interactions was set to 10%. If a significant treatment by strata interaction was seen in the primary endpoint, then the primary efficacy analysis table was produced for each level of the strata. Inference was only made for the primary and secondary endpoints above should the interaction be statistically significant and considered to be clinically relevant.

There were no requirements for multiplicity adjustments in this study. The overall type I error rate is 0.05 (two-sided).

RESULTS

Participant flow



Recruitment
The study was conducted between 6 Feb 2006 – 31 Jan 2007. After the dosing period subjects were assessed at 1, 2, 4 and 6 weeks to assess the durability of the platelet response and safety parameters. Subjects were also to complete an ocular examination 6 weeks and 6 months following the final dose of study medication.

Conduct of the study
There were 4 amendments to the protocol in study TRA100773, however only Amendment 4 pertained to Study TRA100773B. This amendment, dated 28 November 2005, addressed changes on dose selection and revised sample size based on the evaluation of interim data that led to termination of study TRA100773A (because of overwhelming efficacy). In addition it added: a secondary endpoint of "elevation of platelets to ≥50,000/μL and at least twice their baseline value", an additional logistic regression analysis of responders using a Generalized Estimating Equations (GEE) methodology, a follow-up visit at Day 50 and the ITP Bleeding Scale and Patient Preference assessments (as secondary efficacy endpoints).

Six subjects had one or more major protocol violations resulting in full data exclusion. These subjects (placebo: 1 subject; eltrombopag: 5 subjects) were excluded from the PP Population. Two subjects in the eltrombopag treatment group were excluded due to evidence that the subject's underlying condition was not ITP and that the platelet count was ≥30,000/μL at Day 1 or within 24h prior to dosing on Day 1.

Baseline data
The summary of the demographic characteristics in the ITT Population is shown in Table 9.

Table 9: Summary of Demographic Characteristics (ITT Population)

Demographic Characteristic	Treatment Group		
	PBO N=38	Eltrombopag N=76	Total N=114
Age, yrs			
Median	51.0	47.0	48.0
Min – Max	21-79	19-84	19-84
Sex, n (%)			
Female	27 (71)	43 (57)	70 (61)
Male	11 (29)	33 (43)	44 (39)
Race, n (%)			
African American/African	0	1 (1)	1 (<1)
American Indian/Alaskan Native	2 (5)	4 (5)	6 (5)
Asian - East Asian	1 (3)	0	1 (<1)
Asian - South-East Asian	3 (8)[a]	7 (9)[a]	10 (9)[a]
Asian – Central/South Asian	4 (11)	5 (7)	9 (8)
White - Arabic/North African	3 (8)	5 (7)	8 (7)
White - White/ Caucasian/European	23 (61)	53 (70)	76 (67)
Mixed Race	2 (5)	1 (1)	3 (3)
Ethnicity, n (%)			
Hispanic or Latino	6 (16)	10 (13)	16 (14)
Not Hispanic or Latino	32 (84)	66 (87)	98 (86)

Approximately half of the subjects in the placebo and eltrombopag groups (50% and 47%, respectively) were receiving ITP medication at randomization. Similar percentages of subjects (34% and 37%, respectively) had a prior splenectomy and baseline platelet counts of ≤15 ,000/μL (48% and 50%, respectively).

All subjects in both treatment groups had ≥1 prior ITP therapy as determined by clinical review (see Table 10). Approximately 50% of subjects had received at least 3 prior treatments. A higher percentage of subjects in the eltrombopag treatment arm had ≥3 and ≥4 prior therapies compared to

placebo. Prior ITP medications used by subjects were similar across the 2 treatment groups. Corticosteroids were the most commonly reported prior ITP medication taken by approximately 75% of subjects in both treatment groups.

Table 10: Number of Prior ITP Therapies by Subject (Safety Population)

Number of Prior ITP Therapies[a]	Treatment Group, n (%)		Total
	PBO N=38	Eltrombopag N=76	N=114
No prior therapies	0	0	0
≥1 prior therapy	38 (100)	76 (100)	114 (100)
≥2 prior therapy	26 (68)	56 (74)	82 (72)
≥3 prior therapies	16 (42)	42 (55)	58 (51)
≥4 prior therapies	9 (24)	30 (39)	39 (34)
≥5 prior therapies	7 (18)	16 (21)	23 (20)

Numbers analysed

A total of 114 subjects were enrolled in the study, with 76 randomized to the eltrombopag treatment group, and 38 randomized to placebo.

The Efficacy Population was the primary population for efficacy analyses. Additional supportive analyses were performed using the ITT and the PP Populations, which excluded major protocol violators. All safety analyses were reported using the Safety Population. The numbers of subjects in each population are presented in Table 11.

Table 11. Populations analysed.

Population[a]	Number of Subjects in Treatment Group, N		
	PBO N=38	Eltrombopag N=76	Total N=114
Safety Population	38 (100)	76 (100)	114 (100)
ITT Population	38 (100)	76 (100)	114 (100)
Efficacy Population[b]	38 (100)	74 (97)	112 (98)
PP Population	37 (97)	71 (93)	108 (95)

Data Source: Table 6.1

a. Subjects may have been excluded from a population for more than 1 reason.

b. Reasons for exclusion from the Efficacy Population included: Both subjects in the Eltrombopag treatment group excluded from the Efficacy Population had platelet counts ≥30Gi/L on Day 1 or within 24 h prior to dosing on Day

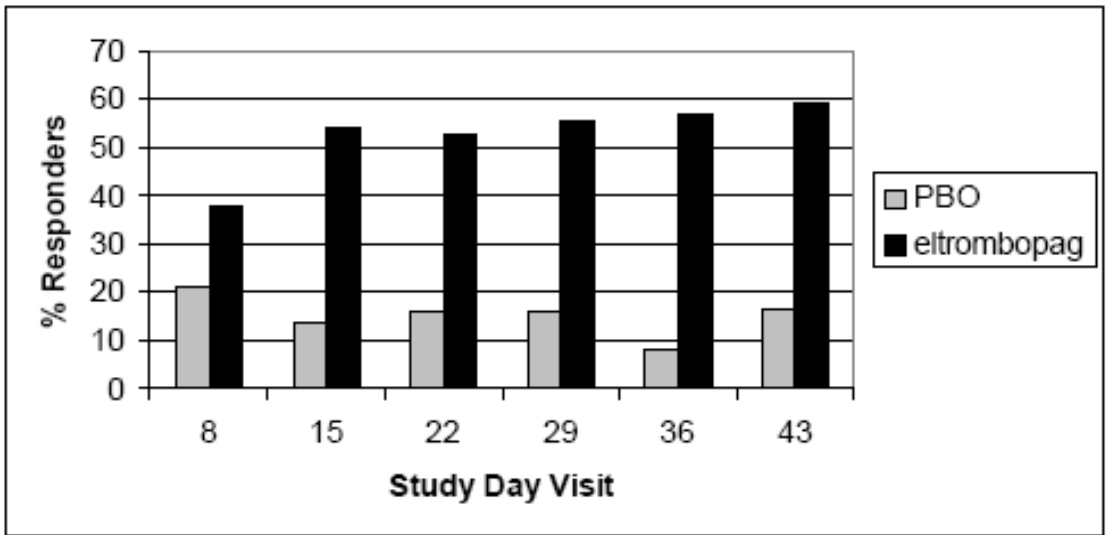
Outcomes and estimation

Primary endpoint: Responders at day 43 visit.

The analysis of the primary endpoint showed that the percentage of subjects with platelet counts ≥50,000/μL after up to 6 weeks of dosing was greater in the eltrombopag treated group compared to placebo. A total of 59% of subjects on eltrombopag attained a platelet count of ≥50,000/μL on Day 43, compared to 16% of subjects on placebo (Efficacy Population). The odds ratio for active/placebo treatment was 9.61 (95% CI 3.31-27.86) showing a statistically significant p-value (two-sided) <0.001.

At each visit, the percentage of responders was greater in the eltrombopag treatment group compared to the placebo treatment group (see Figure 2). Other thresholds included: Platelets >200,000/μL, placebo 1/37 (3%) vs. eltrombopag 18/73 (25%); and Platelets >400,000/μL, placebo 0/371 (0%) vs. eltrombopag 2/73 (3%).

Figure 2. Percentage of Responders by Visit (Efficacy Population)



This effect of eltrombopag relative to placebo was significant across all subgroups regardless of baseline platelet count, use of concomitant ITP medication or splenectomy status (see Table 12). This difference was observed in all study visits.

Table 12. Percentage of responders at day 43 by stratification factors

	Placebo	**50mg**
Use of ITP medication at randomisation		
Yes	2/16 (13%)	17/31 (55%)
No	4/21 (19%)	26/42 (62%)
Splenectomy status		
Yes	2/13 (15%)	18/29 (62%)
No	4/24 (17%)	25/44 (57%)
Baseline platelet count ≤15,000/µL		
≤15,000/µL	2/16 (13%)	16/37 (43%)
>15,000/µL	4/21 (19%)	27/36 (75%)

A total of 35 out of 76 patients in the eltrombopag group were uptitrated to 75 mg after day 22, of whom 31% (11/35) were responders after having their doses increased (see Table 13).

Table 13. Summary of Number of Subjects Requiring a Dose Increase at Day 22 or Subsequent Visit

Visit		PLA (N=38)	497115-50mg (N=76)
Visit 4 (Day 22)	No. Subjects	32	56
	No. Requiring Dose Increase	22 (69%)	22 (39%)
Visit 5 (Day 29)	No. Subjects	32	53
	No. Requiring Dose Increase	4 (13%)	10 (19%)
Visit 6 (Day 36)	No. Subjects	30	52
	No. Requiring Dose Increase	2 (7%)	3 (6%)
Visit 7 (Day 43)	No. Subjects	26	44
	No. Requiring Dose Increase	0	0

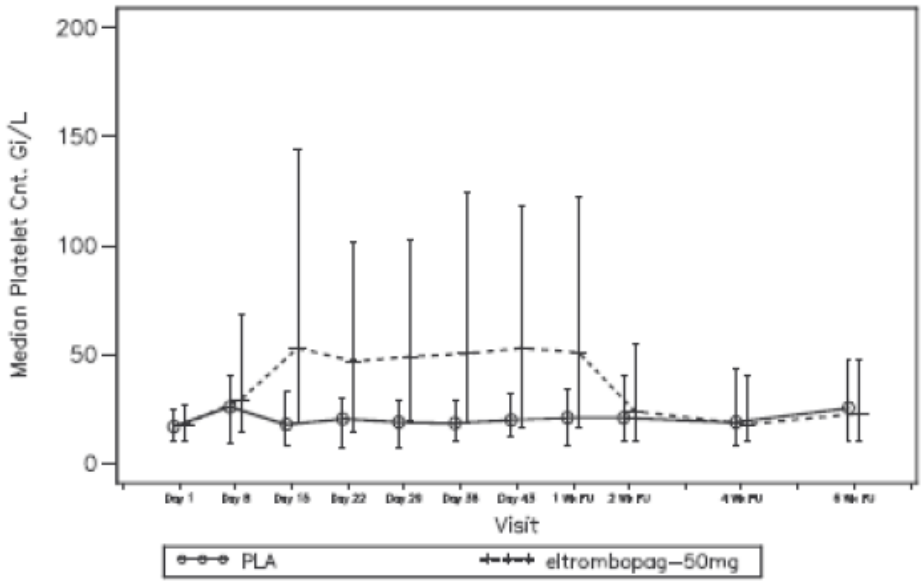
Analysis of responders at Day 43 for the PP Population also showed a statistically significant treatment effect for the eltrombopag treatment group (Odds ratio= 8.51 $p<0.001$), confirming the results obtained with the Efficacy Population.

Secondary efficacy results

- Platelet counts

Median platelet counts at nominal visits with 25th and 75th percentiles throughout the course of the trial are shown in Figure 3.

Figure 3: Median Platelet Counts (Gi/L) with 25th and 75th percentiles (Efficacy Population, Observed Dataset)



- Bleeding

Consistently with the increase in platelet count, an effect on bleeding rates was observed. A statistically significant decrease in any bleeding (WHO grades 1 to 4) at day 43 was observed in secondary analyses in subjects treated eltrombopag compared to placebo (OR=0.27, p=0.029) (see Table 14).

Table 14: Results WHO bleeding scale

	Placebo	**50mg**
Baseline		
No bleeding	12/35 (34%)	27/70 (39%)
Bleeding	23/35 (66%)	43/70 (61%)
Day 43		
No bleeding	12/30 (40%)	31/51 (61%)
Bleeding	18/30 (60%)	20/51 (39%)

Secondary analyses based on updated results showed similar trend with 25/38 (66%) bleedings in placebo treated subjects compared to 30/76 (39%) in eltrombopag treated subjects (ITT population, WHO bleedings grade 1-4 at Day 43). The odds of bleeding were observed to remain significantly lower (p=0.010) in the eltrombopag treated group with an Odds Ratio (95% CI) of 0.30 (0.12, 0.75). Moreover, 11/38 (29%) of placebo treated subjects compared to 12/76 (16%) of the eltrombopag treated subjects had a WHO bleeding grade 2-4 at Day 43. The odds of bleeding was lower in the eltrombopag treated group with an Odds Ratio (95% CI) of 0.46 (0.18, 1.19) and p=0.111

In the group of patients treated with 75 mg a similar percentage of subjects with WHO bleeding scales grades 1 to 4 in placebo (86%) and eltrombopag (83%) group were observed.

In the eltrombopag arm, baseline WHO bleeding scale score grades 0 (43.7%), grades 1 (35.2%), grades 2 (16.9%) and grades 3 (4.2%) changed to grades 0 (60.8%), grades 1 (29.4%) grades 2 (9.8%) in week 6 on treatment, showing that changes mostly affected the lowest grades (0 through 1) and largely by a transition from "petechaie" (grade1) to the absence of petechaie (grade 0).

- Odds of Responding to Treatment during Weeks 2-6

At any point during the 6 week treatment period, subjects in the eltrombopag treatment group had a greater odd of responding than subjects in the placebo treatment group (OR=8.79; CI=3.54, 21.86; $p<0.001$)

- Response in Platelet Count to 50,000/μL or More and at Least 2x Baseline

Logistic regression analysis of the percentage of subjects with a Day 43 platelet count ≥50,000/μL and at least 2x baseline using the primary dataset for the Efficacy Population showed a statistically significant treatment effect of eltrombopag compared to placebo ($p<0.001$).

