

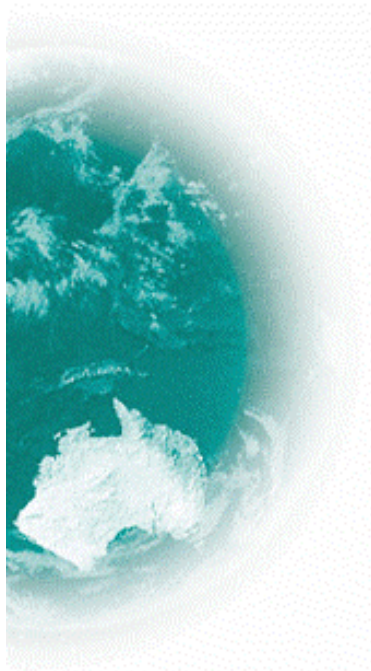


Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report
for
Eltrombopag olamine

Proprietary Product Name: Revolade
Submission No: SM- 2009-00082-3-4
Sponsor: Glaxo Smith Kline Australia Pty Ltd



October 2010

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I. Introduction to Product Submission

Product Details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	2 July 2010
<i>Active ingredient(s):</i>	Eltrombopag olamine
<i>Product Name(s):</i>	Revolade
<i>Sponsor's Name and Address:</i>	Glaxo Smith Kline Australia Pty Ltd 1061 Mountain Highway, Boronia Victoria 3155 Australia
<i>Dose form(s):</i>	Tablets
<i>Strength(s):</i>	25 and 50 mg (as eltrombopag free acid)
<i>Container(s):</i>	Blister packs
<i>Pack size(s):</i>	14, 28 and 84 tablets
<i>Approved Therapeutic use:</i>	<i>Treatment of adult patients with chronic immune (idiopathic) thrombocytopaenic purpura (ITP) who have had an inadequate response, or are intolerant, to corticosteroids and immunoglobulins.</i>
<i>Route(s) of administration:</i>	oral
<i>Dosage:</i>	The proposed initial dose is 50 mg once daily; doses are adjusted based on platelet count. The maximum recommended dose is 75 mg daily.
<i>ARTG number(s)</i>	158419/158356

Product Background

Eltrombopag olamine (INN¹: eltrombopag, SB497115-GR) is an orally bioavailable, small molecule thrombopoietin receptor (TPO-R) agonist. TPO-R receptor agonists function in a similar manner to endogenous thrombopoietin (TPO), inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

Eltrombopag has been developed for the treatment of chronic idiopathic thrombocytopenic purpura (ITP). ITP is an autoimmune disorder characterised by autoantibody-induced platelet destruction and reduced platelet production, leading to a chronically low peripheral blood platelet count (<150 Gi/L²). As indicated by the term 'idiopathic', the exact etiology of ITP is unknown.

The clinical hallmark of the disease is an increased, pathological tendency to bleed spontaneously or after minimal trauma. In principle, there is an inverse relationship between platelet count and bleeding risk: the lower the platelet count, the higher the risk of bleeding. It is recognised that platelet counts of <30 Gi/L are likely to be associated with an increased incidence of bleeding complications. Disease management decisions in patients with chronic ITP are usually based on platelet count and

¹ INN-International Nonproprietary Name.

² The SI (International System of Units) unit for platelet count is 10⁹/L. The sponsor's clinical reports and the clinical evaluator have used Gi/L in their tables and discussions, respectively. As the Delegate used the SI unit for platelet counts, both units have been quoted in this AusPAR.

severity of bleeding. The goal of treatment is to elevate platelet counts to a range 50 to 400 Gi/L (“safe” platelet count) to minimise the risk of bleeding. Current clinical guidelines issued by haematological societies focus on the platelet count as the key parameter to assess the bleeding risk in patients with ITP (George, 1996³; BCSH, 2003⁴).

The drugs most commonly approved for the treatment of ITP are immunoglobulins (anti-D immunoglobulin; intravenous immunoglobulins IVIg). Additional drugs to treat chronic ITP include corticosteroids, azathioprine, cyclophosphamide, or vincristine. First-line treatment with intravenous (IV) immunoglobulins or corticosteroids results in normal or “safe” platelet counts in about 70% of patients with chronic ITP. Use of IVIg can be limited by side effects, limited supplies and inconvenience of permanent intravenous administration. Corticosteroids often induce a response within up to two weeks, but the effect may not be sustained upon dose reduction or cessation of treatment, and long-term administration of corticosteroids is limited by the development of side effects such as peripheral oedema due to fluid retention, hypertension, heartburn/peptic ulcers, anxiety, insomnia, agitation, Cushingoid features, diabetes, cataracts, potassium loss, osteoporosis and increased risk of infections.

Second-line therapy for chronic ITP typically involves splenectomy, the safety and efficacy of which has not been assessed in well-controlled, long-term clinical studies. Splenectomy is considered an effective therapy in many patients, leading to an increase in the platelet count in approximately 50-80% of patients. However, patients and physicians often reject splenectomy for several reasons including severe morbidity resulting from surgery and the risk of relapse despite initial response. Treatment of patients who relapse after splenectomy is particularly challenging because most current therapeutic options for patients with chronic ITP are immunosuppressive, which may potentiate the risk of infectious complications in patients already immune-compromised by splenectomy.

When patients are refractory to treatment with corticosteroids or immunoglobulins and splenectomy is ineffective, they may be treated with alternative therapies, including rituximab, vinca alkaloids, danazol, high dose corticosteroids, azathioprine, cyclophosphamide, cyclosporine A, and dapsone. There are limited data to support the use of these agents and, according to treatment guidelines, these agents are only recommended for use in patients when there is an urgent emergent need to elevate the platelet count.

Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates a signalling cascade similar but not identical to that of endogenous TPO, inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Daily administration of eltrombopag in healthy and thrombocytopenic subjects has been shown to result in a dose-dependent increase in platelet counts in the peripheral blood within 1 to 2 weeks.

The rationale for the development of eltrombopag in patients with chronic ITP is two-fold. Firstly, published data suggest that reduced platelet production is a component of ITP. Kinetic studies using ¹¹¹Indium labelled platelets have shown that platelet turnover is low in some patients with ITP, particularly in those with severe disease (Heyns, 1986⁵). This might reflect an impairment of megakaryocytes in ITP, which leads to premature death of these platelet-producing cells in the bone marrow. In addition, *in vitro* studies have found evidence for deficient platelet production in patients with ITP.

³ George *et al.* 1996. Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for The American Society of Hematology. *Blood* 88(1):3-40.

⁴ BCSH 2003. Guidelines for the investigation and management of Idiopathic Thrombocytopenic Purpura in adults, children and pregnancy. *British Journal of Haematology*, 120: 574–596.

⁵ Heyns *et al.* 1986. Platelet turnover and kinetics in immune thrombocytopenic purpura: results with autologous ¹¹¹In-labeled platelets and homologous ⁵¹Cr- labelled platelets differ. *Blood* 67 (1): 86-92

Secondly, endogenous TPO levels in patients with chronic ITP are often paradoxically normal or below normal, suggesting that megakaryopoiesis could be stimulated further by a thrombopoietic agent. Therefore, thrombopoietic agents might be a treatment option due to their ability to increase platelet production in patients with chronic ITP. Stimulating megakaryocyte growth and differentiation within the patient's own bone marrow should lead to a rise in the patient's own platelets, thereby avoiding exposure to donated platelets and immunosuppressive agents.

Regulatory Status

There is one other TPO agonist currently registered in Australia for the treatment of chronic ITP – romiplostim (Nplate – Amgen). It was considered and recommended for approval by the Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines) at its June 2008 meeting. Romiplostim is a recombinant protein which is administered by weekly subcutaneous injection.

In Australia, several intravenous immunoglobulin (IVIG) products are specifically registered for the treatment of chronic ITP, although only for the short-term use. Several grandfathered corticosteroid products are also registered for this indication.

Eltrombopag olamine was approved in the USA on 20 November 2008. The USA trade name is Promacta. The dataset submitted in the USA included only short-term data (6 weeks).

The approved indication in the USA is as follows:

“Promacta is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding. Promacta should not be used in an attempt to normalise platelet counts”.

An application to register eltrombopag was submitted in the European Union (EU) on 5 December 2008. Eltrombopag received an orphan medicinal product designation in the EU on 03 August 2007 for the treatment of chronic ITP (Community Register of Orphan Medicinal Products (OMP's) EU/3/07/467) and in **Australia (17/07/2009)**. Revolade was approved in the EU on 11 March 2010. The proposed Australian trade name for the product is Revolade. The current Australian marketing authorisation application is for Revolade 25 mg and 50 mg film-coated tablets.

Product Information

The approved Product Information (PI) document current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

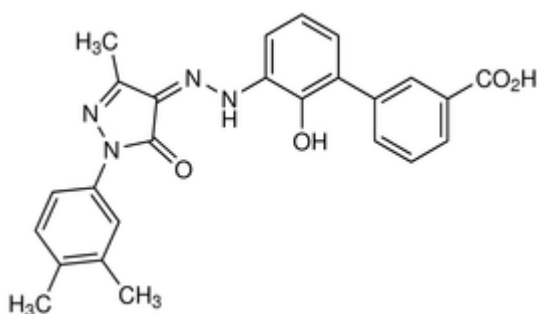
Drug Substance (active ingredient)

Eltrombopag is achiral but potentially shows *E/Z* isomerism around the hydrazone. It is reported to exist as the hydrogen-bonded, *Z* isomer (as shown in Figure 1) in solution and in the solid state.

The drug substance is the bis 2-aminoethanol ('olamine') salt. The molar ratio of eltrombopag to monoethanolamine was monitored in clinical trial batches and has been consistent (circa 1: 2.02).

Eltrombopag olamine is crystalline. It is thermally stable up to about 125°C; only one morphic form is known. It is not hygroscopic.

Figure 1: eltrombopag (C₂₅H₂₂N₄O₄ and MW 442.467).



The solubility of the bis-ethanolamine salt in water is markedly higher.

The drug substance is synthetic. Impurity levels are fairly low.

GlaxoSmithKline has identified genotoxic impurities and demonstrated that levels are below the 'Threshold of Toxicological Concern' (1.5 µg/day) which represents a dose that might increase tumour risk in humans by less than 1 in 100,000 with lifetime (70 years) exposure as detailed in the European Medicines Agency (EMA) *Guideline on the Limits of Genotoxic Impurities* [CPMP/SWP/5199/02].

The drug substance is milled. Residue on ignition is controlled (Ph. Eur. method).

Drug Product

'Revolade' 25 and 50 mg film coated tablets are proposed. Tablets are labelled with the equivalent mass of eltrombopag free acid. Tablets are made using conventional excipients. The two strengths are made with scaled quantities of the same granules, and quantities of the excipients, sodium starch glycollate, magnesium stearate and microcrystalline cellulose are used to compress '25' or '50' mg tablets of the same total mass. The tablets are coated differently, so that while the same size, the strengths are distinguished by colour and tablet markings. Tablets are not scored. Blister packs of 14, 28 and 84 tablets are proposed.

Clinical Trial Formulations

The commercial formulation is identical to the formulation used in the pivotal clinical studies for 25 mg and 50 mg tablets except for debossing and a different film coat colour.

Related Substances

It is not clear that the manufacturing and stability experience is yet sufficient to completely eliminate routine related substance testing.

Bioavailability

Eltrombopag olamine permeability is considered as 'medium': the FDA reviewer put eltrombopag in "BCS Class 2/4"⁶. No *in vitro-in vivo* correlation (IVIVC) has been made.

Eltrombopag is hepatically metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione or cysteine. 59% is excreted via faeces and 31% in urine as metabolites.

Eltrombopag is not detected in urine. The elimination half-life is 21-32 hours.

No absolute bioavailability study has been undertaken since an intravenous formulation cannot be developed (physical instability such as precipitation of drug and chemical instability were observed in all formulations tested).

There was a mass balance study using a radioactive carbon (¹⁴C)-labelled oral solution (75 mg).

⁶ The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility

Three bioavailability studies have been evaluated and one has been summarised:

Study TRA104631

This was a five way crossover study of the effect of food (fasting; low-fat + low calcium; 1 hour before high-fat + high calcium; high-fat meal) and antacid (containing sodium alginate?) on single 75 mg tablet (not proposed for registration) doses in 26 healthy volunteers. Administration of eltrombopag with high-calcium food or an antacid containing Al^{3+} and Mg^{2+} significantly reduced systemic exposure, whereas low-calcium meals did not.

Study SB-497115/005

This was a 3 way crossover bioequivalence study comparing 25 mg capsules and 25 mg tablets plus a study of the effect of food on the tablets in 18 volunteers (50 mg doses). This used a standard high-fat FDA breakfast; the calcium content is not quantified but clearly significant (for example whole milk 240 mL). The bioavailability of 25 mg tablets was **less** than the 25 mg capsule (about 15-18%). Food substantially reduced the bioavailability (about 40%)

Study TRA102863 (summary)

This study involved three separate groups, each in a crossover study [Phase II 50 mg versus Phase III 50 mg tablets; Phase II (1x25 + 1x50 mg) versus Phase III 75 mg tablets; Phase II 2x50 mg versus Phase III 100 mg tablets]. Phase 3 tablets generally had slightly lower bioavailability.

Study TRA10522

Another bioequivalence study comparing Phase II and Phase III tablets (both 25 versus 25 mg and 50 versus 50 mg) in 100 healthy volunteers. The 50 mg tablets were bioequivalent. The 25 mg tablets from the commercial site had 16% higher mean C_{max} .

Quality Summary and Conclusions

There are no quality objections to registration. The application was considered at the November 2009 meeting of the Pharmaceutical Subcommittee of the Advisory Committee on Prescription Medicines (ACPM; former ADEC). No objections to registration were raised at this meeting.

III. Nonclinical Findings

Introduction

The nonclinical dossier comprised a comprehensive set of toxicity studies with pivotal studies conducted under Good Laboratory Practice (GLP) conditions. A summary of pivotal studies are contained in the FDA report (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022291s000_TOC.cfm). During the clinical development of eltrombopag, several salts were examined in nonclinical studies; the parent compound (SB-497115), monosodium salt (SB-497115-Z), disodium salt (SB-497115-X) and the bis-monoethanolamine salt (SB-497115-GR_ the proposed clinical salt). All pivotal pharmacology, safety pharmacology and toxicity studies were conducted using the bis-monoethanolamine salt. There are no novel excipients in the clinical formulation of eltrombopag tablets.

Eltrombopag is not pharmacologically-active in laboratory animal species typically used for toxicity studies. The only identified species, apart from humans, for which eltrombopag is active is the chimpanzee, an endangered species which cannot be used for toxicity studies. Therefore, the full spectrum of safety issues has not been adequately addressed in submitted repeat-dose, carcinogenicity and reproductive toxicity studies. This is considered a deficiency in the nonclinical dossier but was unavoidable due to practical and ethical limitations.

Pharmacology

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease that is linked to the production of antiplatelet auto-antibodies leading to platelet elimination. Thrombopoietin (TPO) is an endogenous hormone produced by the liver and kidney that stimulates the proliferation and

differentiation of megakaryocytes, from which platelets are shed. As an agonist of the TPO receptor, also known as c-Mpl, eltrombopag is envisaged to stimulate megakaryopoiesis and thrombopoiesis to increase platelet counts in patients with ITP. One TPO agonist is currently-registered in Australia, romiplostim (NPlate). Romiplostim is an Fc-peptide fusion protein and is therefore structurally-different to eltrombopag which is a small chemical molecule (Nurden *et al.*, 2009⁷). Differences in receptor specificity and toxicological profiles exist between the two agonists, for example, romiplostim is known to bind to TPO-R (c-Mpl) of mice, rats, monkeys and humans, whereas eltrombopag binds to TPO-R (c-Mpl) of only chimpanzees and humans.

Efficacy

In vitro, eltrombopag demonstrated TPO receptor activation by stimulation of both STAT-based interferon regulatory factor-1 promoter and the megakaryocyte-specific promoter, glycoprotein IIb, with an 50% effective concentration (EC₅₀) of 0.1-0.27 µM. The up-regulation of several megakaryocyte proliferation-associated genes was consistent with TPO receptor agonistic activity. Eltrombopag induced the proliferation of a TPO-dependent human megakaryocytic leukemia cell line with an EC₅₀ of 0.03 µM and induced the differentiation of CD34+ progenitor cells into megakaryocytes. However, eltrombopag did not affect platelet aggregation induced by adenosine 5'-diphosphate (ADP) and did not induce P-selectin expression, which are typical of endogenous TPO and romiplostim activity (Ezumi *et al.*, 1995⁸; FDA report BLA 125268⁹).

The TPO agonistic activity of eltrombopag was observed in platelets from human and chimpanzee but not in platelets from mice, rats or monkeys at concentrations up to 30 µM (13.3 µg/mL). This is due to the absence of a histidine at position 499 in the TPO receptors in these species (Kim *et al.*, 2007¹⁰). Therefore, typical nonclinical models of ITP could not be used to evaluate efficacy. However, a single study in chimpanzees, a species with eltrombopag-responsive TPO receptors, demonstrated a 1.3-2.4 fold increase in platelet counts circa 1 week following 5 daily doses of ≥5 mg/kg. The delay in observed platelet elevations is consistent with the time required for megakaryocyte maturation (Hartwig and Italiano, 2003¹¹).

The lowest effective dose of 5 mg/kg in chimpanzees was associated with a plasma area under the concentration–time curve (AUC) of 12.1 µg.h/mL, which is less than 10% of the AUC_{0-τ} value (168 µg.h/mL) anticipated clinically. Thus, the nonclinical data support the proposed indication at the proposed clinical dose.

Secondary pharmacodynamics and safety pharmacology

The selectivity of eltrombopag was assessed in a panel of standard *in vitro* assays for activity against 41 receptors, enzymes and ion channels (not all of human origin) at 1 µM. Activity was noted for 4 receptors and 50% inhibition concentration (IC₅₀) values determined in a subsequent study were 16, 1.7, 0.3 and 1.9 µM for the rodent α_{2B} and I₂ receptors and human oestrogen α and β receptors,

⁷ Nurden, A.T., J.-F. Viallard and P. Nurden (2009) New-generation drugs that stimulate platelet production in chronic immune thrombocytopenic purpura. *The Lancet* **373**: 1562-1569.

⁸ Ezumi, Y., H. Takayama and M. Okuma (1995) Thrombopoietin, c-Mpl ligand, induces tyrosine phosphorylation of Tyk2, JAK2, and STAT3, and enhances agonists-induced aggregation in platelets *in vitro*. *FEBS Lett.* **374**: 48-52.

⁹ FDA report for Application Number BLA 125268, Romiplostim.

¹⁰ Kim, M.-J., S.H. Park, S.J. Opella, T.H. Marsilje, P.-V. Michellys, H.M. Seidel and S.-S. Tian (2007) NMR structural studies of interactions of a small, nonpeptidyl Tpo mimic with the thrombopoietin receptor extracellular juxtamembrane and transmembrane domains. *J. Biol. Chem.* **282**: 14253-14261.

¹¹ Hartwig J. and J. Italiano (2003) The birth of the platelet. *J. Thromb. Haemost.* **1**: 1580–1586.

respectively. These values are somewhat below the clinical maximum concentration of drug in serum (C_{\max}) of 28.7 μM .

All safety pharmacology studies were performed using the bis-monoethanolamine salt of eltrombopag and performed according to GLP principles. Dedicated central nervous system (CNS), cardiovascular and respiratory studies were conducted. Gastrointestinal (GI) tract and renal safety were assessed in repeat-dose toxicity studies. There was no effect of eltrombopag on CNS or respiratory function in rats with oral doses up to 40 mg/kg (Exposure ratio based on C_{\max} , $ER_{C_{\max}}=6$). *In vitro*, eltrombopag demonstrated concentration-dependent inhibition of hERG K^+ channel tail current with an IC_{50} of 0.69 μM . In isolated dog Purkinje fibres, though action potential was unaffected, eltrombopag at concentrations $\geq 10 \mu\text{M}$ caused a decrease in the maximum rate of depolarisation and action potential duration, similar to those observed with cardiac sodium channel blockers. These concentrations are considerably lower than the clinical C_{\max} of 28.7 μM . However, no electrocardiogram (ECG) effects were observed in dogs treated with up to 30 mg/kg ($ER_{C_{\max}}=3-4$). Though concentrations used in *in vitro* assays are difficult to extrapolate safety margins for clinical use, a 30-fold difference between unbound drug concentrations at the C_{\max} and the hERG K^+ IC_{50} is generally considered a “safe” margin (Redfern *et al.*, 2003¹²). The margin for eltrombopag is just over 2-fold, assuming 1% free eltrombopag. Therefore, an adequate safety margin has not been demonstrated and the results identify potential hazards to the cardiovascular system. An absence of apparent ECG effects in dogs maybe a result of mixed ion channel inhibition rather than an absence of an actual effect.