Study TRA102537 (RAISE)
A randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy, safety and tolerability of eltrombopag olamine, a thrombopoietin receptor agonist, administered for 6 months as oral tablets once daily in adult subjects with previously treated chronic idiopathic thrombocytopenic purpura (ITP).

METHODS

Study Participants

Study sites were located in a total of 23 countries from the following continents/countries: North America (16 Sites), South America (2 Sites), Europe (44 Sites), Africa (1 Site), Asia (8 Sites), and New Zealand (4 Sites).

Inclusion criteria
A subject was eligible for inclusion in this study only if all of the following criteria applied:
1. Subject signed and dated a written informed consent.
2. Adults (≥18 years) diagnosed with chronic ITP according to the ASH/BCSH guidelines, and platelet count <30,000/μL on Day 1 (or within 24 hours prior to dosing on Day 1). In addition, a peripheral blood smear should support the diagnosis of ITP with no evidence of other causes of thrombocytopenia (e.g. pseudothrombocytopenia, myelofibrosis). The physical examination should not suggest any disease which may cause thrombocytopenia other than ITP.
3. Subjects who previously received one or more prior ITP therapies. Previous treatments for ITP included but were not limited to corticosteroids, immunoglobulins, azathioprine, danazol, cyclophosphamide and/or rituximab.
4. Subjects must have had either initially responded (platelet count >100,000/μL) to a previous ITP therapy or have had a bone marrow examination consistent with ITP within 3 years to rule out myelodysplastic syndromes or other causes of thrombocytopenia.
5. Previous therapy for ITP with immunoglobulins (IVIg and anti-D) must have been completed at least 1 week prior to randomization and the platelet count must show a clear downward trend after the last treatment with immunoglobulins. Previous treatment for ITP with splenectomy, rituximab and cyclophosphamide must have been completed at least 4 weeks prior to randomization, or clearly be ineffective.
6. Subjects treated with concomitant ITP medication (e.g. corticosteroids or azathioprine) must have been receiving a dose that was stable for at least 4 weeks prior to randomization. Subjects treated with cyclosporine A, mycophenolate mofetil or danazol must have been receiving a dose that was stable for at least 3 months prior to randomization. The medication should have been continued with a stable dose for the initial 6 weeks of study.

7. Prothrombin time/International Normalized Ratio (PT/INR) and activated partial thromboplastin time (aPTT) must have been within 80 to 120% of the normal range with no history of hypercoagulable state.
8. A complete blood count (CBC), within the reference range (including white blood count (WBC) differential not indicative of a disorder other than ITP), with the following exceptions:
• <30,000/μL on Day 1 (or within 24 hours of Day 1) was required for inclusion,
• Hemoglobin: Subjects with hemoglobin levels between 10 g/dL (100 g/L) and the lower limit of normal were eligible for inclusion, if anaemia was clearly attributable to ITP (excessive blood loss).
• Absolute neutrophil count (ANC) ≥1500/μL (1.5 x 109/L) was required for inclusion (elevated WBC/ANC due to corticosteroid treatment is acceptable).
9. The following clinical chemistries must not have exceeded the upper limit of normal (ULN) reference range by more than 20%: creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase. In addition, total albumin must not have been below the lower limit of normal (LLN) by more than 10%.
10. Subject was practicing an acceptable method of contraception (documented in chart). Female subjects (or female partners of male subjects) must have either been of non childbearing potential (hysterectomy, bilateral oopherectomy, bilateral tubal ligation or post-menopausal >1 year), or of childbearing potential and using one of the following highly effective methods of contraception (i.e., Pearl Index <1.0%) from two weeks prior to administration of study medication, throughout the study, and 28 days after completion or premature discontinuation from the study:
• Complete abstinence from intercourse;
• Intrauterine device;
• Two forms of barrier contraception (diaphragm plus spermicide, and for males condom plus spermicide);
• Male partner was sterile prior to entry into the study and is the only partner of the female;
• Systemic contraceptives (combined or progesterone only).
11. Subject was able to understand and comply with protocol requirements and instructions and intended to complete the study as planned.

Exclusion criteria
A subject was not eligible for inclusion in this study if any of the following criteria applied:
1. Any clinically relevant abnormality, other than ITP, identified on the screening examination or any other medical condition or circumstance, which in the opinion of the investigator made the subject unsuitable for participation in the study or suggested another primary diagnosis (e.g., thrombocytopenia secondary to another disease).
2. Concurrent malignant disease and/or history of cancer treatment with cytotoxic chemotherapy and/or radiotherapy.
3. Any prior history of arterial or venous thrombosis (stroke, transient ischemic attack, myocardial infarction, deep vein thrombosis or pulmonary embolism), AND ≥ 2 of the following risk factors: hormone replacement therapy, systemic contraception (containing estrogen), smoking, diabetes, hypercholesterolemia, medication for hypertension, cancer, hereditary thrombophilic disorders (e.g., Factor V Leiden, antithrombin III deficiency, etc), or any other family history of arterial or venous thrombosis.
4. Pre-existing cardiovascular disease (congestive heart failure, New York Heart Association Grade III/IV), or arrhythmia known to increase the risk of thromboembolic events (e.g. atrial fibrillation), or subjects with a QTc >450 msec.
5. Female subjects who were nursing or pregnant (positive serum or urine β-human chorionic gonadotrophin pregnancy test) at screening or pre-dose on Day 1.
6. History of alcohol/drug abuse.
7. Treatment with an investigational drug within 30 days or five half-lives (whichever was longer) preceding the first dose of study medication.
8. Subject treated with drugs that affect platelet function (including but not limited to aspirin, clopidogrel and/or NSAIDs) or anti-coagulants for > 3 consecutive days within 2 weeks of the study start and until the end of the study.
9. History of platelet agglutination abnormality that prevents reliable measurement of platelet counts.
10. All subjects with secondary immune thrombocytopenia, including those with laboratory or clinical evidence of HIV infection, anti-phospholipid antibody syndrome, chronic hepatitis B

infection, hepatitis C virus infection, or any evidence for active hepatitis at the time of subject screening. If a potential subject had no clinical history that would support HIV infection or hepatitis infection, no further laboratory screening was necessary; however, standard medical practice would suggest further evaluation of subjects who had risk factors for these infections.
11. Previous participation in a clinical study with eltrombopag.
12. Subjects planning to have cataract surgery.
13. In France, a subject was neither affiliated with nor a beneficiary of a social security category.

Treatments

The starting dose was either eltrombopag 50 mg or matching placebo once daily. Throughout the six month treatment period, the dose of the study medication could be up- (75 mg/d) or down- (25 mg/d titrated according to platelet count monitoring). Subjects were allowed a dose increase on or after day 22 if a subject's platelet count did not rise above 50,000/µL for two successive platelet count assessments. The subjects were to reduce their dose of eltrombopag when platelet count exceeded of 200,000 /µL. When platelet counts reached 400,000/µL study medication was interrupted for at least 7 days, until platelet counts fell below 150,000/µL. At that point subjects were re-administrated at next lower dose.

Objectives

Primary objective
To determine the efficacy of eltrombopag as a thrombopoietic agent, when administered once daily for 6 months (RAISE) to previously treated adult subjects with chronic ITP.
Secondary objectives
Secondary objectives of the study were:
• To assess the safety and tolerability of eltrombopag when administered once daily for 6 months to previously treated adult subjects with chronic ITP;
• To assess the impact of eltrombopag on the incidence and severity of symptoms of thrombocytopenia when administered once daily for 6 months to previously treated adult subjects with chronic ITP;
• To assess the impact of eltrombopag on the health-related quality of life when administered once daily for 6 months to previously treated adult subjects with chronic ITP;
• To assess the ability of eltrombopag to prevent the use of rescue treatment (rescue treatment was defined as a composite of: new ITP medication, increased dose of concomitant ITP medication from baseline, platelet transfusion and splenectomy);
• To describe the pharmacodynamics and durability of eltrombopag response (maintenance of an elevated blood platelet count);
• To determine the efficacy of oral eltrombopag, when administered once daily, for 6 weeks duration, to previously treated adult subjects with chronic ITP;
• To describe the effect of eltrombopag on reduction of concomitant ITP medications from baseline.

Outcomes/endpoints

The primary endpoint was the odds of achieving a platelet count ≥50,000/µL and ≤400,000/µL during the 6-month treatment period, for subjects receiving eltrombopag relative to placebo.

Secondary efficacy endpoints included:
• Proportion of subjects receiving a rescue treatment (rescue treatment was defined as a composite of: new ITP medication, increased dose of a concomitant ITP medication from baseline, platelet transfusion, and/or splenectomy) during the 6 month duration of the study.
• Proportion of subjects for whom at least 75% of their assessments were ≥50,000/µL and ≤400,000/µL.
• Maximum duration of response (≥50,000/µL and ≤400,000/µL) for each subject.
• Proportion of subjects achieving a platelet count of ≥50,000/µL and ≤400,000/µL during weeks 2-6 of study treatment.
• Proportion of subjects with a reduction in use of concomitant ITP medications from baseline.

• Incidence and severity of symptoms associated with chronic ITP, including bleeding, bruising, and petechiae, were measured using the WHO Bleeding Scale and the ITP Bleeding Score; and
• Physical and mental health status using the Short Form-36, version 2 (SF-36v2) health-related quality of life (HR-QoL) tool and Patient Preference Assessment.

Sample size

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

Randomisation

Subjects were randomized 2:1, eltrombopag to placebo, and were stratified based upon splenectomy status, baseline use or non-use of ITP medication and baseline platelet count ≤15,000/μL or greater than 15,000/μL.

Blinding (masking)

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

Statistical methods

The subject response profiles during the 6-month treatment period were compared between treatments using a repeated measures model for binary data adjusted for the randomization stratification variables. Generalized estimating equations (GEE) methodology was used to estimate the regression model parameters with the correlation of an individual subject's responder status between visits being modelled as exchangeable (i.e. assuming the correlation between any 2 measures for a subject is the same).

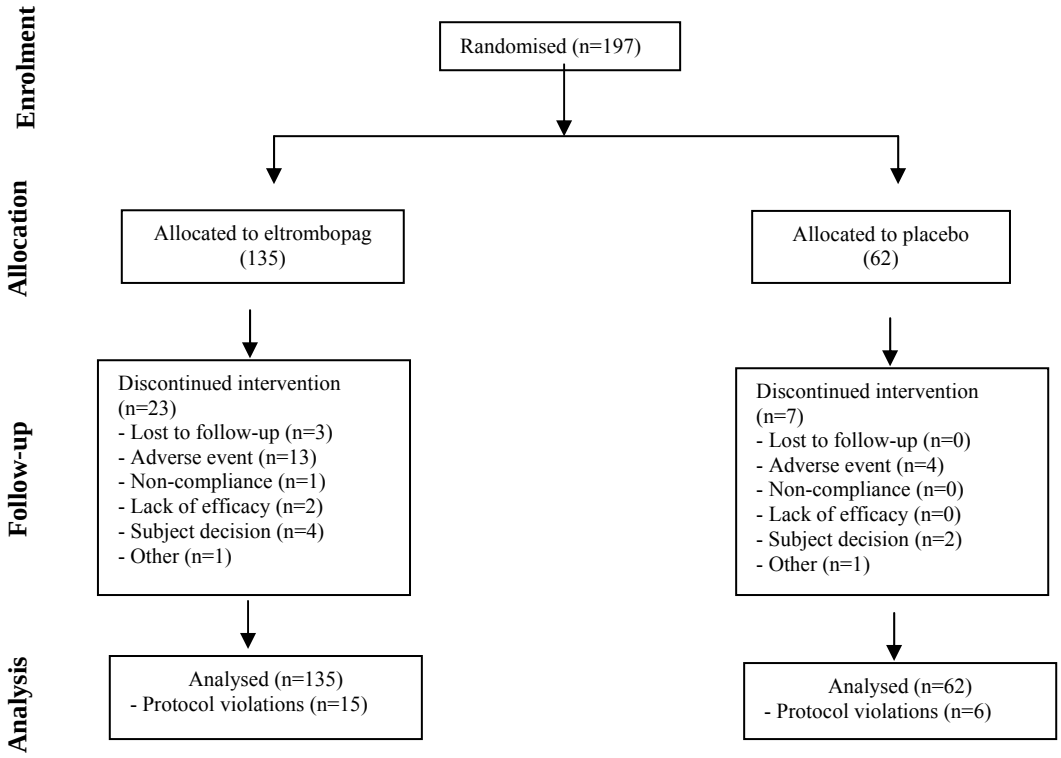
All analyses were performed using Statistical Analysis Software (SAS) version 8 or a later release, in a UNIX environment. Significance testing was two-sided at the 1% level of significance for the primary endpoint, and unless stated otherwise, significance testing was two-sided at the 5% level of significance for all other comparisons. Unless otherwise stated, 95% confidence intervals (CI) around the odds ratios or treatment differences, as appropriate were presented.

There were no requirements for multiplicity adjustments in this study. The overall Type I error rate was 0.01 (two-sided) for the primary efficacy analysis and, unless otherwise indicated, 0.05 (two-sided) for all secondary and exploratory analyses.

Populations for main analysis:
Intent-to-Treat Population: The intent-to-treat (ITT) population was the primary population for analysis and was comprised of all randomized subjects.
Per-Protocol Population: The per-protocol (PP) population was defined as per the Intent-to-Treat population but excluded major protocol violators. Additional analysis based on this population was performed for the primary efficacy endpoint and the main secondary endpoints only.
Safety Population: The safety population was comprised of all randomized subjects who had received at least one dose of the study treatment. All safety parameters were reported using the safety population, all subjects being analyzed under the treatment group to which they were randomized.

RESULTS

Participant flow



Recruitment

The study period was 22 November 2006 – 10 June 2008. As of 27 February 2008, all subjects completed the on therapy and 4-week follow-up visits of the off-therapy period. All data, including data obtained at the 3- and 6-month post-therapy visits, are reported through 10 June 2008, the date of database freeze and unblinding of treatment codes.

Conduct of the study

There were 4 amendments to the protocol. For each amendment, key revisions impacting the study are summarized below.
Amendment 01 and 02 –country specific amendments for France to modify lifestyle and/or dietary restrictions wording to meet agency restrictions for more stringent eye and skin protection precautions.
Amendment 03 - included modification of eligibility criteria to add clarity based on regulatory feedback and the addition of liver chemistry stopping criteria, platelet count assessments after treatment interruption, modification of lifestyle wording concerning precautions to direct sunlight and/or UV exposure for all sites, and a revision to the prohibited medications.
Amendment 04 –included additions of enhanced monitoring for the potential presence of renal toxicity and incorporated study population regulatory requirements for Tunisian subjects.

Baseline data
The summary of the demographic characteristics in the ITT Population is shown in Table 15.

Table 15: Summary of Demographic Characteristics (ITT Population)

Demographic Characteristic	Treatment Group	
	PBO N=62	Eltrombopag N=135
Age, yrs		
Median (Min – Max)	52.5 (18 – 77)	47.0 (18 – 85)
Sex, n (%)		
Female	43 (69)	93 (69)
Male	19 (31)	42 (31)
Race, n (%)		
African American/African	1 (2)	2 (1)
American Indian/Alaska Native	4 (6)	8 (6)
East Asian	10 (16)	19 (14)
South-East Asian	3 (5)	2 (1)
Native Hawaiian or other Pacific Islander	0	1 (<1)
White/Arabic/North African	2 (3)	6 (4)
White/ Caucasian/European	42 (68)	95 (70)
Mixed Race	0	2 (1)
Ethnicity, n (%)		
Hispanic or Latino	6 (10)	13 (10)
Not Hispanic or Latino	56 (90)	122 (90)

Approximately half of the subjects in the placebo and eltrombopag groups (50% and 47%, respectively) were receiving ITP medication at randomization. Similar percentages of subjects (34% and 37%, respectively) had a prior splenectomy and baseline platelet counts of ≤15,000/µL (48% and 50%, respectively). All subjects in both treatment groups had ≥1 prior ITP therapy (including splenectomy) as determined by clinical review (see Table 16). Eighty-one percent of placebo-treated subjects and 78% of eltrombopag-treated subjects received at least 2 prior therapies, and more than 30% of subjects in each group received ≥4 prior therapies.

Table 16. Number of Prior ITP Therapies by Subject (Safety Population)

Number of Prior ITP Therapies[a]	Treatment Group, n (%)	
	PBO N=62	Eltrombopag N=135
≥1 prior therapy	62 (100)	135 (100)
≥2 prior therapy	50 (81)	105 (78)
≥3 prior therapies	32 (52)	75 (56)
≥4 prior therapies	20 (32)	51 (38)
≥5 prior therapies	11 (18)	35 (26)

Numbers analysed

A total of 197 subjects were enrolled in the study, with 135 subjects randomized to the eltrombopag treatment group, and 62 subjects randomized to placebo.

The numbers of subjects in each population are presented in Table 17.

Table 17: Subject Disposition.

Disposition Category	Number of Subjects, n (%)[a]	
	PBO	Eltrombopag
All randomized subjects	62 (100)	135 (100)
Safety Population	61 (98)	135 (100)
ITT Population	62 (100)	135 (100)
PP Population	56 (90)	120 (89)
Completed[b]	55 (89)	112 (83)
Discontinued prematurely from the study	7 (11)	23 (17)

Outcomes and estimation

Primary Endpoint

The effect of eltrombopag on platelet is shown in Table 18. The odds of responding over the 6 months treatment period were greater and significantly different between eltrombopag-treated subjects and placebo-treated subjects ($p<0.001$). Fifty-four percent of the eltrombopag-treated patients and 13 % of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52 % and 16 % of patients responding at the end of the 6-month treatment period. This response was observed regardless of splenectomy status, baseline platelet count and use of baseline ITP medications.

Table 18. Analysis of Responders–Primary Dataset Generalized Estimating Equations (ITT Population)

	Responders
Odds ratio (OR) for eltrombopag/PBO treatments[a]	8.2
99% CI	3.59, 18.73
p-value (two-sided vs. PBO)	<0.001[b]

A sensitivity analysis using the generalized linear mixed model (GLMM) was consistent with these results.

The table below (Table 19) presents the number and percentage of evaluable subjects who achieved a platelet response between 50-400,000/μL at each nominal on-therapy visit.

Table 19: Summary of Responders (ITT Population)

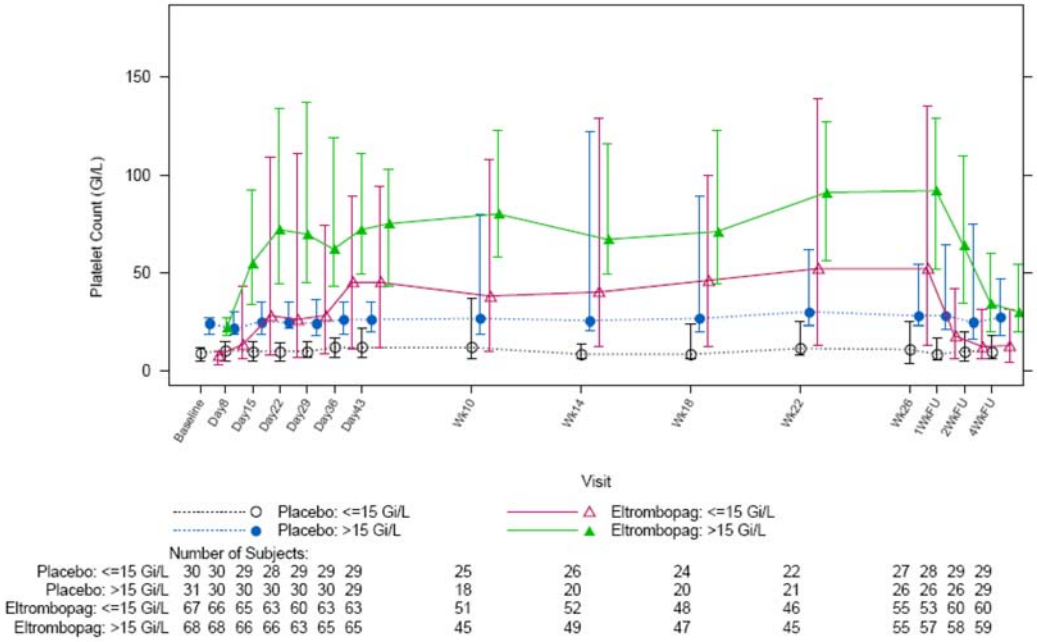
Timing of Assessment	Treatment Group			
	PBO N=62		Eltrombopag N=135	
	Evaluable N	Responders, n (%)	Evaluable N	Responders, n (%)
Baseline[a]	61	1[b] (2)	135	1[b] (1)
Day 8	60	4 (7)	134	50 (37)
Day 15	60	5 (8)	133	61 (46)
Day 22	59	5 (8)	133	68 (51)
Day 29	60	6 (10)	131	64 (49)
Day 36	60	5 (8)	134	75 (56)
Day 43	59	8 (14)	134	73 (54)
Week 10	47	8 (17)	108	56 (52)
Week 14	50	9 (18)	114	52 (46)
Week 18	48	8 (17)	112	52 (46)
Week 22	47	9 (19)	113	55 (49)
Week 26	58	10 (17)	132	68 (52)
1 Week Follow-up	54	8 (15)	110	46 (42)
2 Week Follow-up	55	10 (18)	118	26 (22)
4 Week Follow-up	58	8 (14)	119	24 (20)

Secondary endpoints

Platelet count

The median platelet counts for eltrombopag treated subjects began to rise after 1 week of treatment and remained above 50,000/µL throughout the 6 month treatment period. Two weeks after discontinuation of eltrombopag median platelet counts returned to near baseline levels (see Figure 4).

Figure 4: Median Platelet Counts (25th and 75th percentiles) By Baseline Platelet Count – Baseline to 4-week Follow-up (ITT Population)



The percentage of subjects treated with eltrombopag by dose at each nominal visit was studied. All subjects initiated treatment with eltrombopag 50 mg. Beginning as early as Day 8, a subset of subjects who were sensitive to treatment (achieved platelet counts above 200,000/µL) with eltrombopag 50 mg were down-titrated to 25 mg or less; approximately 20% of subjects were maintained on ≤25 mg throughout the study. The majority of eltrombopag treated subjects received 50 mg from Day 8 through Day 15 (99% and 93% respectively). After the Day 22 visit, subjects who did not achieve platelet counts above 50,000/µL on 50 mg were able to be uptitrated to eltrombopag 75 mg. From Day 29 to the end of treatment, 29 to 53% of eltrombopag treated subjects were

receiving 75 mg. Response to eltrombopag 75 mg was observed after 1 week in over 15% of subjects and in between 30-46% of subjects throughout the remainder of the 6 month study.

Duration of response

Duration of response was assessed using data from all visits for both the continuous and cumulative number of weeks of response. Summary statistics of both the maximum weeks of continuous response (platelet counts between 50 and 400,000/μL) and the cumulative weeks of response are provided in Table 20:

Table 20: Maximum and Total Weeks of Platelet Response (ITT Population)

	Treatment Group	
	PBO N=62 n (%)	Eltrombopag N=135 n (%)
Continuous Response		
n	60[a]	134[a]
Mean (SD)	2.2 (5.5)	9.5 (8.9)
Median (Min – Max)	0 (0 – 25[b])	8.1 (0 – 26)
Cumulative Response		
n	60	134
Mean (SD)	2.4 (5.9)	11.3 (9.5)
Median (Min – Max)	0 (0 – 25)	10.9 (0 – 26)

Additional analyses assessing the durability of the response and further evaluations in the subset of subjects who attained an initial platelet rise following treatment with eltrombopag (for all subjects who had at least one assessment), are shown in Table 21:

Table 21: Percentage of Assessments with a Platelet Count of 50-400,000/μL from Time of First Response (ITT Population)

	Eltrombopag N = 135	Placebo N = 62
Patients with ≥ 75 % of assessments in the target range (50,000 to 400,000/μl), n (%)	51 (38)	4 (7)
P-value [a]	< 0.001	

Reduction in Use of Baseline ITP Medication

At baseline, 31 placebo subjects (50%) and 63 eltrombopag subjects (47%) reported use of ITP medications, of which 10 (32%) and 37 (59%) subjects, respectively, reduced or discontinued at least one concomitant ITP medication (see Table 21). This difference was statistically significant (p=0.016).

Table 22: Reduction in Use of Baseline ITP Medications without Receiving On-Treatment Rescue Therapy (ITT Population)

	Treatment Group	
	PBO N=62	Eltrombopag N=135
Subjects taking an ITP medication at baseline, n (%)	31 (50)	63 (47)
Attempted to reduce or discontinue baseline ITP medications, n (%)	10 (32)	37 (59)
Permanently discontinued or had a sustained reduction[a], n (%)	6 (60)	31[c] (84)
For ≥24 weeks[a,b], n (%)	3 (50)	19 (61)
Permanently discontinued ≥1 baseline ITP medication [a,b], n (%)	4 (67)	24[c] (77)
Permanently discontinued all baseline ITP medication [a,b], n (%)	3 (50)	21[c] (68)

Rescue treatment

Rescue treatment was defined as a composite of: new ITP medication, increased dose of a concomitant ITP medication, platelet transfusion, and/or splenectomy. During the on-therapy period, 25/62 subjects (40%) in the placebo group and 24/135 subjects (18%) in the eltrombopag group required the use of protocol-defined rescue treatment.

An analysis of the proportion of subjects initiating rescue treatment showed the odds of initiating a rescue treatment were 67% lower in the eltrombopag group compared to the placebo group (p=0.001).

Bleedings

Secondary analyses showed that the observed baseline percentage of subjects with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced by approximately 50 % from Day 15 to the end of treatment throughout the 6 month treatment period. Bleedings (Grades 1-4) were reported in 79% of the patients receiving eltrombopag versus 93% receiving placebo. Bleedings (Grades 2-4) were reported in 33% of the patients receiving eltrombopag versus 53% receiving placebo. At each time point in both treatment groups, more than half of the bleeding observed was Grade 1 bleeding. Throughout the treatment period, clinically significant bleeding occurred infrequently, generally in <25% of subjects in the placebo group and in <15% of subjects in the eltrombopag group. At baseline, more than 70 % of patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20 % reported clinically significant bleeding (WHO Grades 2-4), respectively.

Fourteen eltrombopag-treated subjects (10%) and 4 placebo-treated subjects (7%) experienced at least one haemostatic challenge during the study. In the placebo group, 2 of the subjects (50%) required rescue therapy despite the relatively mild nature of the haemostatic challenges (tooth extraction and dental preventative procedure). No bleeding events were reported in conjunction with the haemostatic challenges. In the eltrombopag group, 4 of the 14 subjects (29%) received rescue therapy. Of the 4 subjects, 3 had not consistently responded to eltrombopag treatment (Subjects 406, 407, and 589) and had platelet counts below 40,000/μL at the time of the haemostatic challenge.

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

No studies have been submitted.

- Clinical studies in special populations

There were numerically more responders at each nominal visit amongst females compared to males in both treatment groups; however, there was no significant difference in response to eltrombopag relative to placebo between males and females (p=0.225).

At all on therapy visits, except the Week 26 Visit, there was a higher percentage of Asian subjects who responded to eltrombopag compared to other racial groups.

Subjects were prospectively categorized in the following age groups: 18-49 years, 50-64 years, 65-74 years, and ≥75 years. However, due to the small number of subjects in the ≥75 year age group (2 placebo and 11 eltrombopag, the following categories were defined post-hoc to assess any differences in the response to eltrombopag relative to placebo across age categories: 18-49 years, 50-64 years, and ≥65 years). This analysis indicated no evidence of a difference in response to eltrombopag relative to placebo between the age categories (p=0.342).