Pharmacokinetics

The oral (PO) bioavailability of eltrombopag in rodents was 26-41% but was much higher in dogs (83-92%) and monkeys (89-108%). Absolute bioavailability has not been determined in human subjects but was estimated to be at least 51% based on the excretion of drug-related material. Following a single intravenous (IV) injection to rats, dogs and monkeys, the plasma clearance of eltrombopag was generally low (0.44-3.3 mL/min/kg) with moderate to long half-lives in these species (8-14 h) whilst plasma elimination half-lives in human subjects after PO administration were of comparable length (21-32 h). The volume of distribution was low, with approximately 2-fold the total body water in monkeys but less than half the total body water in rats and dogs. Eltrombopag was more quickly absorbed in rats, dogs and humans (time to maximum concentration of drug in serum T_{\max} 1-2.5 h) than in monkeys (T_{\max} 3-4 h).

Eltrombopag was highly bound to plasma proteins (>99%) in blood from rats, dogs, monkeys and humans. Less protein binding (circa 94%) was observed in blood from mice. Protein binding was largely associated with albumin. In *in vitro* assays, the addition of human serum albumin to physiological levels (44 mg/mL) reduced the potency (based on EC_{50}) of eltrombopag by almost 9-fold but the maximal response was unaffected, suggesting the extensive protein binding of eltrombopag is unlikely to affect biological activity *in vivo*.

Whole body distribution of eltrombopag was qualitatively similar in albino and pigmented mice and rats. Drug-related material distributed widely but with concentrations in most tissues, excluding those involved in absorption and/or elimination, lower than those in blood. Peak radioactivity levels were reached in most tissues 2-4 h after dosing in mice and 4-8 h in rats, and declined with time with elimination complete by 3 days in mice and 7 days in rats. In both species, there was poor penetration of the blood-brain barrier with detectable levels circa 2-3% of blood concentration levels. In mice, drug-related material in ocular tissue was 10-20-fold lower than plasma concentrations, while drug-

¹² Redfern WS *et al.* (2003) Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovascular Res.* **58**:32-45.

related material in the lens was below the level of quantitation in the majority of mice given 150 mg/kg PO eltrombopag. There was no evidence of accumulation in ocular tissue nor any evidence of selective binding of eltrombopag with melanin-containing tissues in the eye or pigmented skin.

The *in vitro* and *in vivo* metabolism of eltrombopag was qualitatively similar between animals and humans. In all animal species tested, with the exception of rabbits, unchanged eltrombopag was the major (circa 60%) drug-related product in the plasma 24 h post-dose. All metabolites found in human plasma were found in species used for nonclinical toxicity studies. Major pathways of metabolism (6-33% in plasma) included oxidation, mediated by cytochrome P (CYP) 1A2 and CYP2C8, and conjugation with glucuronic acid by UDP-Glucuronosyltransferase (UGT) 1A1 and UGT1A3. Minor pathways included conjugation with cysteine or glutathione. Unchanged eltrombopag was also the major component of drug-related material in the faeces (circa 50% in dogs), suggesting metabolism plays only a moderate role in eltrombopag elimination. Metabolites generated by microbial hydrolysis of the hydrazine linkage were the major drug-related products in the urine of mice, rabbits and humans. The overall similarities in metabolite profiles between mice, rats, rabbits, dogs and humans support the use of the chosen animal species in the toxicity studies.

As in humans, the predominant route of excretion in mice, rats and dogs was in the faeces (75-95%) with urinary excretion representing a minor route (2-14%). In bile-duct cannulated (BDC) mice, rats and dogs, biliary excretion accounted for 21%, 43% and 6.7% of drug-related material. Following intravenous (IV) administration of [¹⁴C]-eltrombopag to BDC dogs, 9.6% of the dose was excreted in the faeces, suggesting that drug-related material was secreted into the gut lumen. In humans, the elimination of drug-related material in the faeces and urine was 59% and 31%, respectively, of the administered dose.

Pharmacokinetic Drug Interactions

As oxidation and glucuronidation only play a minor role in eltrombopag elimination and eltrombopag was not a substrate of P-glycoprotein or OATP1B1, co-administered drugs that induce or inhibit CYP450s, UGTs or these transporters are unlikely to affect eltrombopag pharmacokinetics. Eltrombopag was both a substrate and inhibitor of human breast cancer resistance protein (BCRP; IC₅₀ 2.7 µM) and an inhibitor of OATP1B1 (IC₅₀ 2.7 µM). Inhibition of these transporters appears to be clinically-relevant as co-administration of eltrombopag with rosuvastatin, an organic anion transporting polypeptide (OATP) 1B1 and BCRP substrate, was reported to increase plasma rosuvastatin C_{max} by 2-fold and AUC by 55%.

In vitro, eltrombopag inhibited the human CYP2C8 and CYP2C9 isozymes with 50% ineffective concentration dose (IC₅₀) circa 20 µM, but no significant inhibition of CYP1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5 or 4A9/11 was observed at 100 µM. Eltrombopag inhibited UGT1A9, 1A3, 1A1, 2B15, 1A6, 2B7 and 1A4 with IC₅₀ 3-30 µM. There was no induction of CYP1A2, 2B6 or 3A4 at concentrations up to 100 µM and eltrombopag was only a weak activator of human nuclear pregnanex receptor (PXR).

In summary, eltrombopag has the potential to affect the pharmacokinetics of co-administered drugs that are substrates of CYP2C8, CYP2C9, UGTs, OATP1B1 or BCRP. As eltrombopag is a substrate of BCRP, inhibitors of this transporter could potentially affect eltrombopag pharmacokinetics.

Relative Exposure

Table 1. Relative exposure of eltrombopag in repeat-dose toxicity studies.

Species (strain)	Study (duration)	Dose (mg/kg/day)	C _{max} (µg/mL)	C _{max} ratio	AUC _{0-24h} (µg.h/mL)	AUC ratio
Mouse (CD-1)	CD2003/00476/00 (2 weeks)	30	37	3	299	2
		100	116	9	1022	6
	CD2004/00836/00 (2 weeks)	150	107	8	941	6
		200	138	11	1358	8
	CD2004/00627/00 (13 weeks)	10	2.9	0.2	20	0.1
		60	60	5	454	3
		100	105	8	652	4
	CD2006/00751/02 (104 weeks)	25	26	2	198	1
		75	72	6	627	4
		150	106	8	1083	6
Rat (SD)	CD2003/00252/00 (2 weeks)	3	6.5	0.5	27	0.2
		10	34	3	164	1
		40	80	6	650	4
	CD2003/00327/00 (2 weeks)	20	44	4	341	2
		40	109	9	892	5
	CD2004/00332/00 (28 weeks)	3	5.4	0.4	25	0.1
		10	16	1.3	106	0.6
		30	75	6	661	4
		60	149	12	1044	6
	CD2007/00923/00 (104 weeks)	10	16	1.3	92	0.5
		20	39	3	252	1.5
		40	71	6	523	3
Rabbit (NZW)	CD2003/00854/00 (7 days)	80	3.6	0.3	22	0.1
		150	8.4	0.7	59	0.4
		200	18	1.4	183	1
Dogs (Beagle)	RD-2003/01089/00/1 (14 days)	60	84	7	1364	8
	SB-497115/RSD-101V3C/1 (14 days)	3	5.3	0.4	58	0.3
		10	12	1	179	1
		30	51	4	782	5
	CD2003/001148/00 (52 weeks)	3	3.9	0.3	37	0.2
		10	11	1	146	1
		30	35	3	451	3
Human	TRA100773A/B	75 mg	12.7	–	168	–

^a calculated as animal: human AUC_{0-24h}

Toxicology

Acute toxicity

One acute toxicity study at the maximum tolerated PO dose in dogs (300 mg/kg) was submitted. At this dose, emesis, diarrhoea, decreased activity and decreased body weight were observed. No histopathological analyses were performed. Target organs were identified in repeat-dose toxicity studies.

Repeat-dose toxicity

Repeat-dose toxicity studies were conducted in mice, rats and dogs with exposures at or multiples of the clinical exposure (Table 2). Not all studies were conducted under GLP conditions. Eltrombopag is not pharmacologically-active in these species and so exaggerated pharmacological effects cannot be assessed in the submitted studies. Nonetheless, toxicological findings were still observed with the target organs identified as the liver, and, in rodents, the kidneys and eyes. Reversibility of findings was only assessed in a single rat study.

Hepatic toxicity

Hepatotoxic effects included centrilobular vacuolation in mice that had received 100 mg/kg/day (Exposure Ratio based on area under the concentration versus time curve, AUC, $ER_{AUC}=6^{13}$), centrilobular degeneration and necrosis in rats at 60 mg/kg/day ($ER_{AUC}=6$) and hepatocellular hypertrophy in both rats and dogs at exposure ratios (ER_{AUC}) 4 and 8-fold the anticipated clinical exposure, respectively. These microscopic changes in the liver were accompanied by increased serum alkaline phosphatase (ALP) and alanine transaminases (ALT) levels (up to 16-fold) in rats and/or dogs. The mechanisms underlying the hepatotoxic effects are not clear from the submitted animal studies. Although increased CYP450 levels (specific enzymes not identified) were reported in the liver of rats treated with ≥ 100 mg/kg/day eltrombopag for 4 days and dogs treated with 30 mg/kg/day for 14 days, this finding could not fully explain the hepatic changes observed in the toxicity studies (centrilobular degeneration and necrosis as well as elevated ALP and ALT levels). Furthermore, as discussed above, eltrombopag is not extensively metabolized by CYP450 enzymes. Thus, the observed hepatic changes are more indicative of hepatotoxicity, rather than adaptive changes in the liver. The no observed effect level (NOEL) for hepatic toxicity in mice, rats and dogs was 0.6-3-fold the maximum clinical exposure (based on AUC). Caution should therefore be exercised when eltrombopag is used in clinical practice.

Renal toxicity

In mice treated with 100 mg/kg/day eltrombopag ($ER_{AUC}=6$) for 14 days, evidence of cortical renal tubular necrosis and regenerative necrosis of the medullary tubule were observed. The cause of death of the majority of early decedents in the mouse carcinogenicity study was ascribed to renal tubular degeneration/necrosis, although pulmonary and hepatic toxicity also contributed. Evidence of renal toxicity was observed at all doses (≥ 25 mg/kg/day; $ER_{AUC} \geq 1$) in the 2 year study. Although investigative studies were submitted to attempt to identify the mechanism of renal toxicity, the results were inconclusive. Only minimal renal effects were observed in rats with a renal cyst identified in 1 animal per sex in a single study at 40 mg/kg/day ($ER_{AUC}=4$). The sponsor postulated that the degenerative renal findings in mice are a result of the sensitivity of the corticomedullary region of the mouse kidney to reduced perfusion associated with moribundity. While this postulation may be theoretically plausible, in the absence of any conclusive evidence other possible mechanisms (or example, a direct nephrotoxic effect of the drug) cannot be entirely ruled out. Given the low exposure margin for this finding, the potential clinical relevance of the observed renal toxicity should not be dismissed. It was noted that evidence of renal fibrosis was also observed in juvenile rats following short term (28 days) treatment with eltrombopag (see section of *Use in Children* below) and a dose-

¹³ ER_{AUC} , exposure ratio based on animal to human AUC_{0-24h} values

related increase in severity of chronic progressive nephropathy was observed in the 2 year rat study. The relationship of these renal findings to those seen in the mouse studies is unclear.

Ocular effects

In rodents, eltrombopag was associated with an increased incidence of cataracts, a finding that was both dose and time-dependent. No ocular changes were observed in mice treated with 200 mg/kg/day ($ER_{AUC}=8$) for 2 weeks but opacity in the eyes with lenticular degeneration was observed in mice treated for 104 weeks at doses >25 mg/kg resulting in systemic exposures similar or slightly higher (>1 -fold) than the clinical exposure, based on AUC. Opacities in the eyes were identified in Week 8 and were confirmed by slit-lamp biomicroscopy in Week 34 and occurred in the majority of animals treated with 150 mg/kg/day ($ER_{AUC}=6$). Similarly, rats treated with 40 mg/kg/day eltrombopag ($ER_{AUC}=5$) for 2 weeks had no significant ophthalmological findings, but bilateral diffuse cataract or unilateral left diffuse cataract were observed in animals treated for 28 and 104 weeks at doses resulting in systemic exposures at or below the clinical exposure (based on AUC). Cataract formation progressed even after cessation of treatment. There also appeared to be an age-dependent susceptibility where 28 of 38 young adult mice (6 weeks at the initiation of dosing) treated for 12 weeks developed cataracts but minimal ocular findings and no cataracts were observed in older mice (age 26 weeks at initiation) treated with the same dose for the same length of time. Cataract formation appeared to be limited to rodents with no significant ophthalmological findings in dogs treated with 30 mg/kg/day ($ER_{AUC}=3$) for 52 weeks.

Investigative studies were performed in an attempt to identify the mechanism of ocular toxicity in rodents, without success. Eltrombopag does not accumulate in ocular tissues or the lens and is not bound by melanin. There was no difference in cataract formation between pigmented and albino mice. There was no clinical chemistry evidence of metabolic disturbances in treated rodents that may indicate a role of elevated sugars or lipids in cataract formation. While hyperprolactinemia has been known to lead to cataract formation and could potentially explain species differences in the occurrence of ocular findings, there were no other indicators of this phenomenon such as increased pituitary glands or effects on reproductive tissues. Eltrombopag was shown to be both phototoxic and photoclastogenic *in vitro*. Although a number of studies were conducted to determine a role of phototoxicity in cataractogenesis, these were of inadequate design to entirely eliminate the possibility. There is no indication that eltrombopag *per se* was involved in the observed toxicity and thus it could be mediated by (a) specific metabolite(s). Slight differences in eltrombopag metabolism exist between rodents and dogs which could potentially explain the observed species differences as well as differences in susceptibility of young versus older mice. However, as the mechanism of cataract formation has not been established and these ocular toxicities occurred at exposures similar to that expected clinically, with young animals being more susceptible and progression still occurring after cessation of treatment, a potential for adverse ocular findings clinically cannot be ruled out.

Genotoxicity and carcinogenicity

The potential genotoxicity of eltrombopag was assessed in the standard battery of tests conducted in accordance with EU/International Conference on Harmonisation (ICH) guidelines¹⁴. All assays were appropriately validated. Eltrombopag was not mutagenic in the Ames test and was negative in a rat micronucleus assay at 500 mg/kg ($ER_{Cmax}=8$) and in an unscheduled DNA synthesis assay in rat liver (*in vitro* and *in vivo*). In a mouse lymphoma L5178Y cell line assay, eltrombopag was marginally positive based on small (<3 -fold) statistically-significant increases in mutation frequency.

The carcinogenic potential of orally-administered eltrombopag was investigated in 2-year studies in mice and rats (GLP-compliant). Group sizes were appropriate but only single control groups were

¹⁴ [CPMP/ICH/174/95](#) Note for Guidance on Genotoxicity: a Standard Battery for Genotoxicity Testing of Pharmaceuticals.

included rather than the dual control groups recommended in the European Union (EU) guideline on carcinogenic potential (3BS7a). The two highest dose levels used in the mouse study (150 and 300 mg/kg/day) resulted in excessive mortality necessitating early termination for these groups (Week 63 and Week 2 for the 150 and 300 mg/kg/day, respectively). Given the early termination of these groups, the next highest dose (75 mg/kg/day) is considered to be the highest one adequately tested for carcinogenic potential. This dose resulted in a systemic exposure four times the anticipated clinical AUC. The mortality rate at the highest dose used in the rat carcinogenicity study was similar to that observed in the control group. As this dose resulted in a systemic exposure only three times the clinical exposure, testing at a higher dose may have been warranted. However, the dose was selected based on excessive mortality (18 of 24 animals) in the 28 week study at 60 mg/kg/day resulting in six times the clinical AUC. Therefore dose selection in the carcinogenicity study is considered to be acceptable. No significant neoplastic findings were identified in either study that could be attributed to eltrombopag. However, eltrombopag is a thrombopoietic agent which is not pharmacologically-active in the tested species. TPO has been shown to stimulate the proliferation of a subset of acute myeloblastic leukaemia cells *in vitro* (Matsumura *et al.*, 1995¹⁵; Corazza *et al.*, 2006¹⁶). Whilst eltrombopag did not appear to induce proliferation of lymphoblastic leukaemia cells *in vitro*, these cells generally do not respond to TPO (Corazza *et al.*, 2006) and therefore the potential of eltrombopag to stimulate existing myeloid leukemias cannot be discounted.

Although a large number of studies were conducted, the genotoxic and carcinogenic potential of eltrombopag remains inconclusive for the following reasons: some of the starting materials for eltrombopag synthesis are genotoxic (see **Impurities** below), eltrombopag was equivocally positive in the mouse lymphoma assay, was positive for photoclastogenicity (see **Phototoxicity** below) and, based on its pharmacology, has possible mitogenic effects. Therefore, statements to this effect should be included in the Product Information document.

Reproductive toxicity

Reproductive toxicity studies submitted by the Sponsor covered all stages (fertility, early embryonic development and pre- and postnatal development). Numbers of animals in the definitive studies and the timing and duration of treatment were appropriate. Doses selected were at the maximum tolerated doses. Drug administration was by the clinical route.

No functional effect was observed on male fertility in a dedicated rat reproductive toxicity study at doses up to 40 mg/kg/day resulting in exposures (based on AUC) 5-fold the clinical exposure. However, a testicular change was observed in one repeat-dose study; a sperm granuloma in a single male dog at 30 mg/kg/day for 14 days (ER_{AUC}=5). It is unclear if the histopathological change was associated with oligospermia/aspermia or sperm integrity as no sperm analysis was provided. While sperm samples were collected in a rat toxicity study, the report was not provided. The lack of an apparent functional effect on male rat fertility needs to be interpreted cautiously as sperm production may have to be decreased by 80-90% in adult male rats in order to affect fertility. In contrast, human males have substantially less epididymal sperm reserves compared to species routinely used for toxicity testing (Hayes, 1994¹⁷). Hence, a possible adverse effect in humans cannot be dismissed.

¹⁵ Matsumura I., Y. Kanakura, T. Kato, H. Ikeda, J. Ishikawa, Y. Horikawa, K. Hashimoto, Y. Moriyama, T. Tsujimura, T. Nishiura, H. Miyazaki and Y. Matsuzawa (1995) Growth response of acute myeloblastic leukemia cells to recombinant human thrombopoietin. *Blood* **86**: 703–709.

¹⁶ Corazza, F., C. Hermans, S. D'Hondt, A. Ferster, A. Kentos, Y. Benoit and E. Sariban (2006) Circulating thrombopoietin as an *in vivo* growth factor for blast cells in acute myeloid leukemia. *Blood* **107**: 2525-2530.

¹⁷ Hayes, A.W. (1994) *Principles and Methods of Toxicology*, Third Edn, Raven Press, New York. Chapter 27, p 938

There were no observed effects on the fertility of female rats that had received 20 mg/kg/day eltrombopag (ER_{AUC}=2) for 14 days prior to mating. However, at the maternally toxic dose of 60 mg/kg/day in rats (estimated ER_{AUC}=6), there was an increased incidence of pre- and post-implantation loss, resulting in a 27% decrease in live litter size and reduced fetal body weights.

In embryofetal studies in rats and rabbits at doses up to 60 and 150 mg/kg/day, respectively, eltrombopag was not apparently teratogenic but at the maternally-toxic dose of 60 mg/kg/day in rats, fetal weights were significantly reduced and there was an increase in the fetal variation 'cervical rib' (this dose in rats was also associated with evidence of embryofetal toxicity in the early embryonic study). The NOEL for this was 20 mg/kg/day (ER_{AUC}=2). Rabbits appeared to be particularly sensitive to eltrombopag with 150 mg/kg/day being the maximum tolerated dose. Extensive metabolism of eltrombopag occurs in rabbits with unchanged compound comprising only 12% of drug-related material in the plasma, resulting in relatively low exposures reaching only 0.5-fold the expected clinical AUC (Table 2). The greater toxicity in rabbits maybe associated with an eltrombopag metabolite rather than the compound *per se*.

In a peri/postnatal study in rats, the highest dose tested (60 mg/kg/day from gestation day (GD) 6 to lactation day (LD) 20) was maternotoxic with clinical signs of vaginal bleeding, decreased activity, anaemia, rough haircoat, diarrhoea and ptosis. At the next highest dose (20 mg/kg/day), there were no noticeable effects on pregnancy, parturition or lactation. There were no treatment-related effects on growth, development, neurobehavioural parameters and reproductive functions of the F₁ offspring. Eltrombopag was detected in the plasma of all 10 day old pups (F₁) for the entire 22 h sampling period resulting in significant exposures (Table 2). Plasma concentrations were similar at the 3 h, 8 h and 22 h time points. Taken together it suggests eltrombopag may be transferred during lactation and clearance reduced as a result of early postnatal development (see **Use in Children**).

As eltrombopag is not pharmacologically-active in the tested species, the submitted studies are inadequate to fully assess the risks during pregnancy. Given the findings of embryofetal toxicity in the rat studies and the inconclusive findings in the genotoxicity studies, eltrombopag must not be used in pregnant women. Caution should also be exercised when it is used in women with child-bearing potential and in lactating females.