- Supportive studies

REPEAT (Repeated **E**x**P**osure to **E**ltrombopag in **A**dults with Idiopathic **T**hrombocytopenic Purpura)

This is an open-label repeat dosing study of eltrombopag in adult subjects, with chronic idiopathic thrombocytopenic purpura (ITP). This multi-centre, open-label, single-group, repeat-dose, Phase II study was designed to evaluate the efficacy, safety and tolerability of eltrombopag, initially administered as 50 mg oral tablets once daily, over 3 cycles of repeated, intermittent dosing. Other objectives were:

• To assess the number of subjects requiring rescue treatments over 3 cycles of therapy.
• To assess the safety and tolerability of eltrombopag when administered over 3 cycles of therapy.
• To assess anti-platelet antibody levels during the 3 cycles of eltrombopag treatment.
• To assess the impact of eltrombopag on the incidence and severity of bleeding symptoms as measured by the World Health Organization (WHO) Bleeding Scale and ITP Bleeding Score over 3 cycles of therapy.

A cycle was defined as an eltrombopag on-therapy period of up to 6 weeks followed by an off-therapy period of up to 4 weeks. The duration of both the on-therapy and the off-therapy period was defined by the subject's platelet count. Subjects interrupted treatment for the cycle if they achieved a platelet count >200,000/μL, or when they reached Week 6. Subjects began the next cycle when their platelet counts fell below 20,000/μL, or when they reached Week 4 of the off-therapy period and had platelet counts <50,000/μL. Subjects who did not respond in Cycle 1 (response defined as a platelet count ≥50,000/μL and at least 2x baseline at Day 43 or at treatment discontinuation due to platelet counts >200,000/μL) were not eligible to continue into Cycle 2 or 3. If a subject's platelet count did not fall below 50,000/μL by Week 4 of therapy period, the subject did not begin the next cycle of treatment, but a medical monitor was contacted to discuss the subject's case and continuation in the study.

As off-therapy periods were necessary to examine eltrombopag re-treatment, it was important to minimize the bleeding risk patients might be exposed to by participation in the study. Therefore, in contrast to other eltrombopag studies, a higher baseline platelet count (between ≥20,000/μL and ≤50,000/μL) was required for entry into this trial and eltrombopag re-treatment began after 4 weeks off-therapy in the previous dosing cycle, or when subject's platelet counts fell below 20,000/μL.

The study dosage regimen was similar to the Phase III Study TRA100773B. Subjects whose platelet count was below 50,000/μL for 2 successive weeks could have their eltrombopag dose increased to 75 mg on or after Day 22 of the on-therapy period of each cycle. Subjects who had a dose adjustment began the next cycle at the same dose of eltrombopag they were receiving upon completion of the previous cycle.

A total of 66 subjects entered the study. Sixty-six subjects entered Cycle 1, 55 subjects entered Cycle 2 and 51 subjects entered Cycle 3. Eleven subjects did not enter Cycle 2 because 8 were non-responders in Cycle 1, 1 subject had a prolonged response, 1 subject relocated, and 1 subject withdrew due to an AE. Four additional subjects did not enter Cycle 3 because 3 of these were non-responders in Cycle 2, and 1 subject had a prolonged response for >8 weeks after Cycle 2 and was withdrawn from study treatment.

Data on subject discontinuation of study medication is shown in Table 23:

Table 23. Subject Discontinuation of Study Medication (ITT Population)

Subjects, n(%)	Eltrombopag 50 mg N=66
Completed eltrombopag treatment[a]	**38 (58)**
Discontinued eltrombopag prematurely	**28 (42)**
Lack of efficacy[b]	3 (5)
Due to AE	1 (2)
Investigator decision	1 (2)
Other	
Platelet Count >200 Gi/L	18 (27)
Prolonged response	2 (3)
Relocation	1 (2)
Subject decision	2 (3)

Tables below show the results from the primary analyses of REPEAT study:

Table 24. Summary of Subjects with Platelet Counts greater than or equal to 50,000/μL and at least 2x Baseline After up to 42 Days of Dosing (ITT population)

	Eltrombopag 50 mg		
	Cycle 1 (N=66)	Cycle 2 (N=55)	Cycle 3 (N=51)
Evaluable	65	54	51
Responders, n(%)	52 (80)	43 (80)	39 (76)

Table 25. Analysis of Responders in Cycle 1 and in Cycle 2 or 3 (ITT Population)

	Eltrombopag 50 mg
Evaluable in Cycle 1, n	**65**
Response in Cycle 1	**52**
Evaluable in Cycle 2 **or** 3, n	52
Responders in Cycle 1 and in Cycle 2 or 3, n(%)	**45 (87)**
Proportion	0.87
95% CI for Proportion (Exact Methods)	(0.74, 0.94)
Evaluable in Cycle 2 **and** 3, n	48 (92)
Responders in Cycle 1 and in Cycle 2 and 3, n(%)	**34 (71)**
Proportion	0.71
95% CI for Proportion (Exact Methods)	0.56, 0.83)

The duration of response was evaluated by assessment of responder status over time in each cycle (see Table 26).

Table 26. Durability of Platelet Response to Eltrombopag During the On-therapy Period (Subjects who Responded in Cycle 1) (ITT Population)

Continuous Response	Cycle 1 (N=52)	Cycle 2 (N=52)	Cycle 3 (N=49)
	n (%)	n (%)	n (%)
# of subjects in on-therapy period	52	52	49
≥3 weeks	24 (46)	19 (37)	19 (39)
≥4 weeks	21 (40)	15 (29)	15 (31)
≥5 weeks	16 (31)	11 (21)	15 (31)

Eight subjects experienced 10 haemostatic challenges during the study. The diagnostic procedures and surgeries performed varied in the degree of bleeding risk associated with the procedure, from cardiac catheterization and transurethral resection of the prostate to tooth extraction and dental cleaning. All subjects responded to eltrombopag and none required additional treatment to elevate their platelet count before or after the procedure. No abnormal bleeding was reported for any of the procedures.

EXTEND (**E**ltrombopag e**XTEN**ded **D**osing Study)

This is an extension study of eltrombopag in adults with idiopathic thrombocytopenic purpura (ITP) previously enrolled in eltrombopag studies. The primary objective was to describe the long-term safety and tolerability of oral eltrombopag treatment of subjects with ITP with or without concomitant ITP medication.

For subjects receiving concomitant ITP medication, the study design included four stages:
Stage 1: Eltrombopag Initial Dosing. To identify a dose of eltrombopag that increases platelet counts to a level high enough (≥100,000/μL) to support dose reduction of concomitant ITP medication.
Stage 2: Concomitant ITP Medication Minimization. To reduce or eliminate concomitant ITP medication, while maintaining platelet counts ≥50,000/μL.
Stage 3: Eltrombopag Dose Adjustment. To identify the minimal effective dose of eltrombopag necessary to maintain platelet counts ≥50,000/μL in conjunction with the minimal dose of concomitant ITP medication.

Stage 4: Eltrombopag Long-term Dosing. To monitor safety and efficacy of eltrombopag at the minimal effective dose that in conjunction with the minimal dose of concomitant ITP medications maintains platelet counts ≥50,000/μL.

Subjects started the study receiving eltrombopag 50 mg once daily. Based upon the subjects' platelet count at each visit, the dose of eltrombopag could be adjusted (increased or decreased) or the frequency reduced to less than once daily, for example 25 mg every other day. Alternate dosing schedules to achieve average daily doses in between 25 mg, 50 mg or 75 mg were also allowed. Subjects whose platelet count exceeded 200,000/μL were required to decrease the dosage of study medication in order to maintain platelet counts within the target range (50-400,000/μL) and to reduce the possibility of having platelet counts over 400,000/μL. Subjects whose platelet count exceeded 400,000/μL were asked to interrupt study medication for at least 7 days, until platelet counts fell below 150,000/μL; when platelets were <150,000/μL, subjects were re-administered study medication at a lower dose.

Subject disposition in the study is showed in Table 27.

Table 27. Subject Disposition and Previous Eltrombopag Studies (All Subjects)

Received eltrombopag, n	207[b]
TRA100773A, n (%)	**49[c] (24)**
PBO	14 (29)
30 mg	9 (18)
50 mg	12 (24)
75 mg	14 (29)
TRA100773B[d], n (%)	**58[c] (28)**
PBO	19 (33)
50 mg	39 (67)
TRA102537/RAISE[d], n (%)	**67[c] (32)**
PBO	24 (36)
50 mg	43 (64)
TRA108057/REPEAT[e], n (%)	**33 (16)**
Withdrawn from the Study[f], n (%)	35 (17)
Ongoing, n (%)	172 (83)

The results of the study in terms of the number of subjects achieving platelet count of 50,000/μL or above are shown in Table 28:

Table 28. Subjects Achieving Platelet Counts of 50,000/μL or More, 50 to 400,000/μL, and Greater Than 400,000/μL, by Baseline Disease Characteristics.

	Baseline Platelet Counts (Gi/L)			Splenectomy		Use of ITP Medication	
Platelet Counts	<30 N=145	30–50 N=37	>50 N=25	Yes N=82	No N=125	Yes N=69	No N=138
Evaluable, n	142	35	24	79	122	65	136
≥50 Gi/L, n (%)	102 (71.8)	34 (97.1)	23 (95.8)	64 (81)	95 (77.9)	52 (80)	107 (78.7)
≥50 –≤400 Gi/L, n (%)	81 (57)	31 (88.6)	15 (62.5)	44 (55.7)	83 (68)	38 (58.5)	89 (65.4)
>400 Gi/L, n (%)	21 (14.8)	3 (8.6)	8 (33.3)	20 (25.3)	12 (9.8)	14 (21.5)	18 (13.2)

- Discussion on clinical efficacy

The superior efficacy of eltrombopag compared to placebo in terms of platelet count in ITP patients has been shown based on the pivotal studies submitted. The efficacy database was robust and included adequate analyses from pivotal and supportive studies.

An association between eltrombopag and reduced bleedings has also been consistently observed in secondary analyses of both phase III studies, though the effect is essentially driven by mild to moderate cutaneous bleedings.

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts but to maintain

platelet counts above the level for haemorrhagic risk (> 50,000/μL). On the other hand treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily. This information has been included in section 4.2 of the SPC.

Eltrombopag is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy. There are limited data on the use of eltrombopag in patients aged 65 years and older. 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. Initiation of eltrombopag at a reduced dose of 25 mg once daily may be considered for patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese or Korean).

Clinical safety

The safety profile of eltrombopag has been evaluated in 26 completed or ongoing clinical studies in 1616 eltrombopag-treated and 247 placebo-treated healthy volunteers and patients with ITP, Hepatitis C or chemotherapy-induced thrombocytopenia (see Table 28). The doses of eltrombopag used in these studies ranged from 3 mg to 200 mg. The duration of treatment with eltrombopag ranged from 1 day in healthy volunteers up to 560 days in subjects with chronic ITP.

A summary of the subjects contributing to the safety analysis and the main studies performed with eltrombopag in Chronic ITP is shown in Tables 29 and 30.

Table 29. Tabulation of Subjects Contributing to the Safety Analysis of Eltrombopag

	First Exposure[a] (any dose) to Eltrombopag, N	Eltrombopag 50 mg starting dose in any study[b], N	PBO, N	Blinded Study Treatment, N
ITP Program, Phase II/III, Subtotal	**422**	**387[c]**	**128**	**NA**
TRA100773A[d]	88	30	29	NA
TRA100773B	76	76	38	NA
RAISE	135	135	61	NA
REPEAT[e]	66	66	NA	NA
EXTEND (ongoing study)	57[f]	207[g]	NA	NA
Completed Phase I Studies	**572[h]**	**214[i]**	**47[j]**	**NA**
Total Primary Safety Database	**994**	**601[c]**	**175**	**NA**
Completed studies in other indications	**190**	**63**	**64**	**NA**
SB497115/003 CIT	134	44	46	-
TPL102357 HCV	56	19	18	-
Ongoing Studies	**432**	**3**	**8**	**346**
ITP Studies				
TRA108109 ITP	22	0	8	1
TRA111433 ITP (extension study)	0	3	0	NA
Other Indications				
TRC105499 CIT/Sarcoma	11	-	-	NA
TPL108390 HCV	175	-	-	135
TPL103922 HCV	224	-	-	188
TPL104054 Chronic Liver Disease	-	-	-	22
All Eltrombopag Studies - Total	**1616**	**667[c]**	**247**	**346**

Table 30. Summary of the Double-blind, Open-label and Observational studies evaluating safety of Eltrombopag in Chronic ITP.

GSK Study Number	Study Design	Dose Groups	Baseline Platelet Count	Status	Data Cut-off Date
Double-blind Phase II/III Studies					
TRA100773A	Double-blind, randomized, PBO-controlled (up to 6 weeks treatment)	eltrombopag 30 mg, 50 mg, 75 mg, and PBO	<30 Gi/L	Completed	Final study results
TRA100773B	Double-blind, randomized, PBO-controlled (up to 6 weeks treatment)	eltrombopag 50 mg starting dose, and PBO	<30 Gi/L	Completed	Final study results
RAISE	Double-blind, randomized, PBO-controlled (up to 6 months treatment)	eltrombopag 50 mg starting dose and PBO	<30 Gi/L	Completed[a]	CCO: 10-Jun-2008 SAE: 01-Aug-2008
Open-label/Observational Phase II/III Studies					
REPEAT	Open-label, single-group, repeat-dose (up to 3cycles of 6 weeks treatment)	eltrombopag 50 mg starting dose	≥20 Gi/L to ≤50 Gi/L	Completed[a]	CCO: 22-Apr-2008 SAE: 01-Aug-2008
EXTEND	Open-label, dose-adjustment extension for subjects who were enrolled in previous ITP studies (currently treatment duration not limited)	eltrombopag 50 mg starting dose	N/A	Ongoing	CCO: 07-Jan-2008 SAE1[b]: 18-Feb-2008 SAE2[b]: 01-Aug-2008
LENS	Observational study to monitor ocular safety in subjects who were enrolled in previous studies, for 2.5 years after last study drug	N/A[c]	N/A[c]	Ongoing	CCO: 26-Feb-2008 SAE: 01-Aug-2008

N/A = not applicable, CCO: Clinical Cut-off Date, SAE: serious adverse event cut-off date

a. Long-term 3 and 6 month follow-up visits ongoing.

b. SAE1 is the SAE cut-off date applied for the EXTEND clinical study report (CSR). All SAEs up to this date were included in the EXTEND CSR and were included in this document. SAE2 is the SAE cut-off date applied for consistency with all on-going studies described in this document. Any SAE that occurred between the SAE1 and SAE2 dates is included in the SAEs post-CCO section of this document (Section 2.1.4)

c. Observational study where no study medication was administered and there were no platelet counts collected.

- Patient exposure

The following tables summarise patient exposure to eltrombopag:

Table 31. Summary of Exposure to Eltrombopag across ITP Studies

	Eltrombopag N=422[a]
Average Daily Dose (mg)	
N	420[b]
Mean (SD)	52.3 (15.19)
Median (min, max)	50.0 (12 – 75)
Cumulative Dose (mg)	
N	420 [b]
Mean (SD)	8377.4 (7329.36)
Median (min, max)	6750.0 (100 – 40425)
Days on Eltrombopag	
N	421[c]
Mean (SD)	159.3 (126.24)
Median (min, max)	148.0 (2 – 560)
Total Subject Months on Treatment[d]	2203.4

Table 32. Cumulative Exposure to Eltrombopag in Months – All ITP Studies (Safety Population)

Duration of Exposure	**Eltrombopag N=422**
≥1 day, n	422
≥6 weeks (≥42 days), n	358
≥6 months (≥179 days), n	192
≥12 months (≥362 days), n	41
≥15 months (≥453 days), n	12

The observation period (including follow-up time) of the 422 eltrombopag-treated subjects was 228 person years, compared to 26 person years for the 71 placebo-treated subjects.

- Adverse events

Based on an analysis of all chronic ITP patients receiving eltrombopag in 3 controlled and 2 uncontrolled clinical studies (updated cut-off date 10 December 2008), the overall incidence of adverse events in subjects treated with eltrombopag was 82 % (367/446). The median duration of exposure to eltrombopag was 304 days and patient year's exposure was 377 in this study population.

Data on adverse events is summarised for the pooled TRA100773A and B and RAISE studies in Tables 33 and 34.

Table 33. Overall Summary of On-therapy Adverse Events – Pooled TRA100773 Data

	773A + 773B (Pooled)			
	PBO N=67		Eltrombopag 50 mg N=106	
	N Subjects, n (%)	N Events	N Subjects, n (%)	N Events
Any AE	32 (48)	116	60 (57)	143
Any SAE	5 (7)	7	4 (4)	7
Treatment-related AE	14 (21)	32	28 (26)	56
AE leading to withdrawal	5 (7)	7	5 (5)	7
SAE leading to withdrawal	4 (6)	6	3 (3)	5

Tables 34. Overall Summary of On-therapy AEs- RAISE

AEs During Treatment Phase	Treatment Group, n (%)			
	PBO, N=61		Eltrombopag, N=135	
	N Subjects, n (%)	N Events	N Subjects, n (%)	N Events
Any AE	56 (92)	411	118 (87)	749
Any SAE	11 (18)	17	15 (11)	21
Treatment-related AEs	18 (30)	48	48 (36)	158
AEs leading to withdrawal	4 (7)	6	12 (9)	15
SAEs leading to withdrawal	4 (7)	6	7 (5)	10

In addition, data on adverse reactions for all chronic ITP patients receiving eltrombopag is summarised in Table 35.

Table 35. Summary Of Drug-Related Adverse Events While Exposed to Eltrombopag Started On Therapy + 1 Day (updated cut-off date 10 December 2008).

	Eltrombopag (N=446)
System Organ Class	
Preferred Term	
ANY EVENT	180 (40%)
Nervous system disorders	
Any event	74 (17%)
Headache	58 (13%)
Paraesthesia	7 (2%)
Dizziness	4 (<1%)
Dysgeusia, Hypoaesthesia, Somnolence	3 (<1%)
Migraine, Tremor.	2 (<1%)
Balance disorder, Dysaesthesia, Hemiparesis, Migraine with aura, Neuropathy peripheral, Peripheral sensory neuropathy, Speech disorder, Toxic neuropathy, vascular headache	1 (<1%)
Gastrointestinal disorders	
Any event	51 (11%)
Nausea	19 (4%)
Diarrhoea	12 (3%)
Constipation	9 (2%)
Abdominal pain upper	5 (1%)
Abdominal discomfort, Abdominal distension, Dry mouth, Dyspepsia, Vomiting	4 (<1%)
Abdominal pain	3 (<1%)
Gingival bleeding, Glossodynia, Haemorrhoids, Mouth haemorrhage	2 (<1%)
Abdominal tenderness, Faeces discoloured, Flatulence, Food poisoning, Frequent bowel movements, Haematemesis, Oral discomfort	1 (<1%)
Investigations	
Any event	44 (10%)
Alanine aminotransferase increased	18 (4%)
Aspartate aminotransferase increased	16 (4%)
Blood bilirubin increased	7 (2%)
Blood albumin increased, Blood alkaline phosphatase Increased, Protein total increased, Transaminases increased, Weight increased	3 (<1%)
Blood creatinine increased, Haemoglobin increased, Hepatic enzyme increased	2 (<1%)
Band neutrophil count increased, Blood albumin decreased, Blood alkaline phosphatase, Blood urea increased, Blood uric acid increased, Electrocardiogram QT prolonged, Haemoglobin decreased, Myelocyte present, Platelet count increased, Urine protein/creatinine increased, Visual acuity tests abnormal, White blood cell count decreased, pH urine increased	1 (<1%)
Skin and subcutaneous tissue disorders	
Any event	44 (10%)
Rash	11 (2%)

Pruritus	8 (2%)
Alopecia	5 (1%)
Ecchymosis, Hyperhidrosis	4 (<1%)
Pruritus generalised, Urticaria	3 (<1%)
Dermatosis, Petechiae	2 (<1%)
Cold sweat, Erythema, Melanosis, Night sweats, Pigmentation disorder, Skin discolouration, Skin exfoliation, Swelling face	1 (<1%)
General disorders and administration site conditions	
Any event	35 (8%)
Fatigue	15 (3%)
Oedema peripheral	6 (1%)
Chest pain, Feeling hot, Pain, Vessel puncture site haemorrhage,	2 (<1%)
Asthenia, Feeling jittery, Ill-defined disorder, Inflammation of wound, Influenza like illness, Malaise, Mucosal inflammation, Non-cardiac chest Pain, Pyrexia, Sensation of foreign body	1 (<1%)
Eye disorders	
Any event	29 (7%)
Cataract	11 (2%)
Dry eye	5 (1%)
Vision blurred	4 (<1%)
Lenticular opacities	2 (<1%)
Astigmatism, Cataract cortical, Conjunctival haemorrhage, Eye pain, Lacrimation increased, Retinal haemorrhage, Retinal pigment epitheliopathy, Visual acuity reduced, Visual impairment	1 (<1%)
Musculoskeletal and connective tissue disorders	
Any event	21 (5%)
Arthralgia, Myalgia	7 (2%)
Muscle spasms	6 (1%)
Bone pain	5 (1%)
Muscular weakness, Pain in extremity, Sensation of heaviness	1 (<1%)
Hepatobiliary disorders	
Any event	15 (3%)
Hyperbilirubinaemia	10 (2%)
Hepatic function abnormal	5 (1%)
Cholestasis, Hepatic lesion, Hepatitis	1 (<1%)
Vascular disorders	
Any event	14 (3%)
Deep vein thrombosis	4 (<1%)
Hypertension	3 (<1%)
Hot flush, Thrombophlebitis superficial	2 (<1%)
Embolism, Flushing, Haematoma	1 (<1%)
Psychiatric disorders	
Any event	13 (3%)
Insomnia	5 (1%)
Sleep disorder	4 (<1%)
Anxiety, Depression	2 (<1%)
Apathy, Mood altered, Tearfulness	1 (<1%)
Respiratory, thoracic and mediastinal disorders	
Any event	13 (3%)
Epistaxis	4 (<1%)
Pulmonary embolism	3 (<1%)
Pulmonary infarction	2 (<1%)
Cough, Nasal discomfort, Oropharyngeal blistering, Oropharyngeal pain, Sinus disorder, Sleep apnoea	1 (<1%)
Metabolism and nutrition disorders	
Any event	12 (3%)
Anorexia	4 (<1%)
Hypokalaemia	3 (<1%)
Decreased appetite, Increased appetite	2 (<1%)
Gout, Hypocalcaemia	1 (<1%)
Infections and infestations	
Any event	9 (2%)

Pharyngitis, Urinary tract infection	2 (<1%)
Influenza, Nasopharyngitis, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Upper respiratory tract infection	1 (<1%)
Blood and lymphatic system disorders	
Any event	7 (2%)
Anaemia, Anisocytosis, Eosinophilia, Haemolytic anaemia, Leukocytosis, Myelocytosis, Thrombocytopenia	1 (<1%)
Cardiac disorders	
Any event	6 (1%)
Tachycardia	2 (<1%)
Acute myocardial infarction, Cardiovascular disorder, Cyanosis, Palpitations, Sinus tachycardia	1 (<1%)
Renal and urinary disorders	
Any event	6 (1%)
Renal failure	2 (<1%)
Leukocyturia, Lupus nephritis, Nocturia, Proteinuria	1 (<1%)
Injury, poisoning and procedural complications	
Any event	4 (<1%)
Contusion	3 (<1%)
Sunburn	1 (<1%)
Ear and labyrinth disorders	
Any event	2 (<1%)
Ear pain, Vertigo	1 (<1%)
Immune system disorders	
Any event	1 (<1%)
Hypersensitivity	1 (<1%)
NOT CODED	
Any event	1 (<1%)
Blepharitis and Keratoconjunctivitis sicca	1 (<1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Any event	1 (<1%)
Rectosigmoid cancer	1 (<1%)

- Serious adverse event/deaths/other significant events

Deaths
There were a total of 8 deaths in the eltrombopag ITP programme as of 1 August 2008: 1 subject in study TRA100773A, 1 subject in RAISE, 1 subject in REPEAT, 5 subjects in EXTEND.
One death was reported in a subject treated with eltrombopag 50 mg in TRA100773A; this subject had a history of pneumonectomy due to lung cancer and died of cardiopulmonary failure which was not considered related to drug by the investigator, although proximal events of renal insufficiency, embolism, pulmonary embolism and hepatitis were considered related to the drug.

In RAISE, a 43-year old female who had a baseline platelet count of 2,000/μL in the placebo group suffered a fatal brain stem haemorrhage six days after initiation of study medication, which was considered unrelated.

No deaths were reported in REPEAT during the on-therapy or the 4-week follow-up period of the study. One subject was diagnosed with pancreatic cancer (reported as an unrelated SAE) 6 days following the last dose of eltrombopag. Six months post-therapy, the subject died from that cancer.

All 5 deaths in EXTEND were reported as unrelated to study medication. Two deaths occurred while the subjects were on-therapy (passenger in a fatal motor vehicle accident; sudden death, definitive cause of death unknown). Three subjects died >30 days following discontinuation of eltrombopag.

Serious adverse events

Severe adverse events observed during the clinical development in ITP trials are summarised in Tables 36 and 37. The rate of discontinuation due to AEs in double blind trial was similar in both treatment groups, eltrombopag and placebo, although specific AEs (e.g. thromboembolic complications) were numerically higher among eltrombopag patients. In the open label EXTEND trial 9 subjects suffered from AEs (in 6 of them SAEs) leading to drug discontinuation.

Table 36. On-Therapy (+1 day) SAEs in TRA100773A and TRA100773B – Pooled Data

Dose Group, N, n (%)	Subject Number	Event
PBO, N=67; 5(7)	165	Toxic hepatitis[a]
	1233	Gastrointestinal hemorrhage, cerebral hemorrhage, hematuria
	171	Ruptured varicose vein
	1877	Face injury
	1372	Convulsion
Eltrombopag 50 mg, N=106; 4(4)	414	Herpes zoster
	144	Embolism[a], hepatitis[a], renal failure[a], pulmonary embolism[a]
	785	Gastrointestinal hemorrhage
	1846	Cerebral hemorrhage

Table 37. All On-therapy SAEs by Subject in RAISE (Safety Population)

On-Therapy SAEs			
PBO, N=61 11 (18%)		Eltrombopag, N=135 15 (11%)	
Subject	Events	Subject	Events
137	Heart rate increased[a] Menorrhagia	166	Headache
		317	Headache[a] Headache
167	Cataract[a,b]		
316	Gastrointestinal hemorrhage Respiratory tract hemorrhage Retinal hemorrhage Hemorrhage urinary	503	Cataract[a,b]
		530	Aortic aneurysm
		589	Rectosigmoid cancer[c]
		617	Headache[a]
527	Orchitis	641	Pulmonary embolism[a] Pulmonary infarction[a] Thrombophlebitis superficial[a]
572	Brain stem hemorrhage[d]		
579	Urogenital hemorrhage		
580	Hand fracture	656	Spinal compression fracture
663	Cataract[a,b]	667	Loss of consciousness Loss of consciousness
729	Cataract subcapsular[a,b]		
1041	Renal function test abnormal ALT increased Hyperkalemia	699	Duodenal ulcer hemorrhage
		773	Hemorrhagic anemia
		896	Deep vein thrombosis[a]
1073	Cellulitis	1077	ALT increased[a] AST increased[a]
		1115	Hypokalemia Urinary tract infection
		1188	Transaminases increased[a]

Bleedings

A higher proportion of placebo subjects experienced bleeding events on-therapy AE in the pooled data from TRA100773A and TRA100773B. Thirteen percent (13%) of placebo subjects [9 subjects, 13 events] experienced on-therapy bleeding events as compared to 8% [9 subjects, 11 events] in the eltrombopag group. All of these events were reported as unrelated to study treatment with the exception of 3 SAEs (Grade 2 gastrointestinal [GI] haemorrhage, cerebral haemorrhage and haematuria) that occurred in 1 subject in the placebo group. Post-therapy bleeding rates in the 2 double blind studies are shown below in Tables 38 and 39.