Table 2. Relative exposure of eltrombopag in reproductive toxicity studies

Study	Species (strain)	Day of sampling; (treatment period)	Dose (mg/kg/day)	AUC _{0-24h} (µg·h/mL)	AUC ratio
CD2005/00236/00 [male fertility]	Rat (SD)	data from studies CD2003/00252/00 and CD2003/00327/00	10	164	1
			20	341	2
			40	892	5
CD2003/00612/00, CD2003/00938/00, CD2005/00331/03 [fertility, embryo - fetal, postnatal]	Rat (SD)	data from studies CD2003/00327/00 and CD2004/00332/00	10	164	1
			20	341	2
			60	1044	6
CD2005/00331/03 [peri/postnatal]	Rat (SD) F ₁ progeny	post-partum Day 10	10	73 ^a	0.4
			20	226 ^a	1.3
CD2003/01136/00 [embryofetal]	Rabbit (NZW)	GD19; (GD7-GD19)	30	8	0.05
			80	43	0.26
			150	90	0.5
TRA100773A/B	Human	-	75 mg	168	-

^aAUC_{0-22h} recorded

Use in children

Three studies in juvenile rats were submitted. One was a dose-range finding study. Plasma exposures were generally higher in younger (age 14 days) compared with older animals (age 32 or 62) (Table 3), most likely a result of postnatal development of hepatic excretory pathways reducing plasma clearance in neonatal rats (Arrese *et al.*, 1998¹⁸).

Table 3. Relative exposure of eltrombopag in juvenile rat studies

Study	Day of dosing	Age	Dose (mg/kg/day)	AUC _{0-24h} (µg.h/mL)	AUC ratio ^a	
CD2005/00661/00	10	14 days	1	178	1	
			5	451	3	
			15	1202	7	
CD2006/00651/00	30	62 days	5	46	0.3	
			15	227	1.4	
			40	850	5	
CD2005/00660/00	10	14 days	10	977	6	
			30	2274	14	
			60	3990	24	
		Day of dosing	Age (days)	Dose (mg/kg/day)	C _{24h} (µg/mL)	C _{24h} ratio (Day 10/Day 30)
	10/28	14/32	10	33/1.1	30	
			30	80/3.9	21	

^aRatio of animal: human AUC using a clinical AUC of 168 µg.h/mL

Toxicities observed in juvenile animals treated with 15 mg/kg/day eltrombopag (ER_{AUC}=7) that were not seen in adults include slight anaemia, myeloid hypercellularity, renal fibrosis and lymph node haemorrhage. There were no treatment-related ophthalmological changes in these studies but the duration of dosing (28 days) may not have been sufficient for these changes to manifest. Younger adult mice (6 weeks) were more susceptible to cataracts from eltrombopag treatment than older mice, but with an unknown mechanism and insufficient data, it is unclear if juveniles would be more susceptible than young adults.

Local tolerance

Eltrombopag was not classified as a skin irritant in a synthetic reconstituted human epidermal assay or a skin sensitiser in the mouse lymph node assay. However, eltrombopag induced corneal swelling and was classified as a strong eye irritant in a rabbit enucleated eye test. It is unclear if these ocular effects have any connection with cataract formation in rats. Eltrombopag (at ≥1 mg/mL) produced haemolysis in whole rabbit blood but no precipitation was observed in rabbit serum. Haemolysis by eltrombopag occurred at concentrations exceeding that expected clinically and this is not of particular concern.

Immunotoxicity

There was no evidence of immunotoxicity in repeat-dose studies or in a dedicated immunotoxicity study in rats at doses up to 40 mg/kg/day for 4 weeks (estimated ER_{AUC}=4).

¹⁸ Arrese, M., M. Ananthanarayanan and F.J. Suchy (1998) Hepatobiliary transport: molecular mechanisms of development and cholestasis. *Paediat. Res.* **44**: 141-147.

Phototoxicity

Eltrombopag was phototoxic in an *in vitro* assay (IC₅₀ 0.543 µg/mL with 315-400 nm light). However, in *in vivo* studies in hairless mice at 150 mg/kg/day PO for 14 days (ER_{AUC}=10), there was no evidence of cutaneous phototoxicity. There was no indication of ocular phototoxicity in albino or pigmented rats that had received 40 mg/kg/day eltrombopag for 14 days (ER_{AUC}≈10) nor mice that had received 100-150 mg/kg/day PO eltrombopag for 12 weeks. However, treatment was not of sufficient length to eliminate a role of phototoxicity in cataractogenesis (see **Repeat-dose toxicity**). Eltrombopag was also photoclastogenic *in vitro*, but this occurred only at cytotoxic concentrations at high light exposures (700 mJ/cm²). Taken together, eltrombopag was found to be photo active; the potential clinical relevance of this finding largely remains unclear.

Impurities

The genotoxic impurities were demonstrated to be below the threshold for toxicological concern (TTC) limit of 1.5µg/day recommended by the current regulatory guideline for genotoxic impurities (EU guidance document CPMP/SWP/5199/02).

Nonclinical Summary and Conclusions

- Eltrombopag is a thrombopoietin (TPO) receptor agonist. The activation of TPO-regulated genes by eltrombopag was demonstrated *in vitro* and an increase in platelet count was observed in eltrombopag-treated chimpanzees, a species with eltrombopag-responsive TPO receptors. TPO receptor agonistic activity in chimpanzees was observed at concentrations and exposures as low as 1/10th of those expected clinically. The nonclinical data demonstrating thrombopoietic and megakaryopoietic activity support the proposed indication at the proposed clinical dose.
- There was no noticeable effect of eltrombopag on the CNS or respiratory function in rats with oral doses resulting in plasma concentrations 6-fold that expected clinically. *In vitro* concentration-dependent inhibition of hERG K⁺ channel tail current and lower maximum rates of depolarisation and action potential duration in dog Purkinje fibres were observed with eltrombopag concentrations *ca* 40-fold lower than the anticipated clinical plasma concentration. Though no *in vivo* cardiovascular abnormalities were observed at doses reaching plasma concentrations 3-4-fold that expected clinically, the *in vitro* data suggest potential cardiotoxicity.
- Oral bioavailability of eltrombopag was high in dogs (83-92%) and monkeys (89-100%) but relatively low in rodents (26-41%). Terminal elimination was slow. Eltrombopag was highly bound to plasma proteins and wide tissue distribution was observed after systemic administration. Penetration of the blood-brain-barrier was poor and there was no indication of melanin binding or accumulation in ocular tissues. Metabolism of eltrombopag was moderate in all species, except rabbits, with the major pathways involving oxidation and glucuronidation. The predominant route of excretion was in the faeces.
- Submitted studies suggested eltrombopag has the potential to affect the pharmacokinetics of co-administered drugs that are substrates of CYP2C8, CYP2C9, UGTs, OATP1B1 or BCRP. As eltrombopag is a substrate of BCRP, inhibitors of this transporter could potentially affect eltrombopag pharmacokinetics.
- Repeat-dose toxicity studies of adequate length were conducted in mice, rats and dogs. Hepatic toxicity with elevated transaminases was observed in all species with the NOEL at or below the anticipated clinical exposure. These findings are considered to be potentially clinically-relevant. Renal toxicity was observed in mice at exposures similar to that expected clinically. Findings of renal fibrosis were also evident in juvenile rats following short term (28 days) treatment with eltrombopag.

- In rodents, eltrombopag was associated with an increased incidence of cataracts, both dose- and time-dependently. As the mechanism of cataract formation has not been fully established and the ocular change occurred at exposures similar to that expected clinically, with young animals being more susceptible and progression still occurring after cessation of treatment, a potential for adverse ocular findings clinically cannot be ruled out. It is suggested that provisions be put in place to monitor for hepatic, renal and ocular toxicity.
- Eltrombopag was not carcinogenic in mice or rats, and showed no unequivocal evidence of genotoxicity in a standard battery of assays. However, eltrombopag is not pharmacologically active in rodents; this may significantly reduce the negative predicting values of the mouse and rat carcinogenicity studies.
- No adverse functional effects on male or female fertility were observed in rats. Eltrombopag was not apparently teratogenic in rats or rabbits, but at a maternal toxic dose it was associated with increased pre-/post-implantation loss, decreased fetal bodyweight and increased incidences of fetal variations in rats. In a peri/postnatal study in rats, no effects on developmental parameters were apparent. Pups from lactating rats showed significant exposure to eltrombopag, suggesting transfer during lactation.
- Eltrombopag was not a skin irritant or skin sensitiser but was a strong eye irritant.
- There was no evidence of immunotoxicity.
- Eltrombopag was phototoxic and photoclastogenic *in vitro*, but there was no evidence of cutaneous phototoxicity in rodents at 10-fold the expected clinical exposure. A role of phototoxicity in cataract formation cannot be dismissed.
- Genotoxic compounds are used or generated during the synthesis of eltrombopag. Levels of these genotoxic compounds must therefore be kept below the TTC.

There are several nonclinical concerns regarding this application. The toxicological profile does not include receptor-mediated toxicities and negative findings in submitted studies are difficult to interpret due to the lack of suitability of chosen species. Based on currently-available nonclinical data, the safety profile of eltrombopag appears to be inferior to the currently registered TPO agonist, romiplostim, with the following potentially clinically-relevant findings:

- *In vitro* indications of cardiotoxicity at concentrations below the expected clinical C_{max} ;
- The NOEL for hepatic toxicity in animals was only 0.6 to 3-fold the exposure expected clinically.
- Increased incidence of cataracts with chronic administration at doses resulting in exposures similar to the clinical exposure; and
- Evidence of renal toxicity in mice at systemic exposures similar to that anticipated clinically.

Due to deficiencies in the nonclinical dossier and the numerous adverse findings, an acceptable safety profile cannot be considered to have been demonstrated in the submitted nonclinical data for the proposed product (Eltrombopag olamine, Revolade).

IV. Clinical Findings

Introduction

Clinical Pharmacology Data

In addition to a number of clinical pharmacology studies, there were bioequivalence studies conducted to assess the effect of food on the bioavailability of eltrombopag (Study 497115/005) and to assess the relative bioavailability of eltrombopag tablets used in the Phase II and Phase III clinical

studies (Study TRA102863, Study TRA105122). The tablets used in the Phase II were manufactured at the R&D site and for the Phase III studies were manufactured at a commercial site.

Efficacy and Safety Data

This application included efficacy and safety data of eltrombopag for the treatment of chronic ITP, based principally on the results of 3 double-blind, placebo-controlled clinical studies (TRA102537/RAISE, TRA100773A and TRA100773B) and 2 open-label studies (TRA108057/REPEAT and TRA105325/EXTEND). In addition, ocular safety data were provided from an observational study (TRA108132/LENS). Up to the time of this submission date, the clinical development programme has resulted in the largest clinical database of adult patients with previously-treated chronic ITP, with a total of 493 subjects (422 received eltrombopag; 71 received placebo).

All 5 efficacy studies recruited adult subjects with previously treated chronic ITP, as defined in the American Society for Hematology (ASH)/British Committee for Standards in Haematology (BCSH) guidelines. Chronic ITP is a serious and potentially life-threatening disease; therefore, all subjects were allowed to receive standard of care, provided the dose was stable at baseline.

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

TRA100773A was a dose-ranging Phase II trial that used an adaptive sequential design which allowed efficient identification of a safe and efficacious dose through a planned interim analysis. TRA100773B and RAISE were Phase III trials in which subjects were randomised on a 1:2 basis to placebo:eltrombopag 50 mg (starting dose), which was the lowest effective dose identified from TRA100773A. The RAISE study was designed to emulate clinical practice, allowing subjects to taper or discontinue baseline ITP medications (or example, corticosteroids) and to use rescue medication as clinically indicated.

REPEAT and EXTEND were global, open-label, single-group studies designed to evaluate the effect of re-treatment (REPEAT) and long-term treatment (EXTEND) with eltrombopag. Both open-label studies had different platelet count entry criteria compared to the 3 double-blind studies. In REPEAT, subjects were required to have baseline platelet counts between 20 and 50 Gi/L. As off-therapy periods were necessary to examine eltrombopag re-treatment, subjects entering REPEAT were required to have a higher baseline platelet count than in the double-blind studies to minimise any potential bleeding risk through participation in the study. The REPEAT study was designed to evaluate the efficacy, safety and tolerability of eltrombopag, 50 mg (starting dose) once daily, over 3 cycles. The duration of both the on-therapy and the off-therapy periods of each cycle were determined by the subject's platelet count.

In EXTEND no platelet count entry criteria were specified for eligibility, as one of the key secondary endpoints was for subjects to reduce concomitant medications. EXTEND is an ongoing dose-adjustment study designed to evaluate the safety and efficacy of eltrombopag as a treatment for subjects with chronic ITP. Eligible subjects must have been previously enrolled in an eltrombopag trial and could have received either placebo or eltrombopag.

Pharmacokinetics

Healthy Subjects

Study 497115/001 (single dose PK, 3 to 9mg)

Study 497115/001 evaluated plasma eltrombopag pharmacokinetics (PK) following administration of single escalating doses of 3 mg, 6 mg, and 9 mg to healthy adult male subjects. Subjects received a single dose of eltrombopag following an overnight fast and remained fasted for four hours after dosing. Plasma PK samples were collected over 72 hours after single dose administration. Twenty-four subjects were enrolled. All subjects were male; the mean (range) age was 32 years (22 to 42 years) and weight was 80.7kg (54.0 to 101kg). A total of 18 subjects received eltrombopag (six subjects at each dose) and six subjects received placebo.

Pharmacokinetic Results

Plasma eltrombopag concentrations were quantifiable within 1 to 1.5 hours across the doses and remained quantifiable in all subjects through 24 hours for the 3 mg dose, 32 hours for the 6 mg dose, and 72 hours for the 9 mg dose. Plasma eltrombopag AUC from 0 h to infinity ($AUC_{(0-\infty)}$) and C_{max} increased in a greater than dose proportional manner where the slope estimate (90% Confidence Interval, CI) was 1.51 (1.14, 1.88) for $AUC_{(0-\infty)}$ and 1.68 (1.39, 1.97) for C_{max} over a range of 3 mg to 9 mg.

Study 497115/002 (single and repeat dose escalation, 5 to 75 mg once a day)

Pharmacokinetic Results

Results following single dose and repeat dose administration are summarised in Tables 4 and 5. Following single dose administration, plasma eltrombopag concentrations were quantifiable within 1 hour and remained quantifiable through the 48-hour sampling period. Plasma eltrombopag $AUC_{(0-\infty)}$ and C_{max} increased in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.13 (1.04, 1.22) for $AUC_{(0-\infty)}$ and 1.15 (1.07, 1.24) for C_{max} over a range of 5 mg to 75 mg.

Table 4: Summary of Single Dose Plasma Eltrombopag PK Parameters in Healthy Subjects, Study 497115/002.

Dose (mg)	N	AUC(0-∞) (µg.h/mL)	Cmax (µg/mL)	tmax (h)	t1/2 (h)
5	9	3.65 (2.77, 4.81) [35]	0.318 (0.257, 0.394) [25]	2.50 (2.00, 4.00)	10.1 (7.53, 13.6) [36]
10	9	8.72 (6.83, 11.1) [35]	0.625 (0.474, 0.824) [32]	3.00 (2.00, 6.00)	16.1 (13.4, 19.5) [27]
20	9	16.3 (11.9, 22.4) [41]	1.27 (1.02, 1.58) [28]	3.00 (2.00, 6.00)	14.7 (12.5, 17.3) [21]
30	8	29.1 (21.8, 38.9) [28]	2.64 (1.94, 3.60) [31]	2.50 (1.50, 4.00)	15.7 (14.4, 17.1) [11]
50	9	57.8 (42.1, 79.2) [34]	4.90 (3.64, 6.60) [34]	3.00 (2.00, 4.00)	18.0 (15.7, 20.6) [17]
75	8	71.8 (53.5, 96.5) [37]	6.03 (4.79, 7.60) [30]	4.00 (2.10, 6.00)	16.1 (12.2, 21.1) [35]

Data presented as geometric mean (95% CI) [percent **between-subject** coefficients of variation (%CVb)], except t_{max} presented as median (minimum, maximum).

Table 5: Summary of Repeat Dose (Day 10) Plasma Eltrombopag PK Parameters in Healthy Subjects, Study 497115/002

Dose (mg)	N	AUC(0-τ) (µg.h/mL)	Cmax (µg/mL)	tmax (h)
5	9	3.44 (2.73, 4.34) [30]	0.333 (0.277, 0.400) [24]	4.00 (2.00, 6.00)
10	9	7.67 (5.83, 10.1) [34]	0.700 (0.515, 0.952) [32]	3.00 (2.00, 6.00)
20	9	16.8 (12.7, 22.2) [37]	1.53 (1.13, 2.09) [36]	4.00 (2.00, 6.00)
30	8	29.0 (22.4, 37.5) [28]	2.97 (2.36, 3.74) [25]	3.00 (2.00, 4.00)
50	9	57.4 (46.5, 70.9) [28]	5.76 (4.69, 7.08) [29]	4.00 (2.00, 6.00)
75	8	79.0 (65.2, 95.8) [23]	7.27 (6.36, 8.30) [15]	5.00 (2.00, 10.0)

Data presented as geometric mean (95% CI) [%CVb], except t_{max} presented as median (minimum, maximum).

Following repeat dose administration, plasma eltrombopag $AUC_{(0-\tau)}$ (the area under the concentration-time curve calculated by linear trapezoidal rule from time zero to the end of the dosing interval (i.e., 24 h) at steady state) and C_{max} increased in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.19 (1.11, 1.26) for $AUC_{(0-\tau)}$ and 1.20 (1.12, 1.27) for C_{max} over a range of 5 mg to 75 mg once daily (QD). Following QD dosing, geometric least squares (GLS) mean ratio (90% CI) estimates of Day 10 to Day 1 $AUC_{(0-\tau)}$ were; 5 mg: 1.15 (0.91, 1.45), 10 mg: 1.26 (0.987, 1.61), 20 mg: 1.38 (1.17, 1.62), 30 mg: 1.37 (1.20, 1.56), 50 mg: 1.41 (1.20, 1.64), and 75 mg: 1.56 (1.23, 1.97). GLS mean ratios of Day 10 to Day 1 C_{max} indicated no significant accumulation across all doses, where point estimates ranged from 1.05 to 1.21.

Liver Cytochrome P450 (CYP) activity

Eltrombopag did not inhibit or induce the metabolism of probe substrates for CYP1A2, 2C9, 2C19, and 3A4 based on the ratio (95% CIs) for the CYP probe substrate co-administered with eltrombopag versus administration of the CYP probe substrate alone. For CYP1A2, the paraxanthine/caffeine concentration ratio at 8 hours post-dose on Day 9 versus Day 2 was 0.97 (0.91-1.03). For CYP2C9, the urine total 4-hydroxyflurbiprofen recovery ratio over 12 hour post-dose on Day 9 versus Day 2 was 0.96 (0.94-0.98) and the urine free 4-hydroxyflurbiprofen recovery ratio over 12 hour post-dose on Day 9 versus Day 2 was 0.93 (0.89-0.98). For CYP2C19, the plasma omeprazole/5-hydroxyomeprazole concentration ratio at 2 and 3 hours post-dose on Day 9 versus Day 2 was 1.00 (0.93-1.08). For CYP3A4, the plasma midazolam $AUC_{(0-\infty)}$ on Day 8 versus Day 1 was 1.04 (0.96–1.13).

Study TRA105122 (single dose PK, 25 to 50 mg)

Study TRA105122 was a pivotal, Phase I, open-label, randomised, two-period, incomplete crossover study designed to demonstrate bioequivalence of Phase II and Phase III eltrombopag tablets. In each period, subjects received a single dose of eltrombopag following an overnight fast and remained fasted for four hours after dosing. Plasma PK samples were collected over 72 hours after single dose administration in each period. There was a minimum 10-day washout between each period. The primary bioequivalence assessment was between eltrombopag tablets of the same strength, and in addition, comparisons were made between 25 mg and 50 mg tablet strengths to assess dose proportionality.

Pharmacokinetic Results

The Phase II and Phase III 50 mg tablets were bioequivalent. Following single dose administration in the fasted state, the Phase III 25 mg tablet delivered an equivalent mean $AUC_{(0-\infty)}$, but a 16% higher mean C_{max} compared to the Phase II 25 mg oral film-coated tablet. Median time to maximum concentration of drug in serum (t_{max}) occurred between 3 and 4 h post-dose for all tablets. Median percentage of $AUC_{(0-\infty)}$ obtained by extrapolation (%AUC_{ex}) were 7 to 10% across the treatments, with only four subjects having %AUC_{ex} >20% (Table 6).

Table 6: Study TRA105-122 – Summary of eltrombopag PK parameters and bioequivalence results.

Plasma Eltrombopag PK Parameter	Eltrombopag 25 mg (N=48)			Eltrombopag 50 mg (N=46)		
	Phase II Tablet Treatment A	Phase III Tablet Treatment B	Phase III vs. Phase II Treatment B/A	Phase II Tablet Treatment C	Phase III Tablet Treatment D	Phase III vs. Phase II Treatment D/C
AUC(0-∞) (µg.h/mL)	31.0 (26.9, 35.7) [52]	33.9 (29.8, 38.5) [47]	1.10 (0.992, 1.22)	75.6 (65.9, 86.7) [49]	79.5 (69.2, 91.4) [50]	1.05 (0.943, 1.17)
C _{max} (µg/mL)	2.47 (2.13, 2.86) [54]	2.85 (2.51, 3.23) [46]	1.16 (1.04, 1.30)	5.73 (4.99, 6.58) [49]	6.36 (5.64, 7.17) [42]	1.11 (0.989, 1.24)

geometric mean (95% CI) [CVb%] for PK summary and GLS mean ratio (90% CI) for treatment comparisons

ND=not determined

Treatment A: One Phase II 25 mg tablet administered fasted

Treatment B: One Phase III 25 mg tablet administered fasted

Treatment C: One Phase II 50 mg tablet administered fasted

Treatment D: One Phase III 50 mg tablet administered fasted

CVb%=percent between-subject coefficients of variation

Using bioequivalence criteria, the Phase II and Phase III 25 mg tablets each delivered lower dose-normalised plasma eltrombopag AUC_(0-t), AUC_(0-∞), and C_{max} values than the either of the 50 mg tablets, with the exception the 25 mg Phase III vs. 50 mg Phase II tablet which delivered an equivalent C_{max}.

Consistent with the results of Study 497115/002, which assessed dose proportionality over the dose range of 5 mg to 75 mg, plasma eltrombopag AUC_(0-∞) and C_{max} increased in a slightly greater than dose proportional manner between 25 mg and 50 mg in Study TRA105122.

Study TRA102860 (repeat dose escalation, 50 to 200 mg once a day)

Pharmacokinetic Results

PK results are summarised in Table 7 below. Following repeat dosing in Part 2 of the study, plasma eltrombopag AUC_(0-τ) and C_{max} increased in a dose proportional manner between 50 mg and 150 mg, where the slope estimate (90% CI) was 1.04 (0.987, 1.09) for AUC_(0-τ) and 1.01 (0.942, 1.08) for C_{max}. Between doses of 100 mg and 200 mg in Part 1 of the study, AUC_(0-τ) increased with increasing dose; whereas, there did not appear to be a further increase in C_{max} beyond 150 mg. Statistically significant accumulation in AUC_(0-τ) was observed for all three doses between Day 1 and Day 5; GLS mean ratio (90% CI) estimates were for 100 mg: 1.66 (1.35, 2.04), 150 mg: 1.69 (1.39, 2.05), and 200 mg: 1.81 (1.30, 2.52). GLS mean ratio (90% CI) estimates for C_{max} were for 100 mg: 1.45 (1.15, 1.83), 150 mg: 1.32 (0.984, 1.77), and 200 mg: 1.35 (0.975, 1.88).

Table 7: Summary of Repeat Dose (Day 5) Plasma Eltrombopag PK Parameters in Healthy Subjects, Study TRA102860

Dose (mg)	N	AUC(0- τ) ($\mu\text{g}\cdot\text{h}/\text{mL}$)	C _{max} ($\mu\text{g}/\text{mL}$)	t _{max} (h)
Part 1				
100	8	161 (116, 222) [40]	14.9 (10.9, 20.4) [39]	3.00 (2.50, 4.00)
150	8	239 (187, 304) [30]	22.8 (18.2, 28.5) [27]	2.80 (1.50, 4.00)
200	7	302 (198, 463) [49]	24.7 (16.2, 37.7) [48]	2.50 (2.50, 3.00)
Part 2				
50	60	65.4 (59.7, 71.6) [36]	6.40 (5.87, 6.97) [34]	3.19 (2.17, 6.22)
150	73	204 (186, 223) [39]	19.0 (17.4, 20.6) [37]	2.67 (1.67, 6.20)

Data presented as geometric mean (95% CI) [%CVb], except t_{max} presented as median (minimum, maximum).

Study TRA102863 (open-label, two-period, crossover study)

Study TRA102863 was a randomised, open-label, two-period, period-balanced, crossover study with three parallel groups to evaluate the relative bioavailability of single oral doses of SB-497115-GR phase III tablets [50 mg, 75 mg, 100 mg] compared to SB-497115-GR phase II tablets [25 mg and 50 mg] in healthy volunteers.

Primary objectives were:

- To evaluate the relative bioavailability of phase III SB-497115-GR 50 mg tablets relative to phase II SB-497115-GR 50 mg tablets.
- To evaluate the relative bioavailability of one phase III SB-497115-GR 75 mg strength tablet relative to concomitant administration of one phase II SB-497115-GR 25 mg tablet PLUS one SB-497115-GR 50 mg tablet.
- To evaluate the relative bioavailability of one phase III SB-497115-GR 100 mg tablet relative to two phase II SB-497115-GR 50 mg tablets.

Pharmacokinetic Results

Mean %AUC_{ex} values were 11 to 12% for the 50 mg and 75 mg doses and 15 to 16% for the 100 mg doses.

Study TRA102-861(mass balance study)

This was an open-label, single dose, mass balance study. Six healthy adult males received a single 75 mg oral dose of radioactive carbon labelled, [¹⁴C], eltrombopag ($\leq 100 \mu\text{Ci}$).

The primary objectives of the study were:

- To determine the total recovery and relative excretion of radiocarbon in urine and faeces after a single, oral dose of [¹⁴C]-eltrombopag 75 mg (100 μCi) in healthy male subjects.
- To generate samples (for a separate study) with which to characterise and quantify the metabolic profile of eltrombopag in plasma, urine, and faeces following administration of [¹⁴C]-eltrombopag olamine to healthy male subjects.

- To compare total radiocarbon (drug-related material) in blood and plasma relative to parent plasma concentration.

The secondary objectives of the study were:

- To determine plasma eltrombopag PK parameters following single-dose oral administration of [¹⁴C]-eltrombopag 75 mg (100 µCi).
- To evaluate the safety and tolerability of eltrombopag 75 mg following single-dose, oral administration in healthy male subjects.

Pharmacokinetic Results

Eltrombopag rapidly appeared in plasma with a median t_{\max} of 2.5 h. After reaching C_{\max} , plasma concentrations of the parent compound declined with a mean apparent terminal phase half-life ($t_{1/2}$) of 32.3 h. Whole blood and plasma concentrations of total radiocarbon declined more slowly, with mean apparent terminal phase $t_{1/2}$ values of 51.9 and 49.3 h, respectively.

Pharmacokinetic parameters for plasma eltrombopag and plasma and blood total radiocarbon showed that eltrombopag accounted for 64% of total radiocarbon in plasma based on AUC. 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. Eltrombopag, the parent compound, was not detected in urine.

Pharmacokinetics in Subjects with Idiopathic Thrombocytopenic Purpura

Study TRA100773A

Study TRA100773A was a global, dose-ranging Phase II trial that used an adaptive sequential design in adult subjects with previously-treated chronic ITP. Eligible subjects had not responded to or had relapsed within 3 months of their most recent therapy for ITP, and had a platelet count of <30 Gi/L on Day 1 (or within 24 hours prior to dosing). Subjects with known secondary thrombocytopenia were excluded from the trial.

Subjects were randomised to treatment (placebo, eltrombopag 30 mg, 50 mg or 75 mg) in a 1:1:1:1 ratio. Randomisation was stratified based upon use or non-use of ITP medications at baseline, splenectomy status and baseline platelet count (≤ 15 Gi/L or >15 Gi/L). Subjects were administered study medication once-daily for up to 6 weeks; subjects who attained a platelet count >200 Gi/L were to discontinue treatment with study medication.

One-hundred-seventeen subjects received study drug (eltrombopag [N=88] or placebo [N=29]). Seventy-three subjects (62%) were female and 44 (38%) were male, and the majority, 79 (68%), were Caucasian (European descent). Median (range) age was 50 years (18 to 85 years). Overall, 38 subjects (32%) were receiving other ITP medication at randomisation, 55 (47%) had prior splenectomy, and 56 (48%) had baseline platelet counts of <15 Gi/L.

In addition, plasma PK samples were collected from each of an additional 77 subjects. A total of 404 samples from TRA100773A were available for population PK analysis.

Study TRA100773B

Study TRA100773B was a global, randomised, double-blind, placebo-controlled Phase III trial in adults with previously treated chronic ITP. Eligible subjects had not responded to or had relapsed within 3 months of their most recent therapy for ITP and had a platelet count of <30 Gi/L on Day 1 (or within 24 hours prior to dosing). Subjects who enrolled in TRA100773A were not permitted to enrol in TRA100773B.

Subjects were randomised to treatment (eltrombopag 50 mg or placebo) in a 2:1 ratio.

Subjects with a platelet count <50 Gi/L on or after Day 22 were allowed to increase their dose to eltrombopag 75 mg or matching placebo. Randomisation was stratified based upon use or non-use of ITP medications at randomisation, splenectomy status and baseline platelet count (≤ 15 Gi/L or >15 Gi/L). Subjects were dosed once-daily for up to 6 weeks. Subjects who attained a platelet count >200 Gi/L discontinued treatment with study medication to minimise the risk of developing thrombocytosis.

Seventy subjects (61%) were female and 44 (39%) were male and the majority, 76 (67%), were of Caucasian (European descent). Median (range) age was 48 years (19 to 84 years). Overall, 49 subjects (43%) were receiving other ITP medication at randomisation, 45 (39%) had a prior splenectomy, and 55 (48%) had baseline platelet counts of <15 Gi/L.

Pharmacokinetic Results

The plasma eltrombopag concentration-time data collected in subjects with ITP in TRA100773A and TRA100773B were combined with data from healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for patients with ITP are presented for each dose studied in Table 8.

Table 8: Plasma Eltrombopag $AUC_{(0-\tau)}$ and C_{max} Estimates for Subjects with ITP in Studies TRA100773A and TRA100773B

Eltrombopag Dose (QD)	N	$AUC_{(0-\tau)}$ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	C_{max} ($\mu\text{g}/\text{mL}$)
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). $AUC_{(0-\tau)}$ and C_{max} on population PK post-hoc estimates.

The parameters of the final Population PK (PopPK) analysis showed that concurrent administration of corticosteroids reduced plasma eltrombopag total clearance (CL/F) 26% (translating to 35% higher plasma eltrombopag $AUC_{(0-\tau)}$). The mechanism for this potential interaction is not understood.

When adjusting for body weight differences (that is, assuming same weight), East Asian subjects had 33% lower plasma eltrombopag CL/F (translating to 50% higher plasma eltrombopag $AUC_{(0-\tau)}$) compared to non-Asian subjects who were predominantly Caucasian. Based on individual post-hoc estimates from the final PopPK model, where all significant covariates were applied to the ITP subjects (weight, sex, corticosteroid use, race), East Asian ITP subjects had 87% higher plasma eltrombopag $AUC_{(0-\tau)}$.

When adjusting for body weight differences (that is, assuming same weight), female subjects had 19% lower plasma eltrombopag CL/F (translating to 23% higher plasma eltrombopag $AUC_{(0-\tau)}$) compared to male subjects. However, female ITP subjects included in the analysis were, on average, 14 kg lighter than male ITP subjects. Based on individual post-hoc estimates from the final Population PK (PopPK) model, where all significant covariates were applied to the ITP subjects (weight, sex, corticosteroid use, race), women had 50% higher plasma eltrombopag $AUC_{(0-\tau)}$.

Based on the population PK results, plasma eltrombopag exposure in an ITP patient is dependent on weight, sex, race, and corticosteroid use. Race had the largest impact on plasma eltrombopag CL/F, with Asian patients having a mean (95% CI) 33% (26 to 41%) lower CL/F than non-Asian subjects.

Pharmacokinetics in Japanese Subjects

Study TRA104603 (single dose PK in healthy Japanese subjects, 30 to 100 mg)

Study TRA104603 was a single-centre, placebo-controlled, double-blind, randomised, 4-period incomplete crossover, single dose escalation study conducted in Japanese healthy male subjects living in Japan. Subjects were randomised to one of four treatment sequences and received placebo and three of the four eltrombopag doses of 30 mg, 50 mg, 75 mg, or 100 mg. This study used eltrombopag tablets of 5 mg and 25 mg strengths.

Sixteen subjects were enrolled in the study. All subjects were male and Japanese; mean (range) age was 26 years (20 to 33 years) across the doses and weight was approximately 61 kg (55.5 to 69.6kg).

Pharmacokinetic Results

Following single dose administration, plasma eltrombopag $AUC_{(0-\infty)}$ increased in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.11 (1.03, 1.20) and C_{max} increased in a dose proportional manner where the slope estimate (90% CI) was 1.02 (0.931, 1.11) over a range of 30 mg to 100 mg.

Study TRA105580 (single and repeat dose PK in healthy Japanese subjects, 25 to 75 mg QD)

Study TRA105580 was a single-centre, placebo-controlled, single-blind, randomised, parallel, single and repeat dose escalation study in Japanese healthy male subjects living in Japan. Three dose levels, including 25 mg, 50 mg, and 75 mg, were administered as single doses, followed by a 5-day wash-out, then as repeat doses for 10 days. At each dose level, ten subjects received eltrombopag and four subjects received placebo. This study used eltrombopag 25 mg tablets.

Forty-two subjects were enrolled in the study. All subjects were male and Japanese; mean age was 26 years (20 to 34 years) and weight was 63.6kg (55.8 to 82.0kg).

Pharmacokinetic Results

Tabular summaries of results are provided in Tables 9 and 10. Following single dose administration, plasma eltrombopag $AUC_{(0-\infty)}$ and C_{max} increased with increasing dose over the range of 25 mg to 75 mg. Dose proportionality was not statistically tested; however, based on geometric mean values for the 50 mg and 75 mg doses, $AUC_{(0-\infty)}$ and C_{max} increased approximately 30% for a 50% increase in dose, suggesting less than dose proportional increases in exposure.

Table 9: Summary of Single Dose Plasma Eltrombopag PK Parameters in Study TRA105580

Dose (mg)	N	$AUC_{(0-\infty)}$ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	C_{max} ($\mu\text{g}/\text{mL}$)	t_{max} (h)	$t_{1/2}$ (h)
25	10	51.1 (37.5, 69.7) [45]	3.40 (2.70, 4.29) [33]	3.0 (2.0, 5.0)	29.2 (25.8, 33.2) [18]
50	10	101 (78.7, 130) [36]	6.03 (4.50, 8.10) [43]	3.0 (1.5, 5.0)	30.5 (26.4, 35.2) [20]
75	10	130 (105, 161) [31]	7.90 (6.02, 10.4) [40]	3.0 (2.0, 6.0)	31.6 (26.5, 37.6) [25]

Data presented as geometric mean (95% CI) [%CVb], except t_{max} presented as median (minimum, maximum).

Table 10: Summary of Repeat Dose (Day 10) Plasma Eltrombopag PK Parameters in Study TRA105580

Dose (mg)	N	AUC(0- τ) ($\mu\text{g}\cdot\text{h}/\text{mL}$)	C _{max} ($\mu\text{g}/\text{mL}$)	t _{max} (h)
25	10	55.8 (43.0, 72.4) [38]	4.68 (3.86, 5.68) [27]	3.0 (1.5, 5.0)
50	9	130 (107, 158) [26]	10.4 (8.68, 12.4) [23]	4.0 (2.0, 5.0)
75	10	161 (138, 188) [22]	12.5 (10.4, 14.9) [25]	4.0 (2.0, 5.0)

Data presented as geometric mean (95% CI) [%CVb], except t_{max} presented as median (minimum, maximum).

Following repeat dose administration, plasma eltrombopag AUC_(0- τ) and C_{max} increased with increasing dose over the range of 25 mg to 75 mg QD. Dose proportionality was not formally tested; however, based on geometric mean values for the 50 mg and 75 mg doses, AUC_(0- ∞) and C_{max} increased approximately 20 to 25% for a 50% increase in dose, suggesting less than dose proportional increases in exposure.

Statistically significant accumulation in AUC_(0- τ) and C_{max} was observed for all three doses between Day 1 and Day 10; GLS mean ratio (90% CIs) estimates were for 25 mg: 1.75 (1.50, 2.05), 50 mg: 1.95 (1.64, 2.32), and 75 mg: 2.06 (1.74, 2.44). GLS mean ratio (90% CI) estimates for C_{max} were for 25 mg: 1.38 (1.14, 1.65), 50 mg: 1.57 (1.28, 1.93), and 75 mg: 1.58 (1.28, 1.94). Ratios of Day 10 AUC_(0- τ) to Day 1 AUC_(0- ∞), presented as GLS mean ratio (90% CI), indicate that plasma eltrombopag PK was time invariant at 25 mg: 1.09 (0.932, 1.28) and 50 mg: 1.18 (0.998, 1.39), but time-dependent at 75 mg: 1.24 (1.06, 1.45).

Pharmacokinetics in Subjects with Hepatic Impairment

Study TRA103452

Study TRA103452 investigated plasma eltrombopag PK in subjects with mild, moderate, and severe hepatic impairment compared to healthy subjects following administration of a single 50 mg dose of eltrombopag. Healthy subjects were matched to the moderate hepatic impairment group for age, body mass index (BMI), and sex. This study used eltrombopag 50 mg tablets.

Thirty-three subjects were enrolled in the study, including eight subjects with mild (Child-Pugh score of 5 to 6), eight subjects with moderate (Child-Pugh score of 7 to 9), nine subjects with severe hepatic impairment (Child-Pugh score of 10 to 15), and eight healthy control subjects. PK data were available for all except one subject with severe hepatic impairment.

Thirty (91%) subjects were male and 3 (9%) were female and the majority, twenty-eight (85%), were White. Mean (range) age was 51 years (38 to 64 years), weight was 81.1kg (58.6 to 111kg), and body mass index (BMI) was 26.7 kg/m² (20.0 to 34.5kg/m²).

Pharmacokinetic Results

Moderate to high between-subject variability (percent between-subject coefficients of variation (%CVb)) was observed in plasma eltrombopag PK parameters and variability in AUC_(0- ∞) and C_{max} increased, and t_{max} was delayed with increasing severity of hepatic impairment (see Table 11). On average, plasma eltrombopag AUC_(0- ∞) values were 41% higher in subjects with mild hepatic impairment and 80 to 93% higher in subjects with moderate to severe hepatic impairment; t_{1/2} values were 71% higher in subjects with mild hepatic impairment and 2.08 to 2.14-fold higher in subjects with moderate to severe hepatic impairment compared to the healthy subjects (see Table 12). C_{max}

values appeared to decrease with increasing severity of hepatic impairment. Results suggest that caution is warranted when administering eltrombopag to patients with hepatic impairment.

Table 11: Summary of Plasma Eltrombopag PK Parameters Following Single-Dose Administration of 50mg in Study TRA103452

Subject Population	AUC(0-∞) (µg.h/mL)	Cmax (µg/mL)	tmax (h)	t1/2 (h)
Healthy N=8	66.0 (42.1, 104) [58]	5.43 (3.74, 7.88) [47]	3.0 (2.5, 6.0)	21.3 (15.5, 29.4) [40]
Mild Hepatic Impairment N=8	92.8 (65.8, 131) [43]	4.68 (3.16, 6.92) [50]	3.5 (2.5, 4.0)	36.4 (23.4, 56.5) [57]
Moderate Hepatic Impairment N=8	127 (79.5, 203) [61]	3.84 (2.37, 6.25) [63]	4.9 (2.0, 7.0)	44.4 (33.6, 58.7) [34]
Severe Hepatic Impairment N=8	119 (64.8, 217) [83]	2.75 (1.47, 5.16) [87]	4.0 (3.0, 8.0)	45.6 (41.2, 50.6) [12]

Data presented as geometric mean (95% CI) [%CVb], except t_{max} presented as median (minimum, maximum).

Table 12: Comparison of Plasma Eltrombopag PK Parameters for Subjects with Hepatic Impairment versus Healthy Subjects in Study TRA103452

Comparison	AUC(0-∞)	Cmax	t1/2 (h)
Mild Hepatic Impairment vs Healthy	1.41 (0.87, 2.28)	0.86 (0.53, 1.40)	1.71 (1.24, 2.34)
Moderate Hepatic Impairment vs Healthy	1.93 (1.19, 3.13)	0.71 (0.43, 1.15)	2.08 (1.52, 2.86)
Severe Hepatic Impairment vs Healthy	1.80 (1.11, 2.92)	0.51 (0.31, 0.83)	2.14 (1.56, 2.93)

Data presented as geometric least squares mean ratio (90% CI)

Pharmacokinetics in Subjects with Renal Impairment

Study TRA104412

Study TRA104412 investigated plasma eltrombopag PK in subjects with mild, moderate, and severe renal impairment compared to healthy subjects following administration of a single 50 mg dose of eltrombopag. Healthy subjects were matched to the moderate renal impairment group for age, BMI, and sex. This study used eltrombopag 50 mg tablets.

Twenty-nine subjects were enrolled in the study, including eight subjects with mild renal impairment (creatinine clearance [CrCL] 80 to 50mL/min), eight subjects with moderate renal impairment (CrCL 49 to 30mL/min), five subjects with severe renal impairment (CrCL <30mL/min), and eight healthy control subjects. Fifteen (52%) subjects were male and 14 (48%) were female and the majority, twenty-five (86%), were White. Mean age was 61 years (39 to 74 years), weight was 77.8kg and body mass index (BMI) was 27.5kg/m².