Table 38. Post-therapy Bleeding AEs in TRA100773A and TRA100773B Pooled Data

	773A + 773B	
	Placebo, N=67	Eltrombopag 50 mg, N=106
Subjects with event, n (%)	5 (7%)	12 (11%)
Subjects with SAE[a], n (%)	0	4 (4%)

Table 39. Post-therapy Bleeding AEs in RAISE

	Placebo, N=61, n (%)	Eltrombopag, N=135, n (%)
Subjects with event	6 (10%)	6 (4%)
Subjects with SAE[a]	1 (2)	2 (1)

The placebo controlled trials do not show a clinically or statistically significant difference relative to placebo in terms of platelet counts, bleeding events or need for rescue medication in the 4 weeks following discontinuation of therapy with eltrombopag. Observations from the open label studies support the conclusion that there is not an excess bleeding risk associated with interruption of eltrombopag.

In both placebo-controlled trials as well as in open-label studies transient decrease in platelets count after eltrombopag discontinuation has been analysed according to the following definition: "a post therapy platelet count <10,000/µL and at least 10,000/µL less than the baseline within the 4 weeks of study medication discontinuation". The results are summarised in Table 40.

Tables 40. Frequency of platelets count and bleeding after eltrombopag discontinuation.

	RAISE		TRA100773 A and B		OPEN LABEL	
	Placebo n=62	Epag n=135	Placebo n=67	Epag 50mg* n=106	REPEAT n=66	EXTEND n=78
Parameters	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Transient platelet decrease*	4 (7)	9 (7)	6 (9)	11 (10)	8 (12)	5 (6)
Bleeding AE's	0	1[&]	0	2[#]	0	0
Rescue	1	2	0	2	4	1

* <10 Gi/L and 10 Gi/L less than baseline within 4 weeks of discontinuation/interruptions (Bussel 2006)
#: Grade 3 menorrhagia and Grade 1 gingival bleeding
&: Grade 1 mouth haemorrhage and Grade 2 petechiae

In summary in the 3 controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8 % and 8 % of the eltrombopag and placebo groups, respectively.

Thromboembolic complications

From all ITP studies, a total of 17 out of 446 (3.8%) patients experienced TEE which included (in descending order of occurrence) deep vein thrombosis, pulmonary embolism, acute myocardial infarction, cerebral infarction, embolism, transient ischaemic attack, and suspected PRIND (prolonged reversible ischemic neurologic deficiency) (see Table 41). Of them 6 (35%) achieved maximum platelet count >400,000/µL at some time of treatment but only just 1 experienced the TEE close to their maximum platelet count (407,000/µL). The role of other thrombophilic risk factors and conditions in subjects who experienced TEEs during the eltrombopag trials was examined retrospectively, including concomitant therapies. No apparent relationship was shown.

Table 41. Cumulative Summary of Subjects with Confirmed or Suspected TEEs (Safety Update Dataset, cut-off date 10 December 2008).

Study	Subject	Event(s)	Proximal Platelet Count (Gi/L)	Outcome
TRA100773A	144	Pulmonary embolism; embolism	108	Fatal[a]
RAISE	589	Pulmonary embolism (5 days post-therapy)	N/A	Resolved
	641	Pulmonary embolism, pulmonary infarct	55	Resolved
		DVT, DVT (222 and 337 days post-therapy)	N/A	Ongoing
	896	DVT	49	Resolved[b]
EXTEND	55	TIA	27	Resolved
		MI	79	Resolved
	71	Pulmonary embolism (2 days post-therapy)	407	Resolved
	81	DVT	248	Resolved[e]
	731	Pulmonary embolism	246	Resolved[b]
	1060	Ischemic stroke	143	Resolved[b]
	1061	Ischemic stroke	219	Resolved[b]
	1133	Pulmonary embolism (2 days post-therapy)[c]	94	Resolved
	1163	Balance disorder, speech disorder, dizziness (suspected PRIND)	14	Resolved
	1272	DVT (8 days post-therapy)	28	Resolving[d]
	1273	DVT (7 days post-therapy)	214	Resolved

Safety data emerged from study TPL104054/ELEVATE in thrombocytopenic subjects with chronic liver disease and the study was prematurely stopped by the IDMB for safety reasons. As of 20 August 2009, 6 of 261 (2.3%) subjects treated with eltrombopag 75 mg had experienced 7 TEEs (Table 42; Figure 5). These consisted of 7 events of the portal vein system (4 portal vein thromboses [PVT], 3 mesenteric vein thromboses) in 6 subjects and 1 myocardial infarction (MI). The median (range) time to onset since the first dose of study medication was 22 days (15, 53). None of the events occurred on-therapy, the median (range) days since last dose was 9 days (1, 38). Five of the 7 subjects experienced the TEE within 2 weeks of the last dose of study medication. Six of the cases correlated with platelet counts above 200,000/µL (see Figure 5).

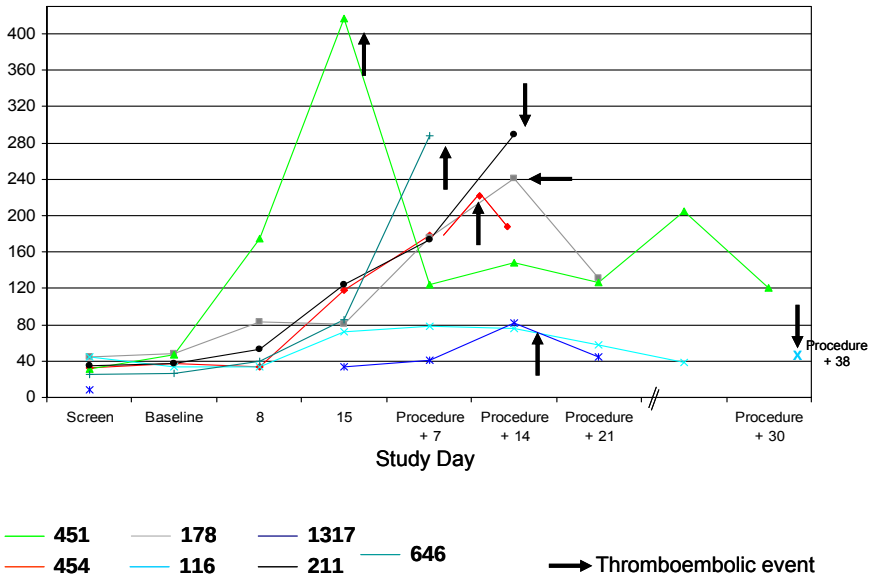
Table 42. ELEVATE Subjects with TEEs.

Subject	Event Verbatim Term	Platelet Count (Gi/L)		Time to Onset/Since Last Dose (Days)	Cancer
		Baseline	At Event		
116	Portal vein thrombosis	34	33	53/38	-
178	Spleno-portal vein thrombosis	48	241	27/14	Hepatocellular carcinoma
211	Thrombosis mesenteric vessel / mesenteric thrombosis	37	289	22/9	Hepatocellular carcinoma
451	Portal vein thrombosis Superior mesenteric vein thrombosis	47	417	15/1	Brain tumor
454	Upper mesenteric vein thrombosis	37	235	21/8	Lymphoma [b]
646	Portal vein thrombosis	26	288	19/5	-
1317 [a]	Acute myocardial infarction	8	83	33/20	Rectal Carcinoma

[a] Subject is still blinded.

[b] Diagnosed during the study.

Figure 5. ELEVATE Subjects and Correlation with Platelet Counts.



In addition the ELEVATE IDMC also reviewed TEEs from the ongoing HCV studies (TPL103922/ENABLE 1 and TPL108390/ENABLE 2), an ongoing Japanese chronic liver disease study (TPL111913, n=38 subjects; recruitment completed), and from post-marketing safety reports (n=1239 patients, approximately 240 patient years, as of 14 August 2009).

The ENABLE studies are 2 ongoing phase III studies of eltrombopag in subjects with HCV associated thrombocytopenia (platelets <75Gi/L). All subjects initiated treatment with 25mg eltrombopag and were able to dose escalate to a maximum of 100mg to achieve platelet counts of >90 or 100Gi/L depending upon the study. A total of 11 of the1185 ENABLE subjects (0.9%) had

experienced a TEE as of 1 September 2009. These consisted of 4 PVT events, 5 venous thrombosis events of the lower extremities, 1 MI event and 1 proximal occlusion of the right superficial femoral artery.

TPL111913 was a dose ranging study in Japanese subjects with chronic liver disease that used 12.5, 25 and 37.5mg dose which may approximate to 25, 50 and 75mg in a non East Asian population. In Part A of this study, 12 subjects were dosed with 12.5mg eltrombopag for 14 days. In Part B of the study, subjects received either 25mg or 37.5mg eltrombopag (14 and 12 subjects, respectively). Subjects were dosed for 14 days or 21 days depending upon whether or not the platelet count was above 80Gi/L at Day 15. One of the 38 subjects (2.6%) experienced an SAE of portal vein thrombosis 34 days after initiation of 37.5mg eltrombopag and 21 days since the last dose of eltrombopag.

In the post-marketing setting, as of 30 September 2009, a total of 1544 patients in the US REMS program were exposed to eltrombopag for approximately 356 patient years. Six of the 1544 patients had reported a TEE. Events included 3 pulmonary embolisms, 1 deep vein thrombosis, 1 embolism and 1 cerebrovascular accident. Of the 6 events 1 was unresolved, 2 had improved outcome and 1 was fatal.

Bone marrow toxicity

In RAISE and REPEAT per protocol, bone marrow examinations were to be performed prior to enrolment to confirm the diagnosis of ITP and to rule out myelodysplastic syndromes or other causes of thrombocytopenia in subjects who responded insufficiently to corticosteroids or if the WBC differential and the subsequent peripheral blood smear confirm the presence of immature or dysplastic cells.

In EXTEND, bone marrow examinations were performed for the following reasons:
a) Prior to enrolment into the study, for subjects who had not responded to prior ITP therapies with a platelet count increase to ≥100,000/μL or had not had a bone marrow examination consistent with a diagnosis of ITP within 3; and
b) During the study, for subjects who had immature or dysplastic cells in the white blood cell (WBC) differential that were confirmed by peripheral blood smear microscopy.
c) After dosing with eltrombopag for one year in EXTEND
d) At any time at the Investigator's discretion
Bone marrow examinations were not required in the 6-week TRA100773A and TRA100773B studies.

Bone marrow toxicity data come from EXTEND (cut-off date 10 December 2008) where subjects were to have a bone marrow examination performed after 12 months of treatment with eltrombopag. Additionally bone marrow examinations may have been performed at any time for other reasons based upon local standards of care.

86 subjects had been dosed for a median time of 12 months, none of the bone marrow exams were prompted by an abnormal peripheral blood smear. Of the 86 subjects 46 had a bone marrow aspirate done, none of which had an abnormal karyotype or an increase bone marrow blast count. The on-treatment reports for three of the 86 subjects did not mention testing for reticulin or fibrosis. The remaining 83 subjects were evaluable for reporting bone marrow fibre information and it is summarised below:
• Forty-eight subjects had either an MF Grade of 0 recorded in the eCRF (42 subjects), or 'no', 'no significant increase', 'no evidence of fibrosis' or 'Grade 0' reticulin documented in the bone marrow report (6 subjects).
• Thirty subjects had either an MF Grade of 1 (26 subjects) recorded in the eCRF or 'focal mild' reticulin documented in the bone marrow report (4 subjects).
o One of these subjects (Subject 58) had a MF Grade of 1 in the eCRF and "slight increase" in collagen documented in the bone marrow report (collagen not documented in the eCRF).
• Five subjects (Subjects 53, 61, 67, 1058 and 1241) had an MF Grade of 2 in the eCRF; with the exception of Subject 67, these subjects were presented in the original MAA.

- 3/5 had no collagen described in the bone marrow report (Subjects 53, 67 and 1058);
- 2/5 had collagen mentioned in the bone marrow report (Subjects 61 and 1241).

4 subjects had a reticulin assessment prior to and after treatment with eltrombopag. Changes in reticulin are described in Table 43, further follow up assessments have not been completed

Table 43.EXTEND Subjects with pre- and on-therapy bone marrow biopsies

Subj. ID	Prior Reticulin Assessment	Time of Prior Assessment and Previous Dose/Trial	On Study Reticulin Assessment	Time of On Study Assessment	F/U Assessment
127	mildly increased reticulin	19 months prior to EXTEND Day 1 (75mg on 773A)	focal mild increase in reticulin	after 8 months on EXTEND	N/A
565	reticulin stain MF-0	on Day 12 of RAISE Study (50mg epag) and 8 months prior to EXTEND Day1)	slight increase in reticulin fibers MF-1	after 12 months on EXTEND	N/A
643	no increased fiber formation	18 days prior to EXTEND Day 1 (PLA on 773A)	no increased fiber content	after 12 months on EXTEND	N/A
1241	MF-1	34 months prior to EXTEND Day 1 (50mg on 773)	MF-2	after 23 months on EXTEND	N/A

Malignancies
Five (1.2%) cases of malignancies in eltrombopag group and 1(1.4%) in placebo group have been detected in all ITP studies. Among the 6 cases of malignancies observed in ITP studies, there were 2 cases of haematological malignancies: 1 in placebo group and one in eltrombopag group.

Hepatotoxicity
Across the 3 placebo-controlled studies, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality.

A review of all cases of liver injury reported in the completed studies and up to 10 December 08 from the on-going EXTEND study was provided. Drug induced liver injury (DILI) screening criteria for hepatobiliary laboratory abnormalities (HBLA) were defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x the upper limit of normal (ULN) and/or bilirubin or alkaline phosphatase (AP) >1.5xULN. An analysis of time to onset, age, sex, dose, concomitant medications, repeated exposure to eltrombopag and outcome/resolution of the HBLA has been provided.

A total of 69 cases of HBLA have been reported (any dose of eltrombopag or placebo). 60 were receiving eltrombopag. Among the 60 cases, 5 cases occurring with the doses of 30 mg (3 cases) and 75 mg (2 cases) were not included in the analysis except for the evaluation of the time to onset. Therefore, 55 cases have been analysed. Summaries of all cases of HBLA for studies TRA100773A and TRA100773B (pooled data) and RAISE are presented in Tables 44 and 45.