Pharmacokinetic Results

Tabular summaries of results are provided in Tables 13 and 14. Following a single, oral 50 mg dose of eltrombopag, moderate to high between-subject variability (%CVb) was observed in PK parameters and variability increased with increasing severity of renal impairment. On average, plasma eltrombopag AUC_(0-∞) was 32%, 36% and 60% lower and C_{max} was 30%, 19% and 54% lower in subjects with mild, moderate and severe renal impairment, respectively, compared with healthy subjects. Plasma eltrombopag AUC_(0-∞), C_{max} and t_{1/2} increased with increasing values of baseline (Screening) CrCL and decreased with increasing values of baseline (Study Day-1) serum creatinine. Based on these results caution is warranted when administering eltrombopag to patients with renal impairment.

Table 13: Summary of Plasma Eltrombopag PK Parameters following Administration of a Single 50mg Dose in Study TRA104412

Subject Population	AUC(0-∞) (µg.h/mL)	Cmax (µg/mL)	CL/F (L/h)	t1/2 (h)
Healthy N=8	64.2 (46.1, 89.3) [41]	6.14 (4.60, 8.21) [36]	0.78 (0.56, 1.08) [41]	25.8 (22.2, 29.9) [18]
Mild Renal Impairment N=8	43.6 (27.4, 69.3) [60]	4.29 (3.00, 6.11) [44]	1.15 (0.72, 1.82) [60]	19.6 (14.0, 27.4) [42]
Moderate Renal Impairment N=8	41.0 (24.9, 67.6) [65]	5.01 (3.03, 8.29) [66]	1.22 (0.74, 2.01) [65]	15.6 (10.6, 22.9) [49]
Severe Renal Impairment N=5	25.9 (4.76, 141) [233]	2.81 (0.616, 12.8) [186]	1.93 (0.35, 10.5) [233]	14.0 (4.73, 41.3) [107]

Data presented as geometric mean (95% CI) [%CVb]

Table 14: Comparison of Plasma Eltrombopag PK Parameters for Subjects with Renal Impairment versus Healthy Subjects in Study TRA104412

Comparison	AUC(0-∞)	Cmax	t1/2
Mild Renal Impairment vs Healthy	0.68 (0.37, 1.26)	0.70 (0.40, 1.22)	0.76 (0.50, 1.15)
Moderate Renal Impairment vs Healthy	0.64 (0.34, 1.19)	0.81 (0.47, 1.42)	0.60 (0.40, 0.91)
Severe Renal Impairment vs Healthy	0.40 (0.20, 0.82)	0.46 (0.24, 0.86)	0.54 (0.34, 0.87)

Data presented as geometric least squares mean ratio (90% CI)

Drug Interactions

Rosuvastatin

Co-administration of eltrombopag with rosuvastatin increased plasma rosuvastatin C_{max} by 2.03-fold and AUC_(0-∞) by 55% overall. In the sub-population of Asian subjects, plasma rosuvastatin AUC_(0-∞) increased by 32% and C_{max} increased by 61%; whereas, in the sub-population of non-Asian subjects, plasma rosuvastatin AUC_(0-∞) increased by 88% and C_{max} increased 2.65-fold. Asian subjects had 2.09-fold higher plasma rosuvastatin AUC_(0-∞) compared to non-Asian subjects when rosuvastatin was given alone. In addition, Asian subjects had 46% higher plasma rosuvastatin AUC_(0-∞) compared to non-Asian subjects when rosuvastatin was co-administered with eltrombopag.

When co-administered with eltrombopag, a reduced dose of rosuvastatin should be considered and careful monitoring for rosuvastatin side effects should be undertaken. Concomitant administration of eltrombopag and other breast cancer resistant protein (BCRP) and organic anion-transporting polypeptide (OATP1B1) substrates should be used with caution.

Antacid (Polyvalent Metal Cations) and Effect of Food

Study TRA104631 evaluated the impact of various meals on plasma eltrombopag PK following administration of a 75 mg dose, and also evaluated the impact of co-administering eltrombopag 75 mg with a polyvalent cation-containing antacid on plasma eltrombopag PK.

This was an open-label, randomised, five-period, period-balanced, crossover study to assess the effect of food and antacid on the pharmacokinetics of a single dose of SB-497115-GR in healthy volunteers. Objectives were:

- To evaluate the effects of high- and low-fat meals consisting of foods with low calcium content (40-50 mg of calcium) and no dairy products on the pharmacokinetics of a single oral dose of 75 mg of eltrombopag in healthy volunteers.
- To evaluate the effect of cation-containing antacid on the pharmacokinetics of a single oral dose of 75 mg of eltrombopag in healthy volunteers.
- To evaluate the effect of timing of meal consumption in relation to study drug administration on the pharmacokinetics of eltrombopag.

Administration of a single 75 mg dose of eltrombopag with either high-fat or low-fat meals that were also low in calcium had minor non-significant impacts on plasma eltrombopag exposure; mean $AUC_{(0-\infty)}$ treatment ratios (90% CIs) were 0.928 (0.763, 1.127) for low-fat/low-calcium meal versus fasted, 1.025 (0.843, 1.247) for high-fat/low-calcium meal versus fasted, and 0.852 (0.703, 1.034) for high-fat/low calcium meal administered one hour after eltrombopag versus fasted.

Co-administration of eltrombopag with a polyvalent cation-containing antacid decreased plasma eltrombopag $AUC_{(0-\infty)}$ and C_{max} by 70%. In order to avoid clinically significant reductions in plasma eltrombopag exposure, eltrombopag should be administered at least four hours apart from antacids and other products containing polyvalent cations, such as mineral supplements and dairy products.

Fluroquinolone antibiotics are susceptible to chelation interactions and exposures are generally decreased by greater than 50% when administered concomitantly with polyvalent cation-containing antacids. Eltrombopag bioavailability is impacted to a similar extent as fluroquinolones; therefore, the 4-hour separation that was successful in lessening or avoiding the reduced bioavailability of the fluroquinolones provides support for a 4-hour dose separation strategy for the administration of eltrombopag and antacids or other polyvalent metal cation-containing products.

Study SB-497115/005

This was an open label, randomised, three period, crossover study to assess the relative bioavailability of SB-497115-GR 25mg capsules and SB-497115-GR 25mg tablets and the effect of food on SB-497115-GR 25mg tablet pharmacokinetics in healthy, adult, volunteer subjects following a 50 mg single dose of SB-497115-GR.

The relative bioavailability of the SB-497115-GR tablet was 82-85% compared to the capsule.

Compared to the fasted state, C_{max} and $AUC_{(0-\infty)}$ for SB-497115 were reduced 60-65% in the presence of food, and t_{max} was slightly prolonged. Compared to the fasted state, C_{max} and $AUC_{(0-\infty)}$ for SB-497115 were reduced in the presence of food (Table 15). The presence of food slightly prolonged the t_{max} of SB-497115-GR; however the terminal phase of SB-497115-GR was not affected by the presence of food.

Table 15: Study SB497115-005 - Summary of the Effects of Food on SB-497115-GR Pharmacokinetic Parameters.

Parameter	Treatment C:Treatment B
AUC(0-∞) (µg.hr/ml)	0.41(0.36, 0.46)
Cmax (µg/ml)	0.35(0.30, 0.41)

Dosing Considerations

Simulations from the ITP patient PK/Pharmacodynamic (PD) data supported eltrombopag 50 mg once daily as an appropriate starting regimen; however some patients will require subsequent dose adjustment to achieve target platelet response. Approximately 50% of the ITP population will not achieve a platelet count >50Gi/L with eltrombopag 50 mg once daily; an increase to 75 mg once daily will result in platelet counts > 50Gi/L in approximately 30% of these patients. A reduced eltrombopag starting dose of 25 mg once daily is recommend for East Asian patients.

Efficacy

The sponsor stated that the primary evidence for the efficacy of eltrombopag was provided from 3 double-blind, placebo-controlled studies (TRA100773A, TRA100773B, and TRA102537/RAISE). TRA100773 consisted of 2 independent, sequentially conducted studies: the Phase II dose-finding TRA100773A study and the Phase III TRA100773B study. RAISE was a double-blind, placebo-controlled, Phase III study of 6- month treatment duration. Additional efficacy data from 2 single-arm, open-label studies (TRA108057/REPEAT and TRA105325/EXTEND) were also submitted as supportive efficacy data.

In this evaluation report efficacy data will be presented in the following manner:

- Efficacy data for eltrombopag compared to placebo following up to 6 weeks of treatment in Studies TRA100773A and TRA100773B (response based on platelet count, median platelet counts and bleeding signs and symptoms)
- Comparison of individual and pooled study results from eltrombopag 50 mg and placebo treatment arms within TRA100773A and TRA100773B
- Efficacy results of eltrombopag compared to placebo following up to 6 months of treatment in the RAISE study (response based on platelet count, median platelet counts, bleeding signs and symptoms, reduction of concomitant ITP medications, use of rescue medications and health related quality of life [HR-QoL])
- Efficacy results with eltrombopag following repeated cycles of treatment in REPEAT (response based on platelet count, median platelet counts and bleeding signs and symptoms)
- Long-term efficacy results with eltrombopag in EXTEND (response based on platelet count, duration of response, reduction of concomitant ITP medications, rescue medication, bleeding signs and symptoms and HR-QoL).

Studies TRA100773A and TRA100773B

Study Designs

TRA100773A was a global, dose-ranging Phase II trial that used an adaptive sequential design in adult subjects with previously-treated chronic ITP. Eligible subjects had not responded to or had relapsed within 3 months of their most recent therapy for ITP, and had a platelet count of <30 Gi/L on Day 1 (or within 24 hours prior to dosing). Subjects with known secondary thrombocytopenia were excluded from the trial. Subjects were randomised to treatment (placebo, eltrombopag 30 mg, 50 mg or 75 mg) in a 1:1:1:1 ratio, with randomisation stratified based upon use or non-use of ITP medications at baseline, splenectomy status and baseline platelet count (≤ 15 Gi/L or >15 Gi/L). Subjects were administered study medication once-daily for up to 6 weeks; subjects who attained a platelet count >200 Gi/L were to discontinue treatment with study medication.

Two interim analyses were planned to be conducted when on-therapy platelet count data were available from approximately one-third (90) and two-thirds (180) of the maximum planned sample size of 272 subjects. The primary comparisons of interest were between the eltrombopag treatment groups (30 mg, 50 mg and 75 mg) and placebo (PBO).

At the first interim analysis, the study was stopped due to overwhelming efficacy as the pre-specified stopping criterion at the first interim analysis was $p \leq 0.0113$ for superiority compared to placebo and $p \geq 0.333$ for futility.

After completion of the dosing period, subjects were followed every 2 weeks for 6 weeks and were assessed for safety and durability of the platelet response following discontinuation of study medication. Subjects were also to complete an ocular examination 6 weeks and 6 months following the final dose of study medication.

TRA100773B

Study TRA100773B was a global, randomised, double-blind, placebo-controlled Phase III trial in adults with previously treated chronic ITP. Eligible subjects had not responded to or had relapsed within 3 months of their most recent therapy for ITP and had a platelet count of <30 Gi/L on Day 1 (or within 24 hours prior to dosing). Subjects who enrolled in TRA100773A were not permitted to enrol in TRA100773B.

Subjects were randomised to treatment (eltrombopag 50 mg or placebo) in a 2:1 ratio.

Subjects with a platelet count <50 Gi/L on or after Day 22 were allowed to increase their dose to eltrombopag 75 mg or matching placebo. Randomisation was stratified based upon use or non-use of ITP medications at randomisation, splenectomy status and baseline platelet count (≤ 15 Gi/L or >15 Gi/L). Subjects were dosed once-daily for up to 6 weeks. Subjects who attained a platelet count >200 Gi/L discontinued treatment with study medication to minimise the risk of developing thrombocytosis.

After completion of the dosing period, subjects were followed 1, 2, 4 and 6 weeks following discontinuation of study medication to assess safety and durability of the platelet response. Subjects were also to complete an ocular examination 6 weeks and 6 months following the final dose of study medication.

Statistical Analysis

In Studies TRA100773A and TRA100773B, the Efficacy Population was the primary population for efficacy analyses and was comprised of all subjects randomised and treated with at least one dose of study medication and with a baseline platelet count of <30 Gi/L. Additional supportive analyses were performed using the Intent-to-Treat (ITT) Population, which was comprised of all randomised subjects who received at least one dose of study medication and had at least one platelet count post-dosing.

For both TRA100773A and TRA100773B, the primary efficacy endpoint was a shift from a baseline platelet count of <30 Gi/L to ≥ 50 Gi/L 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). For this primary analysis of response, only on-treatment platelet counts were included.

Subjects were classified as responders if they achieved a platelet count of ≥ 50 Gi/L (from a baseline platelet count of <30 Gi/L) at the Day 43 Visit. Subjects were also classified as responders if they responded strongly with a platelet count >200 Gi/L and discontinued study medication prior to Day 43 for this reason; their last on treatment platelet count was used to determine response.

Subjects were classified as non-responders if they discontinued treatment with study medication prior to the Day 43 Visit for any reason other than a platelet count >200 Gi/L, irrespective of their last on treatment platelet count.

In the sections on efficacy summarising the results from these studies, the term “Day 43” denotes the day the subject was taken off the therapy which could include any day before Week 6 for the primary dataset as mentioned above. Days 50, 57, 71 and 85 are Days +7, +14, +28 and +42 after the subject came off therapy.

For Study TRA100773A, a logistic regression model adjusting for the stratification variables of use of ITP medication at baseline (Yes/No), splenectomy status (Yes/No) and baseline platelet count ≤ 15 Gi/L (Yes/No) was used to test the global null hypothesis that the odds of response were equal in all 4 treatment arms. If this global null hypothesis was rejected, then the odds of response in each dose of eltrombopag were compared to placebo using a closed testing procedure.

For Study TRA100773B, a logistic regression model adjusted for the same covariates as for TRA100773A was used to compare the odds of response between the eltrombopag 50 mg and placebo treated groups. Supportive data analyses were performed using a dataset of all platelet counts during the treatment and follow-up periods, whether or not the subject discontinued treatment prematurely (observed dataset). This dataset was used to address other aspects of the pharmacodynamic response of platelet counts to study medication, such as duration of response and comparison of bleeding episodes during and after treatment with study medication.

This dataset also allowed a sensitivity analysis of the primary endpoint to be performed at the Day 43 Visit (excluding subjects who withdrew prematurely for any reason). For this sensitivity analysis, the following rules applied:

- Subjects were classified as responders if they achieved a platelet count of ≥ 50 Gi/L (from a baseline platelet count of <30 Gi/L) at the Day 43 Visit;
- Subjects were excluded from the assessment of response at Day 43 if they discontinued treatment with study medication prior to the Day 43 Visit, regardless of the reason for discontinuation.

The primary analysis was repeated for the Per Protocol (PP) Population using the primary dataset.

Study Populations

Double-blind Studies TRA100773A and TRA100773B, Analysis Populations

Table 16 provides a summary of analysis populations (ITT and Efficacy Populations treated with 50 mg) by study and treatment and the pooled analysis populations.

Table 16: Summary of Populations treated with 50 mg in TRA100773A and TRA100773B

	TRA100773A		TRA100773B		Pooled 773A + 773B	
	PBO N=29	50mg N=30	PBO N=38	50mg N=76	PBO N=67	50mg N=106
Intent-to-Treat Population	29	30	38	76	67	106
Efficacy Population	27	27	38	74	65	101

Subject Disposition

A total of 231 subjects with previously treated chronic ITP were randomised and treated in TRA100773A (N=117; includes 58 subjects from 30 mg and 75 mg groups), and TRA100773B (N=114). In both studies, the percentage of subjects who withdrew prematurely from the study was higher in the eltrombopag 50 mg group compared to the placebo group, primarily to the subjects achieving a platelet count >200 Gi/L who discontinued study medication as required by the protocols.

Baseline Demographic Characteristics

Overall the demographic characteristics for both TRA100773A and TRA100773B were well balanced.

Baseline Disease Characteristics (Platelet count, Use of ITP Medication and Splenectomy Status)

Key baseline disease characteristics were similar between studies. The median baseline count was 17.8 Gi/L in the placebo treatment group versus 17.0 Gi/L in the eltrombopag 50 mg treatment group in TRA100773A and 17.0 Gi/L in the placebo treatment group versus 19.0 Gi/L in the eltrombopag treatment group in TRA100773B. Approximately half the subjects in TRA100773A, and 60% of subjects in TRA100773B did not have a splenectomy at baseline. The majority of subjects were not taking ITP medications at time of randomisation.

Prior ITP Medications

All subjects (100%) in TRA100773A and in TRA100773B had at least 1 prior ITP therapy reported. Most subjects in each of the treatment groups had ≥ 1 prior ITP therapy. Substantial proportions of subjects in each treatment group had ≥ 3 prior ITP therapies, with proportions being higher for the 50 mg subjects (57%) compared to placebo subjects (45%). Prior ITP medication use was similar between TRA100773A and TRA100773B. Corticosteroids were the most commonly reported prior ITP medication taken by 76-83% of subjects in each treatment group in TRA100773A and TRA100773B. IVIg was used as a prior therapy in 34-47% of subjects in each treatment group.

Efficacy Results

Analyses presented in this section are based on the primary dataset for the Efficacy Population unless otherwise stated.

Primary Endpoint for Studies TRA100773A and TRA100773B

The primary efficacy endpoint was a shift from a baseline platelet count of <30 Gi/L to ≥ 50 Gi/L after up to 42 days of dosing with study medication using the primary data set for both TRA100773A and TRA100773B. Subjects who met this criterion were defined as responders for the primary analysis.

In study TRA100773A only 11% of subjects on placebo attained a platelet count of ≥ 50 Gi/L on Day 43, compared to 70-80% of subjects on eltrombopag 50 mg and 75 mg. Results for the 30 mg, 50 mg, and 75 mg dose levels of eltrombopag are provided in Tables 17 (a)-(c), below.

Table 17(a): Responders – Efficacy Population in TRA100773A

Day 43 Visit	Treatment Group			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
n	27	29	27	26
Responders, n (%)	3 (11.1)	8 (27.6)	19 (70.4)	21 (80.8)

a. includes subjects who achieved a platelet count >200 Gi/L at any time during the 6-week treatment period.

Table 17(b): Analysis of Responders – Efficacy Population in TRA100773A

	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

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

Table 17(c): Responders at the Day 43 Visit – ITT Population in TRA100773A

Day 43 Visit	Treatment Group			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
n	29	30	29	28
Responders, n (%)	3 (10.3)	8 (26.7)	19 (65.5)	21 (75)
Odds ratio ^a	NA	3.20	17.39	28.50
95% CI	NA	(0.73,13.99)	(4.02,75.13)	(6.22,130.57)
p-value (one-sided)	NA	0.062	<0.001	<0.001

N=number of patients in efficacy population.

Prior to comparing each eltrombopag dose to placebo, an analysis was performed to determine if there were differences among the treatment groups. The results of this test demonstrated a significant overall treatment effect ($p<0.001$), enabling the comparison of each eltrombopag dose to placebo under the pre-defined closed testing procedure to assess efficacy and futility.

Both the eltrombopag 50 and 75mg treatment groups achieved a statistically significant treatment effect compared to placebo ($p<0.001$), thus meeting the pre-specified p-value ($p<0.0113$) for stopping the study at the first interim analysis based upon efficacy using a closed testing procedure (see results in Table 17(b)). The odds of responding were greater for each of the eltrombopag treatment groups compared to the PBO treatment group. The primary method of analysis was a logistic regression model adjusted for ITP medication use at randomisation, splenectomy status and baseline platelet count $\leq 15\text{Gi/L}$.

For study TRA100773A the logistic regression analysis of the responders at Day 43 was repeated using the observed dataset for the Efficacy Population. A statistically significant overall treatment effect ($p<0.001$) confirmed the results obtained with the primary dataset for both the Efficacy and the PP Populations. The odds ratio was >1 for each of the eltrombopag treatment groups compared to placebo, and statistical significance compared to placebo was obtained for the 50mg and 75mg treatment groups, but not the 30mg group. When the ITT Population was analysed for the primary endpoint, results were similar to the analysis with the Efficacy Population (see Table 17(c)). There was a statistically significant treatment effect for the 50 mg and 75 mg treatment groups compared to placebo ($p<0.001$ for both), but not for the 30 mg group.

These results support the 50mg and 75 mg dose levels as effective in the treatment of patients with ITP.

The odds of responding were significantly greater for the eltrombopag 50 mg treatment groups compared to placebo in both studies TRA100773A and TRA110773B ($p < 0.001$). A summary of results is presented in Table 18. Analysis of the pooled data demonstrated that eltrombopag 50 mg significantly ($p < 0.001$) increased the odds of responding (shift from a baseline platelet count < 30 Gi/L to ≥ 50 Gi/L after up to 6 weeks of dosing) compared to placebo.

Table 18: Primary Endpoint in TRA100773A and TRA100773B

Day 43 Visit	TRA100773A		TRA100773B		Pooled 773A + 773B	
	PBO N=27	50mg N=27	PBO N=38	50mg N=74	PBO N=65	50mg N=101
N	27	27	37 ^a	73 ^a	64 ^a	100 ^a
Responders, n (%)	3 (11)	19 (70)	6 (16)	43 (59)	9 (14)	62 (62)
Odds ratio for Active/placebo treatments ^b	21.96		9.61		12.40	
95% CI	(4.7, 102.2)		(3.3, 27.9)		(5.2, 29.7)	
p-value ^c	< 0.001		< 0.001		< 0.001	

Data Source: SDAP Table 7.1, SDAP Table 7.3, TRA100773A Table 7.1 and Table 7.4, TRA100773B Table 7.1 and Table 7.4

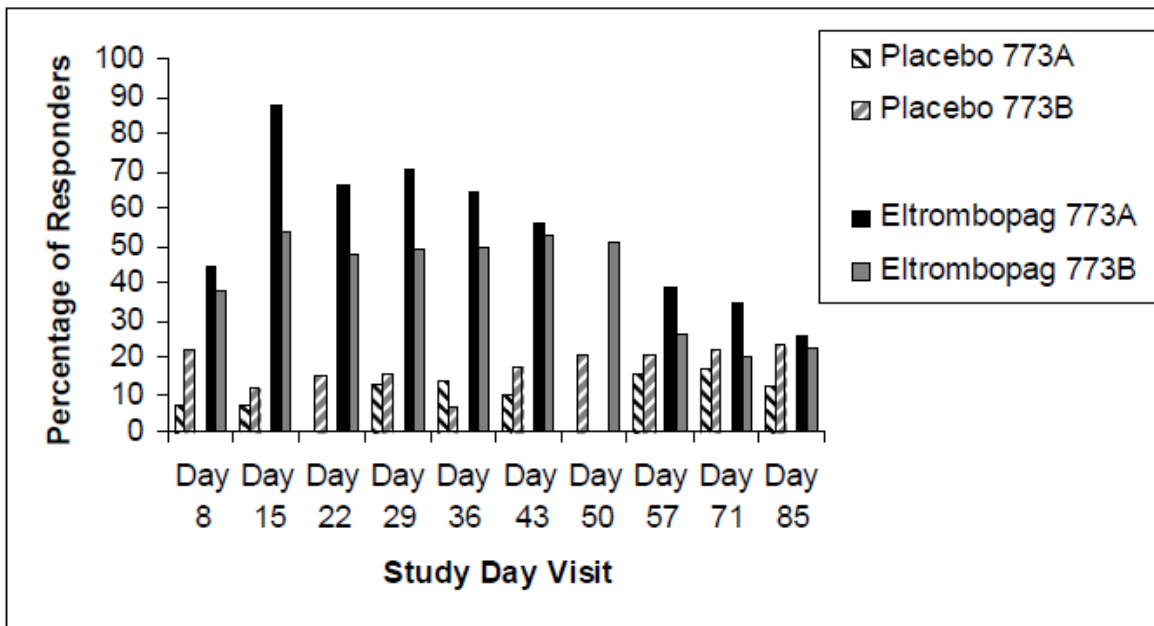
- a. Two subjects, one in each treatment group did not have platelet counts at the Day 43 Visit.
- b. The odds ratio indicates the odds of responding to eltrombopag compared to placebo.
- c. One-sided for TRA100773A; two-sided for TRA100773B and for the pooled analysis.

In TRA100773B, subjects with platelet counts < 50 Gi/L on or after Day 22 were permitted to have their dose increased to eltrombopag 75 mg (or matching placebo). More subjects (28, 74%) in the placebo treatment group required a dose increase during the study compared to the eltrombopag treatment group (35, 46%). Most of the dose increases occurred at the day 22 Visit. More subjects in the eltrombopag treatment group (11/35, 31%) responded after having their dose increased to 75 mg, compared to the placebo treatment group (3/28, 11%) in the study.

Percentage of Responders (Shift from Baseline < 30 Gi/L to ≥ 50 Gi/L) by Visit (Observed Dataset)

The percentage of subjects who achieved platelet counts ≥ 50 Gi/L from a baseline of < 30 Gi/L at each weekly visit for TRA100773A and TRA100773B is shown in Figure 2. At each on-treatment visit, the percentage of responders was greater in the eltrombopag treatment group compared to the placebo treatment group for both studies. Forty-four percent and 38% percent of subjects at the Day 8 Visit for the eltrombopag treatment group in TRA100773A and TRA100773B, respectively, achieved platelet counts ≥ 50 Gi/L compared to 7% and 22% of subjects, respectively, in the pooled placebo treatment group. At the Day 15 Visit, 88% and 54% of subjects in the eltrombopag treatment groups in TRA100773A and TRA100773B, respectively, achieved platelet counts ≥ 50 Gi/L compared to 7% and 12% in the placebo treatment groups in TRA100773A and TRA100773B. The observed decrease in percentage of responders observed after Day 15 in the eltrombopag treatment groups was probably due to the responders withdrawn from study medication due to a platelet count of > 200 Gi/L. Subjects who discontinued study medication continued to participate in the follow-up visits (Day 50 and beyond) and their data are included in the follow-up visits (1, 2, 4 and 6 weeks after discontinuation of study medication [nominal Days 50, 57, 71 and 85]) shown in Figure 2.

Figure 2: Percentage of Responders by Visit in TRA100773A and TRA100773B (Observed Data)



Note: subjects in TRA100773A did not have platelet counts assessed on Day 50.

Odds of Responding to Eltrombopag during Weeks 2-6 Compared to Placebo (Observed Data)

Analysis of the odds of responding (OR) during weeks 2-6 demonstrated a statistically significant difference between the eltrombopag 50 mg treatment group and placebo in TRA100773A (OR=29.84, $p<0.001$), and in TRA100773B (OR=8.79, $p<0.001$). Furthermore, when the data were pooled, the results again demonstrated a statistically significant difference (OR=13.89, $p<0.001$) between eltrombopag and placebo.

Percentage of Subjects Achieving Platelets Counts at least 2 times Baseline

In both studies, the percentage of subjects whose platelet count at Day 43 (primary dataset) was at least 2x baseline, but not necessarily ≥ 50 Gi/L, was analysed. Results are summarised in Table 19. In both studies >10% of additional subjects in the eltrombopag 50 mg treatment group achieved a potential clinical benefit even though they did not achieve the 50 Gi/L threshold (3/27 in TRA100773A and 8/73 in TRA100773B). An additional 8% and 3% of subjects in studies TRA100773A and TRA100773B, respectively, also achieved this response in the placebo treatment groups. The odds of response on eltrombopag relative to placebo were similar to the primary endpoint, with a statistically significant higher percentage of responders in the eltrombopag treatment groups compared to placebo ($p<0.001$). When data were pooled, the eltrombopag treatment group achieved a statistically significant treatment effect compared to placebo ($p<0.001$).

Table 19: Subjects with a Platelet Count of at least 2x Baseline, TRA100773A and TRA100773B

Day 43 Visit	TRA100773A		TRA100773B		Pooled 773A + 773B	
	PBO N=27	50mg N=27	PBO N=38	50mg N=74	PBO N=65	50mg N=101
N	27	27	37 ^a	73 ^a	64 ^a	100 ^a
Responders, n (%)	5 (18.52)	22 (81.48)	7 (18.92)	51 (69.86)	12 (18.75)	73 (73.0)
Odds ratio for Active/placebo Treatments ^b	21.62		10.43		13.47	
95% CI	(5.21, 89.70)		(3.89, 27.95)		(5.97, 30.36)	
p-value ^c	<0.001		<0.001		<0.001	

Data Source: SDAP Table 7.14, TRA100773A Table 7.26 and Table 7.46, TRA100773B Table 7.31 and Table 7.51

- a. Two subjects, one in each treatment group, were not evaluable at the Day 43 Visit.
- b. The odds ratio indicates the odds of responding to eltrombopag compared to placebo.
- c. One-sided for TRA100773A: two-sided for TRA100773B and for the pooled analysis.

Response in Platelet Count to 50 Gi/L or More and at Least 2x Baseline

The percentage of responders, defined as subjects whose platelet count on Day 43 was ≥ 50 Gi/L and at least 2x baseline was analysed using the primary dataset. Results are shown in Table 20. The pattern of response was similar to the primary efficacy analysis. The eltrombopag treatment groups achieved a statistically significant treatment effect compared to placebo ($p < 0.001$). When data were pooled, the odds of responding were significantly greater for the eltrombopag treatment group compared to placebo ($p < 0.001$).

Table 20: Subjects with a Platelet Count of 50 Gi/L or More and 2x at least Baseline in TRA100773A and TRA100773B

Day 43 Visit	TRA100773A		TRA100773B		Pooled 773A + 773B	
	PBO N=27	50 mg N=27	PBO N=38	50 mg N=74	PBO N=65	50 mg N=101
N	27	27	37	73	64	100
Responders, n (%)	3 (11.1)	19 (70.4)	5 (13.5)	42 (57.5)	8 (12.5)	61 (61.0)
Odds ratio for Active/placebo Treatments ^b	20.85		11.18		13.77	
95% CI	(4.55, 95.56)		(3.63, 34.36)		(5.57, 34.01)	
p-value ^b	<0.001		<0.001		<0.001	

Data Source: SDAP Table 7.11, TRA100773A Table 7.2 and Table 7.45, TRA100773B Table 7.2 and Table 7.50

- a. The odds ratio indicates the odds of responding to eltrombopag compared to placebo.
- b. One-sided for TRA100773A: two-sided for TRA100773B and for the pooled analysis.

Subjects Who Achieved a Platelet Count >200 Gi/L and >400 Gi/L

In study TRA100773A a dose dependent increase in the number and percentage of subjects in each treatment group who achieved a platelet count >200 Gi/L was observed. Results are shown for each dose level at Day 43 in Table 21(a). These subjects discontinued study medication, their last on-treatment platelet count was used to determine response and as such they were considered responders. Fewer subjects in each eltrombopag treatment group exceeded 400 Gi/L than 200 Gi/L (see Table 21(a)). Six subjects in the 50mg and four subjects in the 75mg treatment groups exceeded 400 Gi/L, compared to one each in the placebo and 30mg treatment groups.

A greater number of subjects achieved a platelet count >200 Gi/L in the eltrombopag 50 mg treatment groups compared to placebo in both studies (see Table 21(b)). A higher percentage of subjects in the

eltrombopag treatment groups also achieved platelet counts >400 Gi/L compared to placebo treatment groups at each visit. When pooled, the data again demonstrated that the eltrombopag treatment group had a higher percentage of subjects with platelet counts >200 Gi/L compared to placebo.

Table 21(a): Subjects with Platelet Counts >200 Gi/L at the Day 43 Visit (Efficacy Population) in TRA100773A

Day 43 Visit	Treatment Group			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
Platelets >200Gi/L				
n	27	29	27	26
Responders, n (%)	1 (3.7)	4 (13.8)	10 (37.0)	13 (50.0)
Platelets >400Gi/L				
n	27	29	27	26
Responders, n (%)	1 (3.7)	1 (3.4)	6 (22.2)	4 (15.4)

Table 21(b): Subjects with Platelet Counts >200 Gi/L and >400 Gi/L in TRA100773A and TRA100773B at the Day 43 Visit

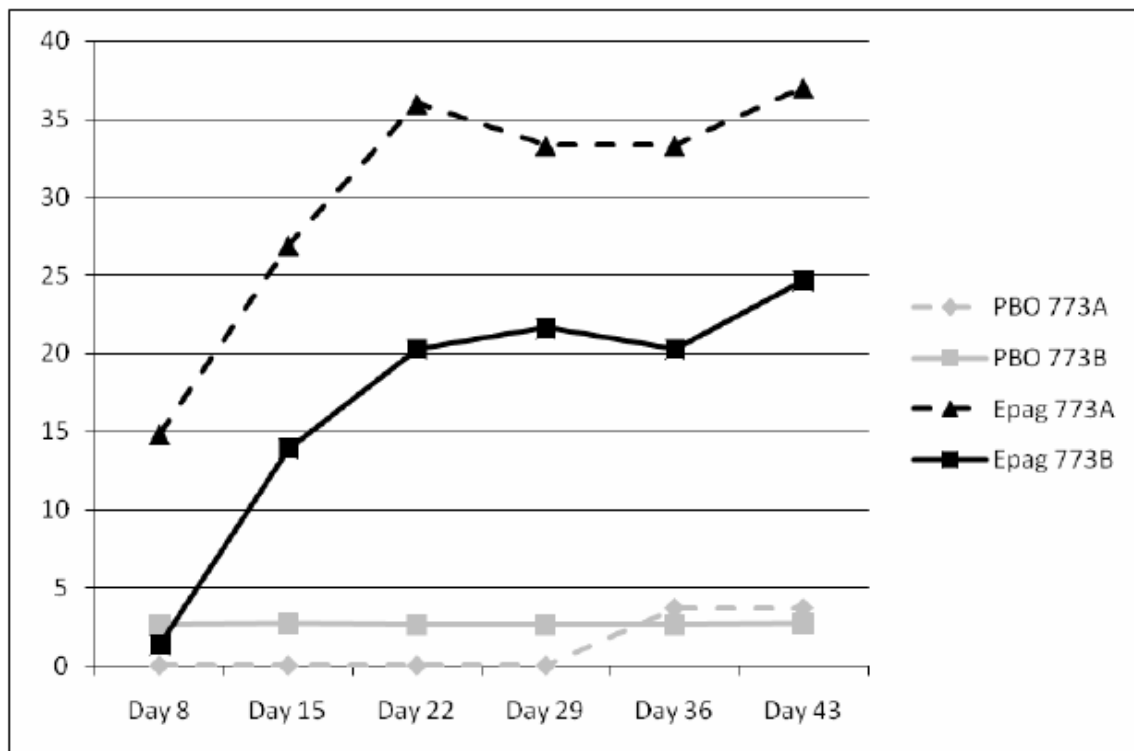
Day 43 Visit	TRA100773A		TRA100773B		Pooled 773A + 773B	
	PBO N=27	50 mg N=27	PBO N=38	50 mg N=74	PBO N=65	50 mg N=101
n	27	27	37	73	64	100
Platelets >200Gi/L, n (%)	1 (4) ^a	10 (37)	1 (3) ^b	18 (25) ^c	2 (3)	28 (28)
Platelets >400Gi/L, n (%)	1 (4) ^a	6 (22)	0	2 (3)	1 (2)	8 (8)

Data Source: SDAP Table 7.45, Table 7.52, TRA100773A Table 7.7 and Table 7.75, TRA100773B Table 7.8 and Table 7.82.

- One subject had evidence that the underlying condition may not have been ITP based upon clinical laboratory values at screening and medical history, they were subsequently excluded from the Per Protocol population.
- Subject received IVIg on Day 1.
- Includes one subject who discontinued treatment on Day 8 due to a platelet count of 198 Gi/L.

In TRA100773A, 27% of subjects in the eltrombopag 50 mg treatment group reached platelet counts of >200 Gi/L on Day 15 (after two weeks of dosing), and in Study TRA100773B, 14% of subjects in the eltrombopag treatment group reached platelet counts >200 Gi/L on Day 15 (see Figure 3).

Figure 3: Percentage of Subjects with Platelet Counts >200 Gi/L by Visit



Note: in TRA100773A, only the placebo and 50 mg treatment groups are presented.

Median platelet counts

In study TRA100773A the mean change in platelet count from baseline using the primary dataset was analysed with an analysis of covariance (ANCOVA) model, including actual baseline platelet count, ITP medication use at randomisation, and splenectomy status as covariates. Results at Day 43 are shown in Table 22. There were greater increases in each of the eltrombopag treatment groups compared to placebo at the Day 43 Visit, although the mean increases were several-fold larger for the 50 mg and 75 mg treatment groups than for the 30 mg treatment group. The difference in the model-adjusted mean changes from baseline were statistically significant for the 50 mg and 75 mg treatment groups compared to placebo ($p < 0.001$ and $p = 0.001$, respectively). These data provided support for the recommendation of 50mg as the minimum effective dose of eltrombopag.

Median platelet counts in the eltrombopag 50 mg treatment groups in both studies TRA100773A and TRA100773B rose from baseline as early as Day 8 and continued to rise to Day 15. The median platelet counts in patients randomised to 50 mg remained elevated (>50 Gi/L) through all on-treatment visits after Day 15.

Table 22: Analysis of Change in Platelet Counts (Gi/L) From Baseline to the Day 43 Visit (Efficacy Population) in TRA100773A

	Treatment Group			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
Baseline Mean (SD)	15.1 (7.00)	14.5 (6.26)	16.7 (8.63)	15.2 (9.79)
Day 43 Visit Mean (SD)	35.7 (78.12)	67.8 (99.64)	241.3 (296.32)	205.1 (163.55)
Change from Baseline Mean (SD)	20.6 (79.76)	53.3 (100.54)	224.5 (292.62)	189.9 (162.85)
Model-adjusted Change from Baseline Mean (SE)	27.3 (36.22)	57.9 (34.23)	224.9 (35.07)	192.8 (35.88)
Mean Difference from PBO Treatment		30.5	197.6	165.5
95% CI		(-65.36,126.39)	(98.90,296.26)	(66.02,264.91)
p-value		0.529	<0.001	0.001

Analyses of Bleeding (Studies TRA100773A and TRA100773B)

WHO Bleeding Scale

The World Health Organization (WHO) Bleeding Scale has 5 grades: Grade 0 - no bleeding; Grade 1 –petechiae; Grade 2 - mild blood loss; Grade 3 - gross blood loss; and Grade 4 - debilitating blood loss. To analyse the data, subjects' assessments were summarised into categories: no bleeding (Grade 0), any bleeding (Grade 1 to Grade 4) and clinically significant bleeding (Grade 2 to Grade 4).

In both studies there was a decreased incidence of any bleeding (Grade 1 to Grade 4) on treatment relative to baseline in subjects who received eltrombopag. At the baseline visit, 61%-63% of subjects in each eltrombopag 50 mg treatment group and 56%-66% of subjects in the placebo treatment groups reported any bleeding (Grades 1-4). At the Day 43 Visit, 50% and 60% of subjects in the placebo treatment groups in TRA100773A and TRA100773B, respectively, had bleeding compared with only 25% in the eltrombopag treatment group in TRA100773A and 39% in TRA100773B (see Table 23).

Table 23: WHO Bleeding Scale Assessment of Subjects in TRA100773A and TRA100773B (Observed Dataset)

Assessment Visit	TRA100773A (Efficacy Population)		TRA100773B (Efficacy Population)		Pooled 773A + 773B (ITT Population) ^d	
	PBO N=27	50 mg N=27	PBO N=38	50 mg N=74	PBO N=67	50 mg N=106
Day 1, n (%)	27	27	35	70	64	102
No bleeding ^a	12 (44)	10 (37)	12 (34)	27 (39)	26 (41)	39 (38)
Any bleeding ^b	15 (56)	17 (63)	23 (66)	43 (61)	38 (59)	63 (62)
Clinically significant bleeding ^c	3 (11)	4 (15)	9 (26)	15 (21)	12 (19)	19 (19)
Day 43 Visit, n (%)	22	16	30	51	53	68
No bleeding ^a	11 (50)	12 (75)	12 (40)	31 (61)	24 (45)	43 (63)
Any bleeding ^b	11 (50)	4 (25)	18 (60)	20 (39)	29 (55)	25 (37)
Clinically significant bleeding ^c	3 (14)	1 (6)	4 (13)	5 (10)	7 (13)	7 (10) ^d
Day 57 Visit, n (%)	25	26	34	72	61	102
No bleeding ^a	11 (44)	14 (54)	14 (41)	43 (60)	27 (44)	58 (57)
Any bleeding ^b	14 (56)	12 (46)	20 (59)	29 (40)	34 (56)	44 (43)
Clinically significant bleeding ^c	2 (8)	2 (8)	6 (18)	5 (7)	8 (13)	8 (8) ^d

Data Source: SDAP Table 7.68, TRA100773A Table 7.21 and TRA100773B Table 7.23

- WHO Bleeding Scale Grade 0
- WHO Bleeding Scale Grade 1 to 4
- WHO Bleeding Scale Grade 2 to 4
- Pooled data is based on ITT Population, whereas individual study data for TRA100773A and TRA100773B is based on Efficacy Population. As a result, an additional subject in the ITT Population (from TRA100773A) in the pooled data at Day 43 and at Day 57 on eltrombopag 50 mg was identified as having clinically significant bleeding (Grade 2).

In TRA100773B, at the first off-treatment assessment, one week after discontinuation of study medication (Day 50 Visit), the proportion of subjects with any bleeding (Grades 1- 4) remained lower in the eltrombopag treatment group (29%) compared to placebo (41%).

A review of clinically significant bleeding (WHO Bleeding Grades 2-4) was also performed. This demonstrated a decreased incidence of clinically significant bleeding on treatment relative to baseline in subjects who received eltrombopag 50 mg in TRA100773A and TRA100773B (Table 23).