Table 44. Summary of Subjects Meeting the DILI Screening Criteria for HBLA – Pooled Data TRA100773A and TRA100773B

Laboratory Criteria	TRA100773A + TRA100773B	
	PBO N=67	Eltrombopag[a], 50 mg N=106
Subjects, n (%)	**5 (7)**	**11 (10)**
>3x ULN AT and >2.0x ULN Total Bilirubin	0	1 (<1)
>3x ULN AT and >1.5x ULN Total Bilirubin	0	1(<1)
≥20x ULN ALT and AST	0	0
≥10x ULN ALT and AST	1 (2)	2 (2)
≥5x ULN ALT and AST	1 (2)	2 (2)
≥3x ULN ALT and AST	1 (2)	3 (3)
≥20x ULN ALT	0	1(<1)
≥10x ULN ALT	1 (2)	2 (2)
≥5x ULN ALT	1 (2)	4 (4)
≥3x ULN ALT	1 (2)	6 (6)
≥20x ULN AST	0	0
≥10x ULN AST	1 (2)	2 (2)
≥5x ULN AST	1 (2)	2 (2)
≥3x ULN AST	1 (2)	3 (3)
>2x ULN Total Bilirubin	2 (3)	4 (4)
>1.5x ULN Total Bilirubin	4 (6)	4 (4)
>1.5x ULN Alkaline Phosphatase	0	2 (2)

Data Source: SDAP Table 8.200, TRA100773A CSR and TRA100773B CSR, m5.3.5.3, sequence 0000
ULN = upper limit of normal, AT = Aminotransferases, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase
Note: Subjects are counted in more than one category if they fulfill multiple criteria.
a. 3 subjects receiving 30 mg eltrombopag and 2 subjects receiving 75 mg eltrombopag also experienced HBLA that met the DILI screening criteria in TRA100773A (1 subject with bilirubin >1.5xULN, 1 subject with bilirubin >2xULN, 1 subject with alkaline phosphatase >1.5xULN, 1 subject with ALT and AST ≥3xULN, 1 subject with AST ≥3x ULN)

Table 45. Summary of Subjects Meeting the DILI Screening Criteria for HBLA-RAISE

Parameters and Thresholds	PBO N=61	Eltrombopag N=135
Subjects, n (%)	**4 (7)**	**17 (13)**
>3x ULN AT & >2x ULN Bili total	0	0
>3x ULN AT & >1.5x ULN Bili total	0	0
≥20x ULN ALT & AST	0	0
≥10x ULN ALT & AST	0	0
≥5x ULN ALT & AST	1 (2)	3 (2)
≥3x ULN ALT & AST	1 (2)	3 (2)
≥20x ULN ALT	1 (2)	0
≥10x ULN ALT	1 (2)	2 (1)
≥5x ULN ALT	1 (2)	4 (3)
≥3x ULN ALT	2 (3)	9 (7)
≥20x ULN AST	0	0
≥10x ULN AST	0	1 (<1)
≥5x ULN AST	1 (2)	4 (3)
≥3x ULN AST	1 (2)	5 (4)
>2x ULN Bili total	0	4 (3)
>1.5x ULN Bili total	0	5 (4)
>1.5x ULN AP	2 (3)	1 (<1)

Data Source: TRA102357 CSR, Table 8.90, m5.3.5.3, sequence 0000
Abbreviations: AP=alkaline phosphatase; AST=aspartate aminotransferase; ALT=alanine aminotransferase; Bili=bilirubin; ULN=upper limit of normal; AT=ALT and/or AST
Subjects are counted in more than one category if they fulfill more than one criterion.

Time to onset varied broadly. In TRA100773A-B and RAISE studies, DILI occurred in the first month of treatment (median: 15, 29 days respectively) but in EXTEND the median of time onset was 3.5 months. Bilirubin occurred in a shorter time than transaminases in all studies, except in TRA100773A-B in which median of time to onset for both bilirubin and ALT was 8 days.

HBLA was observed across all age ranges. Of the eltrombopag-treated subjects who developed, HBLA 66% were female and 34% were male. Hepatotoxicity was more frequent in Asian subjects.

The outcome was analysed in 61 cases (7 of them occurred in both EXTEND and previous studies). In 37 cases the HBLA resolved, 12 resolved after eltrombopag discontinuation and 2 after dose decrease. The remaining 23 cases the event resolved despite eltrombopag therapy continued. Of the

24 cases in which the event did not resolve, 10 were only bilirubin elevation (6 with Gilbert's Syndrome).

Half of the patients experienced only bilirubin or alkaline phosphatase. 5 patients had elevations of transaminases with bilirubin increases and met Hy's Rule Criteria. In two cases alternative causes were identified (thromboembolism of the liver and cardiac failure, cholecystitis). In one case the patient experienced sudden elevations of transaminases and bilirubin 1 year after starting therapy with eltrombopag. The other two cases fluctuations on elevations of transaminases and bilirubin occurred during a long period of time (1 year, 5 months). Bilirubin increase was due to indirect bilirubin in the 3 cases.

A pharmacogenetic study identified the *UGT1A1*28* allele as being associated with elevated total bilirubin in the White subjects included in the eltrombopag clinical development program. This allele has been associated with Gilbert's Syndrome in populations of European ancestry as well as hyperbilirubinaemia and toxicity following administration of some drugs in which UGT1A1 contributes to the elimination of parent drug or metabolites. In East Asian populations *UGT1A1*28* is of lower frequency and other alleles of diminished activity such *UGT1A1*6* (absent in European populations) and *UGT1A1*60* are important and these alleles contribute to Gilbert's syndrome and are associated with some drug toxicities. The eltrombopag PGx analysis did not report an association of *UGT1A1* alleles with total bilirubin elevation in Asian ITP patients; however, only a limited number of Asian patients could be included in this analysis (3 Asians with elevated total bilirubin and 33 Asian controls).

Cataracts
In the double-blind RAISE study patients had an ocular exam prior to enter in study and after starting the study at month 3 and 6. The frequency of incident cases of cataracts was similar for eltrombopag group (4.5%) and placebo group (4.9%). The frequency in cataract progression was slightly higher in eltrombopag group compared with placebo group. Prior to enter in the study 25 patients had cataracts (13 placebo, 12 eltrombopag group) and during the study, 4(33%) patients had a cataract progression in the eltrombopag group and 3(23%) in the placebo group.

The frequency of cataracts (incident/progression) was similar in open label studies (REPEAT 3%, EXTEND 5%). All patients who developed cataracts in ITP studies had chronic treatment with corticosteroids.

Phototoxicity
No difference in the frequency of skin and subcutaneous adverse events was demonstrated between the eltrombopag and placebo groups in the controlled trials. The frequency reported in the open label studies was similar to the placebo controlled studies.

- Laboratory findings

Haematological evaluation

Haematologic assessments were reported using NCI CTCAE version 3 toxicity grades. Haematologic assessments are presented in Table 46:

Table 46. Maximum Toxicity Grade in RAISE

Laboratory Parameter		PBO, N=61, n (%)	Eltrombopag, N=135, n (%)
Hemoglobin	n	60	135
Anemia	Grade 3	0	1 (<1)
Anemia	Grade 4	0	2 (1)
Lymphocytes	n	60	135
Lymphopenia	Grade 3	2 (3)	5 (4)
Lymphopenia	Grade 4	2 (3)	0[a]
Neutrophils	n	60	135
Neutropenia	Grade 3	3 (5)	2 (1)
Neutropenia	Grade 4	0	0
WBCs	n	60	135
Leukocytopenia	Grade 3	0	1 (<1)
Leukocytopenia	Grade 4	0	0

Data from open label studies and EXTEND are consistent with this data.

Renal laboratory values

Across the pooled data from TRA100773, 22 subjects showed an increase from baseline in creatinine (placebo: 4 subjects; 30 mg: 3 subjects; 50 mg: 13 subjects; 75 mg: 2 subjects). Five of these subjects (all receiving eltrombopag) were considered of clinical interest because they had multiple on-therapy creatinine values ≥0.3 mg/dL above their individual baseline. These subjects did not experience any AEs potentially related to renal function, and an improvement or normalization of their creatinine values was reported while continuing on drug, except for one subject whose creatinine, albeit remaining within normal values, had not yet returned to baseline at the end of the study.

In the RAISE one subject treated with eltrombopag had at least 2 consecutive assessments ≥0.3 mg/dL above baseline and above the ULN (peaked at 1.5xULN). Thereafter, the values decreased during treatment with eltrombopag. A summary of the subjects with increases in serum creatinine from baseline is presented in Table 44.

Table 44. Summary of Subjects with Increase(s) in Serum Creatinine from Baseline (greater than or equal to 0.3 mg/dL) at any Post-Baseline Visit - RAISE

	PBO N=61, n (%)	Eltrombopag N=135, n (%)
At least 1 assessment ≥0.3 mg/dL	2 (3)	10 (7)
≥2 assessments ≥0.3 mg/dL	1 (2)	2 (1)
≥2 consecutive assessments ≥0.3 mg/dL	0	1 (<1)
At least 1 assessment ≥0.3 mg/dL and ≥ULN	1 (2)	2 (1)
≥2 assessments ≥0.3 mg/dL and ≥ULN	0	1 (<1)
≥2 consecutive assessments ≥0.3 mg/dL and ≥ULN	0	1 (<1)

The rate of serum creatinine abnormal values was similar in the open label studies.

Enhanced renal monitoring was added to the ongoing RAISE, REPEAT, and EXTEND studies to detect the potential occurrence of renal toxicity. In this review eltrombopag was associated with liver injury with a frequency of 10-13%.

Platelet function and antiplatelet antibodies

No systemic change in the detectable anti-platelet antibody levels for antibodies to glycoproteins Ia/IIa, Ib/IX, and IIb/IIIa has been detected.

- Safety in special populations

Clinical pharmacology studies have been conducted in patients with renal impairment. No relevant difference in the type and frequency of adverse events were noted. However, both the number of patients and duration of treatment are not appropriate to draw clinical safety conclusions.

Gender and age did not appear to have a critical impact in the safety of the drug. Representation of elderly (>65 years) and very elderly (>75 years) is limited, though age and gender distribution in clinical trials generally mimics the real prevalence of the disease.

Hepatic impairment
The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. In a placebo-controlled study where eltrombopag was administered for 2 weeks in preparation for invasive procedures, 6 of 261 patients with chronic liver disease experienced 7 thromboembolic events of the portal venous system. One additional patient developed a myocardial infarction 20 days after the last dose of study medication, which remains blinded (see section on thromboembolic complications).

- Safety related to drug-drug interactions and other interactions

No studies have been submitted.

- Discontinuation due to adverse events

See section on “Serious adverse event/deaths/other significant events”.

- Post marketing experience

No studies have been submitted.

- Discussion on clinical safety

The safety profile of eltrombopag has been evaluated in 26 completed or ongoing clinical studies in 1616 eltrombopag-treated and 247 placebo-treated healthy volunteers and patients with ITP, hepatitis C or chemotherapy-induced thrombocytopenia. The total exposure in the ITP safety database is 446 patients, being the main limitation of this safety database the long-term treatment.

The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. This data emerged from the study ELEVATE in thrombocytopenic subjects with chronic liver disease and the study was prematurely stopped for safety reasons. The CHMP consulted an *ad hoc* expert group to provide guidance on the significance of these events. The questions and responses from the expert group are summarised below:

1. Please discuss the possible mechanism for the observed increase in thromboembolic events in the ELEVATE study.

The group agreed that it is difficult to speculate on the possible mechanism for the observed thromboembolic events in ELEVATE as the study remains blinded. A plausible explanation was based on the rapid increase in platelet counts observed in the liver impaired population due to the administration of a higher dose of eltrombopag (75 mg compared to 25 mg or 50 mg in the ITP population). However in order to be reassured on this point information on whether the patients that experienced thromboembolic events received transfusions in addition to drug treatment and what platelet counts were achieved in the patients who had no TEEs was needed. In addition, it could not

be excluded that an enhancement of the pro-thrombotic state (hypercoagulability) due to an imbalance in coagulation factors and/or the presence of endothelial damage seen in liver disease had contributed to the thromboembolic events.

In order to clarify the pathophysiology of the observed events the experts expressed the need for further characterisation upon unblinding of the ELEVATE study:
- Levels of pro- and anti- coagulant factors in all patients (i.e. protein C, protein S, anti-thrombin, factor VIII, von Willebrand factor). Time points suggested were: pre eltrombopag/placebo, at day 15 and at time of TEE/ end of monitoring period.
- Platelet activation status.
- Endothelial activation status.

Although the group acknowledged that some of these studies would not be feasible if not pre-specified in the original protocol of ELEVATE, it was recommended exploring them pre- and post-treatment with eltrombopag/placebo in the context of liver impaired patients independently of the ELEVATE study if needed. Doppler ultrasound to assess asymptomatic portal vein thrombosis should also be considered.

2. Do the experts consider that the safety findings triggering the decision of the IDMC results seen in the Elevate study are relevant to the ITP population?

The group was of the opinion that the thromboembolic events observed in the ELEVATE study are unlikely to be relevant to the ITP patient population. The main reasons for this conclusion are the different pathophysiology of the two diseases, the different aetiology of the thrombocytopenia and the different type and pattern of thromboembolic events observed in the two populations.

3. What additional precautions do the experts think that could be taken to ensure a safe use of Revolade in ITP patients?

The group expressed the need to include a strong warning in the SPC highlighting the risk of thromboembolic events in patients with moderate and severe hepatic impairment. In this regard a full contraindication was not supported, however it was recommended the inclusion of a clear statement indicating that eltrombopag should not be used in these patients unless the expected benefit outweighs the risk of portal vein thrombosis and including a recommended dose in those cases. The group voiced that especially for those patients undergoing invasive procedures, platelet transfusion remains a safer option.

The experts agreed that the SPC should contain a clear cut definition of the term “moderate to severe” liver impairment, including Child-Pugh and Meld scores.

Regarding posology, the group agreed that the revised cut-off values of platelet counts for dose adjustment and treatment interruption proposed by the Rapporteurs were adequate to minimise the risk of thromboembolic episodes in the ITP population.

The CHMP concurred with the expert group recommendations and concluded that the TEE findings in the ELEVATE study are unlikely to be relevant to the ITP patient population. However, it was agreed that strong warnings hightlighting the risks associated with moderate to severe liver impairment should be included in the SPC (sections 4.2, 4.4 and 4.8). The agreed wording was the following:

“Eltrombopag should not be used in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) unless the expected benefit outweighs the identified risk of portal venous thrombosis.