In Study TRA100773B, at the first off-treatment assessment, one week after discontinuation of study medication (Day 50 Visit), the proportion of subjects with clinically significant bleeding remained lower in the eltrombopag treatment group (8%) compared to placebo (17%). In TRA100773B, the results of the logistic regression analysis, adjusting for the covariates (concomitant medication at randomisation, splenectomy and baseline platelet count ≤ 15 Gi/L) and dichotomised baseline WHO bleeding grade showed that the odds of any bleeding (Grades 1-4) in the eltrombopag arm were significantly lower in the eltrombopag treated group at Day 43 (OR=0.27, p=0.029). A lower proportion of eltrombopag subjects had any bleeding (as indicated by WHO Bleeding Grade 1-4) at any point in time over the course of their treatment (Day 8 up to Day 43) compared to subjects in the placebo group (OR=0.49, p=0.021).

Over the on-treatment period, there was a decrease in any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) for subjects in the 50 mg eltrombopag and placebo treatment groups compared to baseline.

The logistic regression analysis adjusted for study, use of ITP medication at baseline, splenectomy, baseline platelet count, and dichotomised WHO Bleeding Grade at baseline also showed a statistically significant lower proportion of subjects with any bleeding (Grades 1-4) at Day 43 in the eltrombopag-treatment group compared to the placebo treatment group (OR=0.34, p=0.018).

Subjects with Haemostatic Challenges

Data regarding haemostatic challenges were collected retrospectively in TRA100773A and prospectively in TRA100773B. Seven subjects faced a haemostatic challenge during the observation periods of TRA100773A and TRA100773B. Four subjects received eltrombopag, 3 at 50 mg (baseline platelets 10 Gi/L, 17 Gi/L, and 25 Gi/L), 1 at 75 mg (baseline platelets 10 Gi/L), and 3 subjects received placebo (baseline platelets 12 Gi/L, 18 Gi/L and 27 Gi/L). All 3 subjects treated with eltrombopag in TRA100773A discontinued treatment early due to strong platelet responses of >200 Gi/L. Each eltrombopag subject successfully mastered the haemostatic challenge (two surgeries and one car accident) without needing rescue medication or having bleeding complications.

In TRA100773B, the subject who received eltrombopag responded to treatment with platelet counts of >100 Gi/L and had teeth extracted 1 week after discontinuation of eltrombopag with no additional medication or reported bleeding events. The placebo subject received IVIg to elevate platelet counts prior to undergoing surgery during TRA100773A. In TRA100773B, the 2 placebo subjects received treatment to prevent bleeding: IVIg, platelets and red blood cells (RBCs) for a hip replacement, and tranexamic acid for extirpation of papillomic change in the throat.

Health Outcomes

In both studies, there were no statistically significant or clinically meaningful changes in health related quality of life, across domains and in summary component scores.

Study TRA102537 (RAISE)

Study Design

RAISE was a global, randomised, double-blind, placebo-controlled, Phase III study to evaluate the efficacy, safety and tolerability of eltrombopag, initially administered as 50 mg oral tablets once daily for 6 months in adult subjects with previously-treated chronic ITP and platelet counts <30 Gi/L. Subjects were randomised 2:1, eltrombopag to placebo, and were stratified based upon use or non-use of ITP medications at randomisation, splenectomy status and baseline platelet count (≤ 15 Gi/L or >15 Gi/L).

Subjects initiated treatment with either 50 mg eltrombopag or matching placebo once daily and followed specific instructions for dosing modifications based upon their individual platelet count response. In general, the dose modification guidelines allowed subjects to: increase the dose of study medication (to a maximum of 75 mg or matching placebo, once daily), if platelet count elevation was insufficient (for example <50 Gi/L); maintain the dose of study medication if platelet counts were between 50-200 Gi/L; reduce the dose of study medication if platelet counts had risen to values between 200-400 Gi/L; or interrupt treatment with study medication if platelet counts exceeded 400 Gi/L with restart at a lower dose when platelet counts return to ≤ 150 Gi/L. Subjects were permitted to taper or discontinue concomitant ITP medications upon completion of the first 6 weeks of treatment and at any point in time could have received rescue treatments as dictated by local standard of care. After discontinuation of study medication, subjects completed follow-up visits at Weeks 1, 2, 4 and Months 3 and 6.

Statistical Analysis

The primary comparison of interest in RAISE was the relative difference between eltrombopag and placebo with respect to the odds of achieving a platelet count of ≥ 50 Gi/L and ≤ 400 Gi/L during the 6 months of study treatment. This comparison was made using a repeated measures model for binary data and Generalised Estimating Equations (GEE) methodology to estimate the regression parameters and was carried out at the 1% (2-sided) level of significance.

Primary Analysis Platelet Data Set: Data Set 1

Due to the nature of dose adjustments allowed in this study and the corresponding need for weekly platelet counts in the event of a dose adjustment, subjects did not all have evaluations at the nominal visits (defined as Weeks 1 to 6 inclusive, Week 10 and every 4 weeks thereafter). For the purposes of the analysis, if a subject did not have an evaluation at a nominal visit due to receiving a dose adjustment, information from the immediately preceding, non-nominal visit was used, provided the subject had not withdrawn from the study. Evaluations for a subject who withdrew from the study were classified as a negative response from the time of withdrawal.

All efficacy analyses were performed on a data set based on observed cases (unless data from an immediately preceding non-nominal visit had been carried forward to populate a nominal visit as defined above) with no imputations for missing data. Therefore, all intermittent missing data (apart from withdrawals) were treated as missing in the primary analysis data set (Data Set 1).

For all the analysis datasets, a subject's assessments were classified as negative responses for the duration of any rescue treatment, irrespective of the platelet counts achieved, up until the subject's platelet counts fell back below 50 Gi/L.

Study Populations

197 subjects were randomised in RAISE: 62 subjects in the placebo treatment arm and 135 subjects in the eltrombopag treatment arm. All subjects were included in the ITT population.

Subject Disposition

30 subjects (15%) withdrew prior to completion of the study (26-week treatment period and 1-, 2-, and 4-week follow-up visit). Twenty-eight subjects prematurely discontinued treatment with study medication: 6 placebo subjects (10%) and 22 eltrombopag subjects (16%). The percentage of subjects who withdrew prematurely from the study was higher in the eltrombopag group compared to the placebo group. The most common reason for withdrawal from the study in both groups was AE, which occurred in 4 (6%) placebo-treated subjects and 13 (10%) eltrombopag-treated subjects.

Baseline Demographic Characteristics

Demographic characteristics were generally well balanced between the two treatment arms, and were similar to the demographics of the study populations in studies TRA100773A and TRA100773B.

Baseline Disease Characteristics (Platelet count, Use of ITP Medication and Splenectomy Status) for RAISE

Overall, the treatment groups were balanced regarding stratification parameters. Approximately half of the subjects in the placebo and eltrombopag groups (50% and 47%, respectively) were receiving concomitant ITP medication at randomisation and had baseline platelet counts ≤ 15 Gi/L (48% and 50%, respectively). A similar percentage of subjects in the placebo and eltrombopag groups (34% and 37%, respectively) had a prior splenectomy. The percentages in both treatment groups in RAISE were lower than those in TRA100773A (48% and 50%) and TRA100773B (37% and 41%).

Prior ITP Medications and Number of Prior ITP Therapies

Prior ITP medications used by subjects were similar between the treatment groups. Corticosteroids were the most commonly reported prior ITP medication taken by 88-90% of subjects in each treatment group. IVIg was used as a prior therapy in 40-44% of subjects in each treatment group.

All subjects (100%) in RAISE had at least one prior ITP therapy reported. More than half of subjects in each treatment group had ≥ 3 prior ITP therapies, and a higher percentage of eltrombopag-treated subjects (26%) had received at least five prior therapies compared to placebo-treated subjects (18%). These percentages were similar to those in studies TRA100773A and TRA100773B.

Efficacy Results

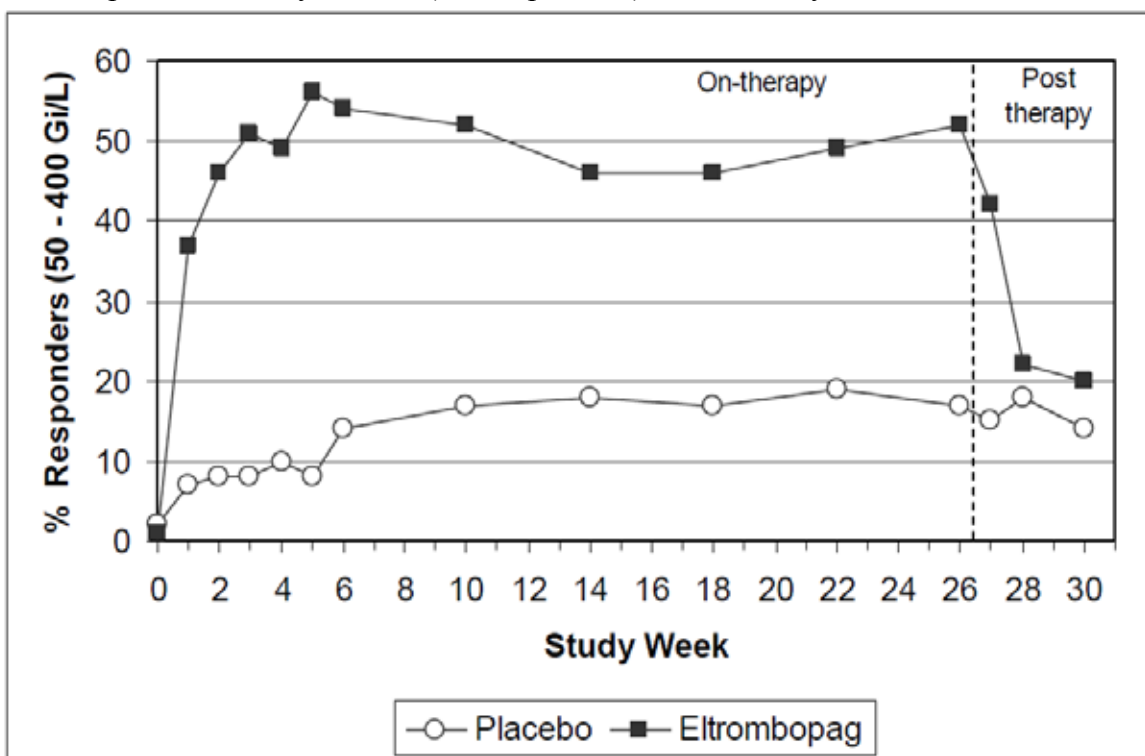
RAISE Primary Endpoint

The primary endpoint in RAISE, the odds of achieving a platelet count ≥ 50 Gi/L and ≤ 400 Gi/L during the 6 month treatment period, for subjects receiving eltrombopag relative to placebo was significant at the 1% level.

In eltrombopag-treated subjects, the odds of achieving a platelet response between 50 Gi/L and 400 Gi/L were 8 times greater throughout the 6 month treatment period compared to placebo-treated subjects ($p < 0.001$), providing strong evidence of the efficacy of eltrombopag compared to placebo.

Figure 4 presents the percentage of evaluable subjects who achieved a platelet response between 50-400 Gi/L at each nominal on-therapy visit. At baseline, 1 subject in each treatment group (placebo, 2%; eltrombopag, 1%) had platelet counts between 50-400 Gi/L. One week after treatment with study medication, platelet counts rose to between 50-400 Gi/L in 37% of eltrombopag-treated subjects and 7% of placebo-treated subjects. The proportion of responders in the eltrombopag group was between 37% and 56% for all nominal on-therapy visits (a minimum of 37% at Day 8 and a maximum of 56% at Day 36). One week after discontinuation of treatment, 42% of subjects treated with eltrombopag maintained platelet counts between 50-400 Gi/L, compared to placebo (15%).

Figure 4: Summary of Responders (Platelet Counts between 50 and 400 Gi/L), Baseline to 4-Week Follow-up Visit, Primary Dataset (ITT Population) RAISE Study

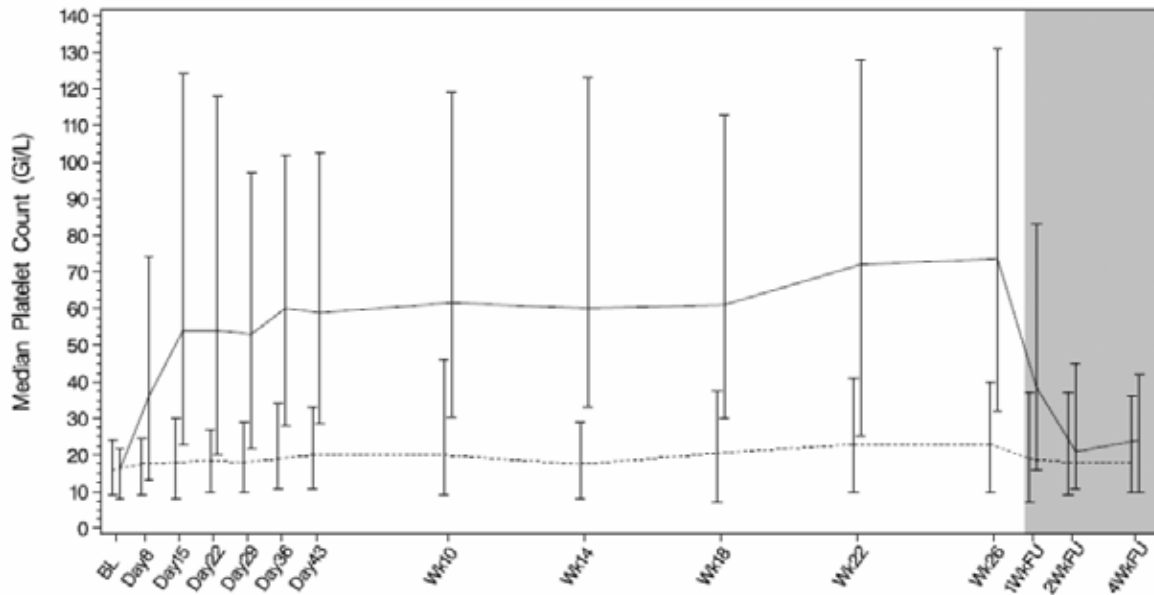


Vertical dotted line separates on-treatment visits from follow-up visits.

Median Platelet Counts

Similar to results from the TRA100773A and TRA100773B studies, platelet counts began to rise after 1 week of eltrombopag treatment, rose above 50 Gi/L after 2 weeks (Day 15), and remained elevated throughout the treatment period (see Figure 5). One week following discontinuation of eltrombopag, median platelet counts began to fall but did not reach near baseline levels until 2 weeks after discontinuation.

Figure 5: Median Platelet Counts (25th and 75th percentiles) By Assessment – Baseline to 4-week Follow-up (Primary Data Set, ITT Population) RAISE Study



BL=baseline, Wk=Week, FU=follow-up visit; Follow-up visits are shaded.

Duration of Response

The median duration of the maximum continuous response for subjects in the placebo group was 0 weeks and 8.1 weeks in the eltrombopag group, the median cumulative weeks of response for subjects in the placebo group was 0 weeks, compared to 10.9 weeks in the eltrombopag group.

Proportion of subjects with at least 75% of their assessments between 50 and 400 Gi/L

The majority (72%) of subjects in the placebo group did not achieve platelet counts in the target range of 50-400 Gi/L at any time during the study, compared to 21% of subjects in the eltrombopag group (see Table 24). Analysis of durability of response between the treatment groups using a logistic regression model demonstrated that this difference was statistically significant (p<0.001). The odds of having a platelet response between 50-400 Gi/L at least 75% of the time was 10 times greater in the eltrombopag group compared to the placebo group.

Table 24: Summary of Subjects by the Percentage of Assessments with a Platelet Response between 50-400 Gi/L (ITT Population, Dataset 4) RAISE Study.

	Treatment Group	
	PBO N=62 n (%)	Eltrombopag N=135 n (%)
N Subjects with at Least One Assessment, N	60 ^a	134 ^a
Subjects without a platelet response	43 (72)	28 (21)
Subjects with platelet response for 1-<25% of assessments	6 (10)	14 (10)
Subjects with platelet response for 25-<50% of assessments	5 (8)	15 (11)
Subjects with platelet response for 50-<75% of assessments	2 (3)	26 (19)
Subjects with platelet response for ≥75% of assessments	4 (7)	51 (38)
OR of responders ≥75% eltrombopag/PBO ^b	10.53	
95% CI	3.48, 31.91	
p-value (two-sided vs. PBO)	<0.001 ^c	

Data Source: Table 7.72, Table 7.73

- a. One placebo subject did not receive study medication and one placebo and one eltrombopag subject did not have any post-baseline assessments on treatment.
- b. Logistic regression model adjusting for use of baseline ITP medication, splenectomy, and baseline platelet count ≤15 Gi/L.
- c. Indicates significance at the 5% level (two-sided).

Weeks 2 Through 6 On-therapy Platelet Count Assessments

Platelet counts were measured weekly during the initial 6 weeks of the study and a summary of subjects achieving platelet counts between 50 and 400 Gi/L for at least 4 assessments during weeks 2 through 6 is provided in Table 25. Significantly more subjects in the eltrombopag group achieved this level of response compared to the placebo group (p<0.001), similar to that observed in TRA100773A and TRA100773B.

Table 25: Summary and Analysis of Responders During Weeks 2 through 6 (ITT Population, Primary Data Set) RAISE Study

	Treatment Group	
	PBO N=62 n (%)	Eltrombopag N=135 n (%)
Subjects with ≥ 4 Assessments between Weeks 2– 6	59	126
Subjects Responding in ≥4 Assessments between Weeks 2– 6	4 (7)	59 (47)
Odds-ratio of responding eltrombopag/PBO ^a	17.78	
95% CI	5.68, 55.71	
p-value (two-sided vs. PBO)	<0.001 ^b	

Data Source: RAISE Table 7.79

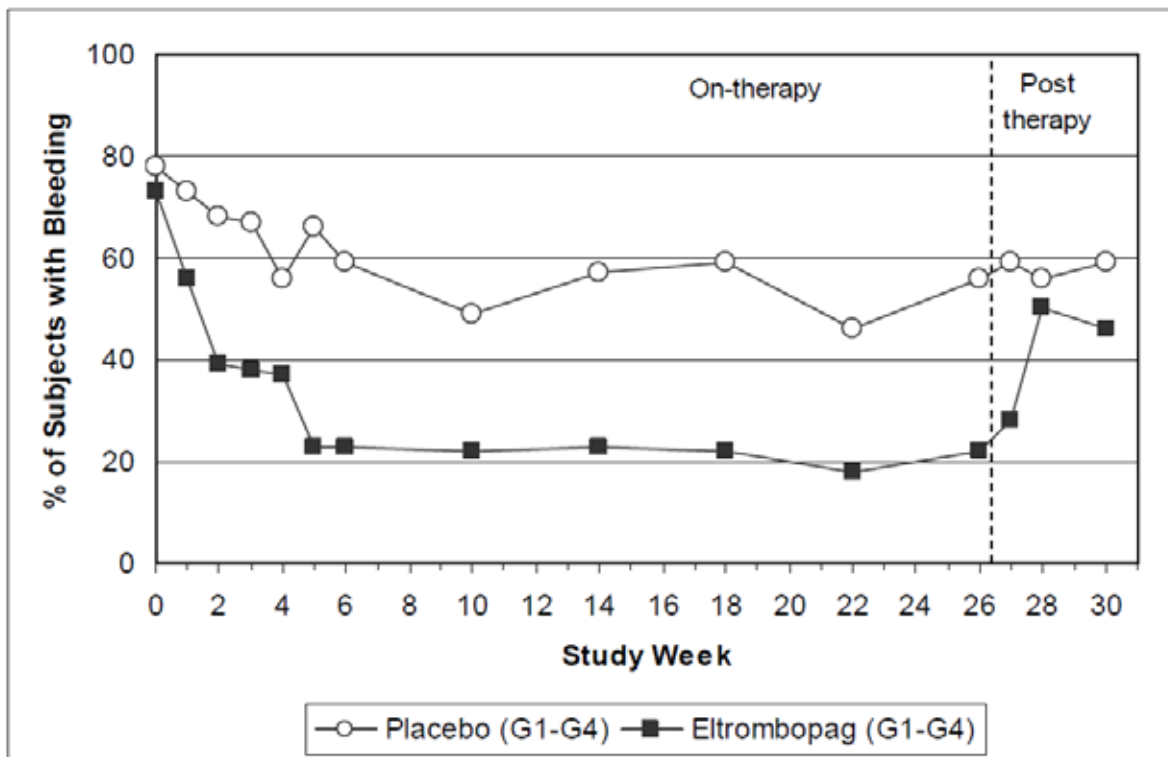
- a. Logistic regression model adjusting for use of baseline ITP medication, splenectomy, and baseline platelet count ≤15 Gi/L.
- b. Indicates significance at the 5% level (two sided).