If the use of eltrombopag is deemed necessary, the starting dose must be 25 mg once daily.

The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures"

In order to further characterise the risk associated with liver impairment, the Applicant has committed to provide to the CHMP the final results of the ELEVATE study (Study TPL104054) including PK and PD data when they become available (study still blinded, report expected to be available September 2010). Moreover, the Applicant will further assess, from stored samples in the ELEVATE study, the potential effect of eltrombopag on the unstable coagulation balance (pro- vs. anti-coagulant factors production) in this patient population.

Based on the result ELEVATE study in which there was an observable close relationship between high platelet counts and TE complications (five out of 7 patients, thromboembolic complications took place at the time of the maximum platelet count above 200,000/μL for each individual) the CHMP requested the Applicant a revised and more conservative cut-off points for dosing adjustment, taking on board that the key aspect in the ITP patient population is to maintain platelet count above the threshold considered to be associated to bleeding risk (50,000/μL). The CHMP considered that there was no clinical justification for the administration of eltrombopag in patients with platelet count ≥ 250,000/μL. With this value there is a broad safety margin of bleeding due to thrombocytopenia (more than 200,000/μL). This was also agreed by experts consulted by the CHMP as summarised above. The following posology has been recommended in the SPC:

Platelet count	**Dose adjustment or response**
< 50,000/μL following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
≥ 50,000/μL to ≤ 150,000/μL	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/μL to ≤ 250,000/μL	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/μL	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/μL, reinitiate therapy at a daily dose reduced by 25 mg.

Several risks need to be further assessed in a larger population than the one studied, therefore the Applicant has submitted a comprehensive risk management plan and has committed to perform additional post-authorisation studies. Safety concerns included hepatobiliary laboratory abnormalities, thromboembolic events, post therapy recurrence of thrombocytopenia, bone marrow reticulin formation and risk of bone marrow fibrosis, haematological malignancies, cataracts and loss of response to eltrombopag (all reflected in sections 4.4 and 4.8 of the SPC). Eltrombopag has been contraindicated in patients with hypersensitivity to eltrombopag or to any other of the excipients, this information has been included in section 4.3 of the SPC.

The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia and myelodysplastic syndromes (MDS).

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are

confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥ 3X the upper limit of normal [ULN]) and are: progressive, persistent for ≥ 4 weeks, accompanied by increased direct bilirubin, or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation. Caution should be taken when administering eltrombopag to patients with hepatic disease.

There are no or limited amount of data from the use of eltrombopag in pregnant women therefore the potential risk for humans is unknown and eltrombopag is not recommended during pregnancy and in women of childbearing potential not using contraception. In addition it is not known whether eltrombopag or its metabolites are excreted in human milk. Warnings during pregnancy and lactation have been included in section 4.6 of the SPC.

In order to further characterise the uncertainties associated with eltrombopag treatment, the applicant has provided new information clarifying how the risk of eltrombopag will be estimated. The US Risk Evaluation and Mitigation Strategy (REMS) program will be the main source to obtain data for eltrombopag-risk, and two registries included in the pharmacovigilange plan (UK-ITP and PARC-ITP registries) will provide information on the background risk of ITP disease. Comparison on incidence rates among REMS and UK-ITP or PARC-ITP registry should be used to estimate risk of thromboembolic events and malignancies.

In addition the applicant has committed to assess the levels of bone marrow fibers (reticulin and/or collagen) at baseline and any change from baseline after 1 and 2 years of treatment with eltrombopag in adult subjects with chronic ITP (study TRA112940). The final study report will be submitted as a post-authorisation commitment.

Additional risk minimization activities have been agreed for hepatic events, thromboembolic events, reoccurrence of thrombocytopenia, bone marrow fibrosis and malignancies. These risks will be addressed in a healthcare professional information pack containing educational materials to be provided prior to launch to all physicians who intend to prescribe eltrombopag.

An evaluation of the proposed risk minimization plan should be submitted periodically. Specifically, for the hepatic monitoring an evaluation should be presented every 6 months together with the PSURs and RMP updates.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Hepatotoxicity	• Routine pharmacovigilance • Targeted Follow Up Questionnaires • Ongoing & planned studies including • EXTEND TRA105325 • Japanese study TRA108109 • Japanese Extension TRA111433 • Bone Marrow Study TRA112940 Sarcoma TRA105499 • MDS Study • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054	• Statement in Section 4.4. (Special warnings and precautions) of the SmPC advising to monitor and manage patient with hepatotoxicity. Also specifies liver testing before initiation, every 2 weeks during the first 3 months, thereafter every 4-6 weeks • Increased ALT, AST and indirect bilirubin included in Section 4.8 (Undesirable effects). • Patient Information Leaflet • Educational materials • US REMS
Thromboembolic events	• Routine pharmacovigilance • Targeted Follow Up Questionnaires • Pharmacogenetics studies • UK ITP Registry • (PARC)ITP Registry • Ongoing & planned studies including • EXTEND TRA105325 • Japanese study TRA108109 • Japanese Extension TRA111433 • Bone Marrow Study TRA112940 Sarcoma TRA105499 • MDS Study • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054 • US REMS	• Section 4.2 (Posology and method of administration), section 4.4 (Special warnings 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. • 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. • Patient Information Leaflet • Educational materials with benefit risk communication regarding thromboembolic events • US REMS
Post Therapy Reoccurrence of thrombocytopenia	• Routine pharmacovigilance • Targeted Follow Up Questionnaires • Ongoing & planned studies including • EXTEND TRA105325, • Japanese study TRA108109 • Japanese Extension TRA111433 • Bone Marrow Study TRA112940 Sarcoma TRA105499 • MDS Study • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054	• A statement in Section 4.4 (Special warnings and precautions) regarding the potential for decrease in platelet counts post discontinuation of therapy. • Thrombocytopenia following discontinuation of treatment included in Section 4.8 (Undesirable effects). • Patient Information Leaflet • Educational materials • US REMS
Potential for Increase in Bone Marrow Reticulin Formation	• Routine pharmacovigilance • Targeted Follow Up Questionnaires • EXTEND study will continue to actively collect bone marrow reports	• A statement in Section 4.4 (Special warnings and precautions) regarding the potential for increase in bone marrow reticulin fibres is included.

	after 12 months of treatment • Bone Marrow Study to assess serial bone marrow samples at baseline, 12 and 24 months • Ongoing & planned studies including • Japanese study TRA108109 • Japanese Extension TRA111433 • Sarcoma TRA105499 • MDS Study • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054	• Patient Information Leaflet • Educational materials • US REMS
Haematological Malignancies	• Routine pharmacovigilance • Targeted Follow Up Questionnaires • MDS Study PMA112509 • Bone Marrow Study TRA112940 to assess serial bone marrow samples at baseline, 12 and 24 months • Ongoing & planned studies including • In-vitro and ex-vivo studies • EXTEND TRA105325 • Japanese study TRA108109 • Japanese Extension TRA111433 • Sarcoma TRA105499 • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054 • US REMS	• 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 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. • A statement in Section 4.4 (Special warnings and precautions) regarding the theoretical risk of malignancies is included in the SmPC. • Patient Information Leaflet • Educational materials • US REMS
Cataracts	• Routine Pharmacovigilance • Adjudication of reports of cataract • LENS TRA108132 observational study • UK ITP Registry • Ongoing & planned studies including • EXTEND TRA105325 • Japanese study TRA108109 • Japanese Extension TRA111433 • Sarcoma TRA105499 • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054	• A statement in Section 4.4 (Special warnings and precautions) regarding the routine monitoring for cataracts is included.
Renal Tubular Toxicity	• Routine pharmacovigilance • Ongoing & planned studies including • EXTEND TRA105325 • Japanese study TRA108109 • Japanese Extension TRA111433 • Sarcoma TRA105499 • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054	• Section 4.2 of the SmPC (Posology and method of administration) and Section 5.2 (Pharmacokinetic properties) stating that patients with impaired renal function should use eltrombopag with caution and close monitoring, for example, by testing serum creatinine and/or performing urine analysis. • A statement in Section 5.3 (Pre-clinical safety data) that the clinical relevance of the renal tubular toxicity finding in rodents is unknown
Phototoxicity	• Routine pharmacovigilance • Ongoing & planned studies including • EXTEND TRA105325 • Japanese study TRA108109 • Japanese Extension TRA111433	• 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.

	• Sarcoma TRA105499 • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054	
Potential for Haematological Changes	• Routine pharmacovigilance • Ongoing & planned studies including • EXTEND TRA105325 • Japanese study TRA108109 • Japanese Extension TRA111433 • Sarcoma TRA105499 • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054	• 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 • A warning is in Section 4.4 (Special warnings and precautions) of the SmPC informing prescribers to monitor for immature or dysplastic cells.
Potential for Endosteal Hyperostosis	• Routine pharmacovigilance • Ongoing & planned studies including • EXTEND TRA105325 • Japanese study TRA108109 • Japanese Extension TRA111433 • Sarcoma TRA105499 • ENABLE1 TPL103922 • ENABLE2 TPL108390 • ENABLE ALL TPL108392 • ELEVATE TPL104054	• 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.
Paediatric Population	• Routine pharmacovigilance • Paediatric study (PETIT) to establish safety and efficacy in this population	• 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.
Pregnant or lactating females	• Routine pharmacovigilance • Targeted Pregnancy Follow Up Questionnaires • Pregnancy Registry in the US • Lactation Study	• Section 4.6 in SmPC (Fertility, pregnancy and lactation) states that there is no or limited data on the use of eltrombopag in pregnant women and it is unknown whether eltrombopag/metabolites are excreted in human milk

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. Cataracts have not been observed in dogs after 52 weeks of dosing (2 times the human clinical exposure based on AUC). The clinical relevance of these findings is unknown (see section 4.4).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterized by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times respectively, the human clinical exposure based on AUC. The clinical relevance of these findings is unknown.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) or dogs (52 weeks) at exposures up to 4 or 2 times, respectively, the human clinical exposure based on AUC.

At poorly tolerated doses in rats and dogs (> 10 times maximum human clinical exposure based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times the maximum human clinical exposure based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times the maximum human clinical exposure based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times the maximum human clinical exposure based on AUC.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.5 times the human clinical exposure based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 times the human clinical exposure based on AUC) or ocular phototoxicity (≥ 5 times the human clinical exposure based on AUC).

Efficacy

Eltrombopag increases platelet count in patients with chronic ITP unresponsive to at least one first line therapy (corticosteroids or immunoglobulins). This effect has been shown to be superior to placebo in both splenectomised and non-splenectomised patients in two well-designed and conducted placebo-controlled clinical trials of short-term (6 weeks) and medium-term (6 months) duration. Open label extension studies have confirmed this effect. Duration of response in platelet count is longer with eltrombopag than with placebo, being consistently shown in the clinical database.

Secondary analyses have consistently reported an association between eltrombopag and reduced bleedings. The association was essentially driven by mild to moderate cutaneous bleedings, however an effect on severe bleedings has also been consistently observed in secondary analyses. In addition, greater discontinuation of concomitant therapies was observed with eltrombopag compared to placebo.

The response to eltrombopag shows variability, especially in cases with over-response (platelet count above 400,000/µL). This is particularly relevant considering that full therapeutic response can take place as early as during the first week of therapy. In addition, response to eltrombopag in patients with very low platelet count (<15,000/µL) is considerably lower, although it is significantly different from placebo.

Safety

The safety profile of eltrombopag has been evaluated based on data from 26 completed or ongoing clinical studies in 1616 eltrombopag-treated and 247 placebo-treated healthy volunteers and patients with ITP, hepatitis C or chemotherapy-induced thrombocytopenia. The doses of eltrombopag used in these studies ranged from 3 mg to 200 mg. The duration of treatment with eltrombopag ranged from 1 day in healthy volunteers up to 560 days in subjects with chronic ITP.

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

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

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

Among 446 adult chronic ITP patients receiving eltrombopag, 17 subjects experienced thromboembolic events, which included deep vein thrombosis, pulmonary embolism, acute myocardial infarction, cerebral infarction, embolism, transient ischaemic attack, and suspected PRIND (prolonged reversible ischemic neurologic deficiency).

The risk of thromboembolic events has been found to be increased in patients with chronic liver disease treated with eltrombopag. These findings have been considered unlikely to be relevant to the ITP patient population (conclusion supported by an *ad hoc* expert group).

The induction of reticulin formation and the potential development of bone marrow fibrosis is a serious safety concern. There are limited data suggesting that eltrombopag is associated with reticulin formation in the bone marrow (collagen formation in 3 cases) however whether this is a finding likely to have clinical consequences on the long term is still uncertain. In addition, for Mpl ligands, such as eltrombopag, there is a theoretical concern that they may stimulate the growth haematopoietic malignancies, or increase progression of MDS to acute myelogenous leukaemia (AML).

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

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Applicant performed a readability testing ("user consultation") and a satisfactory report has been provided.

Risk-benefit assessment

The benefits of eltrombopag in terms of platelet counts have been established in several independent clinical trials on a short and long-term basis. In secondary analyses, eltrombopag was also consistently associated with a reduction of the risk of bleedings.

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

In addition during treatment with eltrombopag a number of risks and uncertainties have been identified. These include hepatobiliary laboratory abnormalities, thromboembolism events and post therapy recurrence of thrombocytopenia as identified risks and bone marrow reticulin formation, haematological malignancies, renal toxicity, phototoxicity, cataracts, haematological changes and endosteal hyperostosis as potential risks.

In splenectomised patients refractory or intolerant to first line therapies (corticosteroids and immunoglobulins), the benefits of eltrombopag outweigh the risks. However, considering the unknown risks, the benefit-risk balance cannot be considered positive for non-splenectomised patients, for whom splenectomy is a therapeutic option that could potentially affect the course of the disease. Therefore, the indication for non-splenectomised patients has been restricted from the one that the Applicant initially applied and eltrombopag may be considered as second line treatment only when surgery is contra-indicated.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- the following additional risk minimisation activities were required: see as detailed in section 2.3.

Similarity with authorised orphan medicinal products

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

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Revolade in the treatment of:

'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'

was favourable and therefore recommended the granting of the marketing authorisation.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Revolade not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Nplate for the same therapeutic indication.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is not completed yet as none of the measures are completed.