Analyses of Bleeding

WHO Bleeding Score

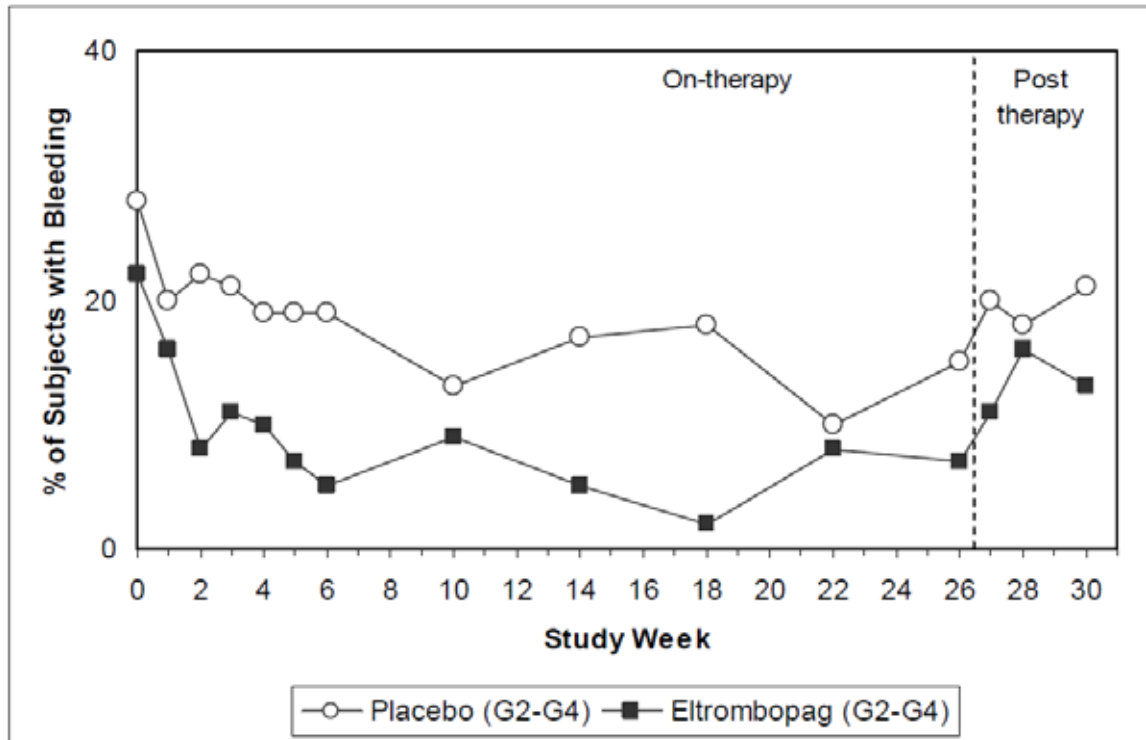
Graphical representations of the proportion of subjects in both treatment groups with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) at each nominal visit assessment in the RAISE study is provided in Figures 6 and Figure 7. The baseline percentage of subjects with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced by approximately half at each visit after the first 2 weeks of treatment with eltrombopag. At each time point in both treatment groups, more than half of the bleeding observed was Grade 1 bleeding.

Figure 6: Subjects with Any Bleeding (WHO Bleeding Grades 1-4) (ITT Population)



Vertical dotted line separates on-treatment visits from follow-up visits.

Figure 7: Subjects with Clinically Significant Bleeding (WHO Bleeding Grades 2-4) (ITT Population)



Vertical dotted line separates on-treatment visits from follow-up visits.

Any Bleeding, WHO Grades 1-4

Two weeks after initiating treatment with study medication, the percentage of subjects with any bleeding in the eltrombopag group decreased to 39% and after the first month of treatment was below 25% at every nominal visit throughout the 6 month study. In the placebo group, the percentage of subjects with bleeding was >45% at all nominal assessments. One week following discontinuation of eltrombopag, the proportion of subjects with any bleeding was similar to that observed on-therapy.

The reduction in the percentage of eltrombopag-treated subjects with any bleeding compared to placebo was statistically significant (see Table 26). Throughout the entire treatment period, the odds of any bleeding (Grade 1-4) were 76% lower in subjects treated with eltrombopag compared to those treated with placebo (p<0.001). Analysis of any bleeding (Grade 1-4) on at least 1 on-therapy visit, showed a statistically significant difference (p=0.012) between the groups, with fewer eltrombopag-treated subjects experiencing any bleeding at any point in the study (79%) compared to placebo-treated subjects (93%).

Table 26: Analysis of Bleeding – Primary Dataset (ITT Population)

Analysis of Any Bleeding (WHO Grades 1-4)	Treatment Group	
	Placebo N=62	Eltrombopag N=135
OR bleeding throughout 6 months, eltrombopag/PBO ^a	0.24	
95% CI	0.16, 0.38	
p-value (two-sided, vs PBO)	<0.001 ^b	
N Subjects with end of treatment WHO Bleeding Score	60	135
Subjects with bleeding at end of treatment, n (%)	34 (57)	37 (27)
OR bleeding at end of treatment, eltrombopag/placebo ^c	0.25	
95% CI	0.12, 0.51	
p-value (two-sided, vs PBO)	<0.001 ^b	
Subjects with bleeding at any time during 6 months	56 (93)	106 (79)
OR bleeding at any time in 6 months, eltrombopag/placebo ^c	0.21	
95% CI	0.06, 0.71	
p-value (two-sided, vs PBO)	0.012 ^b	
Data Source: RAISE Table 7.114, Table 7.112, Table 7.106, Table 7.110		
a. Repeated measures model for binary data adjusted for use of ITP medication at baseline, splenectomy status, baseline platelet count ≤15 Gi/L and baseline dichotomized WHO Bleeding Scale using GEE methodology.		
b. Indicates significance at the 5% level (two-sided).		
c. Logistic regression model adjusted for use of ITP medication at baseline, splenectomy status, baseline platelet count ≤15 Gi/L and baseline dichotomized WHO Bleeding Scale.		

Clinically Significant Bleeding, WHO Grades 2-4

Two weeks after initiating treatment with study medication, the percentage of subjects with clinically significant bleeding in the eltrombopag group decreased to 8% and remained ≤ 16% throughout the remainder of the on-therapy period, whereas in the placebo group between 10 to 25% of subjects were bleeding at most assessments (see Figure 7). The odds of clinically significant bleeding were 65% lower in the eltrombopag-treated subjects compared to placebo-treated subjects (p<0.001).

At the end of treatment, 13% of subjects in the placebo group had clinically significant bleeding (Grades 2-4) compared to 10% of eltrombopag-treated subjects. This difference at the end of treatment was not statistically significant; however the incidence of clinically significant bleeding at any one time point was low. When subjects were categorised into presence or absence of clinically significant bleeding (Grades 2-4) on at least 1 on-therapy visit throughout the 6 month treatment period, there was a statistically significant difference (p=0.002) between the groups, with fewer eltrombopag-treated subjects experiencing clinically significant bleeding at any point in the study (33%) compared to placebo-treated subjects (53%).

Haemostatic Challenge

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 (defined as a composite of: new ITP medication, increased dose of a concomitant ITP medication, platelet transfusion, and/or splenectomy) 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%) required rescue therapy. Of the 4 eltrombopag subjects who required rescue therapy, 3 had not consistently responded to eltrombopag treatment and had platelet counts below 40 Gi/L at the time of the haemostatic challenge.

Proportion of Subjects Receiving a Rescue Treatment

Rescue treatment was conservatively 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 rescue treatment. Corticosteroids followed by IVIg were the most commonly used rescue therapies in both treatment arms. In the placebo group, 15 subjects (24%) received rescue treatment with a corticosteroid compared to 14 subjects (10%) in the eltrombopag group. The odds of initiating a rescue treatment were 67% lower in the eltrombopag group compared to the placebo group ($p=0.001$). Of the 24 subjects in the eltrombopag group, 15 (63%; 15 of 24) who received rescue treatment on study did not respond to eltrombopag for the majority of their assessments.

ITP Medication Discontinuation and/or Dose Reduction

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(s). This difference was statistically significant; the odds of reducing or discontinuing at least 1 baseline ITP medication during the treatment period was 3 times higher in the eltrombopag-treated group compared to the placebo-treated group ($p=0.016$). Of the subjects who reduced or discontinued at least 1 baseline ITP medication, 6 subjects treated with placebo (60%) and 31 subjects treated with eltrombopag (84%) did not require any rescue medication following permanently discontinued or sustained reduction of their baseline ITP medication(s).

Health Outcomes

Baseline HRQoL scores indicated that subjects were slightly impaired in both treatment groups. Statistically significant improvements were observed in the eltrombopag group compared to the placebo when comparing baseline to the last on-therapy visit for vitality, and both physical and emotional role domains, as well as in mental health component summary. Greater improvements among those treated with eltrombopag compared to those treated with placebo were seen for bodily pain and social function domains as well as the physical component summary, and the differences were statistically significant ($p<0.10$). Statistically significant improvements from baseline were also observed with thrombocytopenia-impacted activities. Changes in motivation and energy and fatigue were also positive and significant at $p<0.01$.

Comment: The efficacy results from the RAISE study confirmed the efficacy findings from the short term studies and provided evidence that eltrombopag raises and maintains platelet counts to safe levels during 6 months of treatment in subjects with previously treated chronic ITP. Significant differences between eltrombopag and placebo were seen in primary and secondary efficacy endpoints. There was a statistically significant decrease in bleeding symptoms and improvement in ability of eltrombopag-treated subjects to successfully master haemostatic challenges without the need for additional therapies to prevent bleeding. There was a greater reduction in the use of baseline concomitant ITP medications in the eltrombopag group compared to placebo, and less use of rescue medication throughout the trial in the eltrombopag group compared to placebo.

Open-label Studies REPEAT and EXTEND

TRA108057 (REPEAT) Study Design

REPEAT was a multicentre, single arm, open-label, intermittent dose, Phase II study 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, in adult subjects with previously-treated chronic ITP. In contrast to the 3 double-blind, placebo-controlled studies, subjects in REPEAT were eligible to enrol with platelet counts between 20 Gi/L and 50 Gi/L, while in studies TRA100773A, TRA100773B and RAISE subjects were required to have platelet counts below 30 Gi/L at study entry.

In the REPEAT study, a cycle was defined as an eltrombopag on-therapy period of up to 6 weeks and an off-therapy period of up to 4 weeks. The duration of both the on-therapy and the off-therapy

periods were determined by the subject's platelet count. As in the double-blind studies, subjects in REPEAT interrupted treatment for the cycle if they achieved a platelet count >200 Gi/L, or if they had completed 6 weeks of dosing. The next cycle of treatment with eltrombopag was initiated when their platelet counts fell below 20 Gi/L, or when they reached Week 4 of the off-therapy period, and had platelet counts <50 Gi/L. Subjects who did not respond in Cycle 1 (platelet count ≥ 50 Gi/L and at least 2x baseline) were not eligible to continue into Cycle 2 or 3. Similar to the double-blind phase III study design (TRA100773 and RAISE), the dose could be increased to eltrombopag 75 mg on or after Day 22 of each Cycle if a subject's platelet count did not rise above 50Gi/L.

Statistical Analysis

The primary endpoint in REPEAT was the proportion of subjects who achieved a platelet count ≥ 50 Gi/L and at least 2x baseline in Cycle 2 or 3 given they achieved this response in Cycle 1. This proportion, together with 95% confidence intervals, was presented.

Study Population

All 66 subjects enrolled in REPEAT were included in the ITT Population. Eighteen subjects (27%) withdrew prior to completion of the REPEAT study. The most common reason for withdrawal in REPEAT was 'other', primarily due to subjects (9 subjects, 14%) who were non-responders in Cycle 1 and, per protocol, who were not eligible to enter Cycles 2 or 3.

Demographic characteristics for the open-label studies were generally similar to the characteristics of the populations treated in the double-blind studies. The baseline disease characteristics in REPEAT and EXTEND were similar to those in the double-blind studies, with the exception of baseline platelet counts. Fifty percent of subjects in REPEAT had baseline platelet counts ≥ 30 Gi/L.

All subjects in REPEAT received ≥ 1 prior ITP therapy, which included ongoing ITP medications and splenectomy. Sixty subjects (91%) in REPEAT reported previous treatment with ITP medications with a stop date prior to the start of the study. Similar to the double-blind studies, corticosteroids were the most commonly reported prior ITP medications taken by subjects in REPEAT (77%).

Efficacy Results

Primary Endpoint: Response in Cycles 2 or 3 in Subjects who Responded in Cycle 1

In Cycle 1, 52 of 65 evaluable subjects (80%) achieved a platelet count ≥ 50 Gi/L and 2x baseline at Day 43 or at treatment discontinuation for subjects who withdrew early due to achieving a platelet count >200 Gi/L. Of the 52 subjects who responded in Cycle 1, 33 (63%) and 37 (79%) satisfied the response criteria by Day 8 and Day 15 in Cycle 1, respectively. All 52 of the Cycle 1 responders continued into Cycle 2. Of the 13 Cycle 1 non-responders, 2 subjects continued into Cycle 2. One subject, who was not evaluable for Cycle 1 due to a missing Day 43 platelet count for the on-therapy period, also entered Cycle 2.

Fifty-five subjects entered Cycle 2 with 54 subjects in the ITT population evaluable for response in Cycle 2. Of the 54 evaluable subjects, 43 were considered responders (80%) in Cycle 2. Of the 43 responders, 42 continued into Cycle 3. Of the 11 non-responders, 8 subjects continued into Cycle 3. One subject, who was not evaluable for Cycle 2 due to a missing Day 1 platelet count, also entered Cycle 3.

Fifty-one subjects in the ITT population, regardless of Cycle 1 response status, entered Cycle 3 and were evaluable for response in Cycle 3. Of those, 39 were considered responders (76%) in Cycle 3.

Of the 52 subjects in the ITT population who achieved platelet counts ≥ 50 Gi/L and at least 2X baseline in Cycle 1, 51 and 49 were evaluable for response in Cycles 2 and 3, respectively. Forty-one subjects (80%) responded again in Cycle 2 and 38 (78%) subjects responded again in Cycle 3. All (52) of the subjects who had responded in Cycle 1 had evaluable data in Cycle 2 or 3 for the ITT analysis. Forty-five subjects (87%) responded again in Cycle 2 or 3.

Forty-eight subjects (92%) who had responded in Cycle 1 had evaluable data in both Cycles 2 and 3. Thirty-four subjects (71%) responded in all 3 cycles.

Percentage of subjects with platelets >200Gi/L

Subjects with a platelet count of >200 Gi/L at any time during a cycle were discontinued from eltrombopag in that cycle. By Day 8 of each cycle, 8%, 14% and 12% of subjects in Cycles 1, 2 and 3, respectively, had achieved a platelet response >200 Gi/L in the primary population for the efficacy analysis. The highest proportions occurred at Day 15, at which 19-31% of subjects in each cycle achieved platelet counts >200 Gi/L. One week after discontinuation of eltrombopag in each cycle, 15-24% of subjects remained >200 Gi/L. Similar to the double-blind studies, two weeks after discontinuation of eltrombopag, only 3-5% of subjects maintained this magnitude of platelet elevation in each cycle.

Median Platelet Counts

Across all 3 cycles, the median platelet counts at baseline of each cycle were similar. An elevation in median platelet counts was observed by Day 8 of each cycle. By Day 15, median platelet counts were 125, 126, and 118 Gi/L in each cycle, respectively. Median platelet counts remained \geq 79 Gi/L for the remainder of the on-therapy period in all 3 cycles.

To analyse the consistency of the peak and trough platelet counts across all 3 cycles, summary statistics of the highest and lowest platelet levels achieved were reviewed for subjects who responded in Cycle 1. A tabular summary of results is presented in Table 27. Few differences were observed with regard to the median lowest platelet count in the off-therapy periods between the 3 treatment cycles, indicating no systematic worsening of thrombocytopenia following multiple cycles of treatment with eltrombopag.

Table 27: Summary of Platelet Count (Gi/L) Peaks and Troughs (Subjects Responded In Cycle 1) – ITT Population (Observed Data) REPEAT

Observed Platelet Levels	Eltrombopag 50 mg		
	Cycle 1 (N=52)	Cycle 2 (N=51)	Cycle 3 (N=49)
Baseline, n	52	51	49
Mean (SD)	33.5 (12.77)	27.8 (15.82)	32.4 (26.8)
Median (Min, Max)	33.0 (7.0-82.0)	25.0 (0.0-66.0)	26.0 (8.0-167.0)
On-therapy Period			
Highest, n	52	52	49
Mean (SD)	225.8 (134.69)	209.1 (115.08)	175.6 (82.54)
Median (Min, Max)	200.5 (52.0-762.0)	196.0 (31.0-613.0)	174.0 (10.0-366.0)
Lowest, n	52	52	49
Mean (SD)	94.1 (67.52)	99.6 (91.51)	78.6 (72.69)
Median (Min, Max)	72.0 (6.0-354.0)	67.5 (7.0-454.0)	59.0 (2.0-344.0)
Off-therapy Period			
Highest, n	52	52	49
Mean (SD)	157.2 (114.83)	141.8 (143.37)	144.5 (116.45)
Median (Min, Max)	118.5 (0.0-662.0)	92.5 (12.0-701.0)	125.0 (21.0-594.0)
Lowest, n	52	52	49
Mean (SD)	23.4 (11.6)	25.6 (13.81)	29.0 (32.64)
Median (Min, Max)	21.0 (0.0-59.0)	22.5 (8.0-75.0)	22.0 (0.0-187.0)

Use of Rescue Medication

No subject received a rescue medication during treatment with eltrombopag or during the off therapy periods between Cycles 1 and 2 or Cycles 2 and 3.

Analyses of Bleeding

Bleeding assessed by WHO Bleeding Scale

No WHO assessments of Grade 3 or 4 bleeding were reported during the study up to and including the 4-week post-therapy period. The highest incidence of any bleeding (Grades 1-4) was observed at the baseline or Day 1 visit of each cycle, with 50, 60 and 35 percent of subjects reporting any bleeding in Cycles 1, 2 and 3 respectively, corresponding with the lowest median platelet counts in each cycle. The increase in bleeding at baseline in Cycle 2 was due to an increase in Grade 1 bleeding. Across all 3 cycles: $\leq 19\%$ of subjects had clinically significant bleeding (Grade 2). No subjects had Grade 3 or 4 bleeding.

Haemostatic Challenges

Eight subjects experienced ten haemostatic challenges during the study. All subjects responded to eltrombopag and none required additional treatment to elevate their platelet count before or after the procedure.

TRA105325 (EXTEND)

Study Design

EXTEND is an ongoing, global, single arm, open-label, extension study to evaluate the long-term safety of eltrombopag in subjects with chronic ITP who had previously been enrolled in an eltrombopag study (TRA100773A, TRA100773B, REPEAT or RAISE). The clinical data cut-off used for this report was 07 January 2008. Long-term efficacy of eltrombopag was a secondary endpoint. Notably, no platelet count entry criteria were specified for EXTEND (for example, subjects with platelet counts ≥ 50 Gi/L were allowed into the study). Similar to the RAISE study, eltrombopag dose modifications were permitted in order to maintain each subject's platelet count in the desired range (50–400 Gi/L) in EXTEND.

Subjects initiated treatment with eltrombopag 50 mg once daily and followed specific instructions for dosing modifications based upon their individual platelet count response. In general, the dose modification guidelines allowed subjects to: increase the dose of eltrombopag (to a maximum of 75 mg, once daily), if platelet count elevation was insufficient (for example < 50 Gi/L); maintain the dose of eltrombopag if platelet counts were between 50-200 Gi/L; reduce the dose of eltrombopag if platelet counts had risen to values between 200-400 Gi/L; or interrupt treatment with eltrombopag if platelet counts exceeded 400 Gi/L with restart at a lower dose when platelet counts return to ≤ 150 Gi/L.

The study is structured into stages, depending on the subjects' use of concomitant ITP medications. In stage 1, subjects are administered a starting dose of 50 mg/day in order to reach a platelet count of ≥ 50 Gi/L or ≥ 100 Gi/L depending on whether they were taking a concomitant ITP medication at study entry. Concomitant ITP medications, if taken at study entry, can then be tapered to a minimal dose or discontinued entirely (stage 2), while maintaining a platelet count of ≥ 50 Gi/L. Eltrombopag dose can then be titrated to a minimal effective dose to maintain platelet counts of ≥ 50 Gi/L (stage 3) and continued for as long as the subject continues to benefit (stage 4).

Statistical Analysis

For EXTEND, summary statistics were provided; no formal statistical analyses were planned or conducted.

Study Population

Of the 283 subjects enrolled in EXTEND, 207 subjects were included in the ITT Population. Seventy-six subjects were not included in the ITT Population since they had not been dispensed study medication at the time of the clinical cut-off. The populations for EXTEND are based on the availability of data from the ongoing study through the cut-off date.

In EXTEND, 35 subjects withdrew from the study. The most common reason for withdrawal from the study was lack of efficacy in 13 subjects (6%).

The baseline disease characteristics in EXTEND were similar to those in the double-blind studies, with the exception of baseline platelet counts. Thirty per cent of subjects in EXTEND had baseline platelet counts ≥ 30 Gi/L. All subjects received ≥ 1 prior ITP therapy, which included ongoing ITP medications and splenectomy. One hundred and ninety five subjects (94%) in EXTEND reported previous treatment with ITP medications with a stop date prior to the start of the study. Similar to the double-blind studies, corticosteroids were the most commonly reported prior ITP medications taken by subjects in EXTEND (80%).

Efficacy Results

Subjects Achieving a Platelet Count ≥ 50 Gi/L

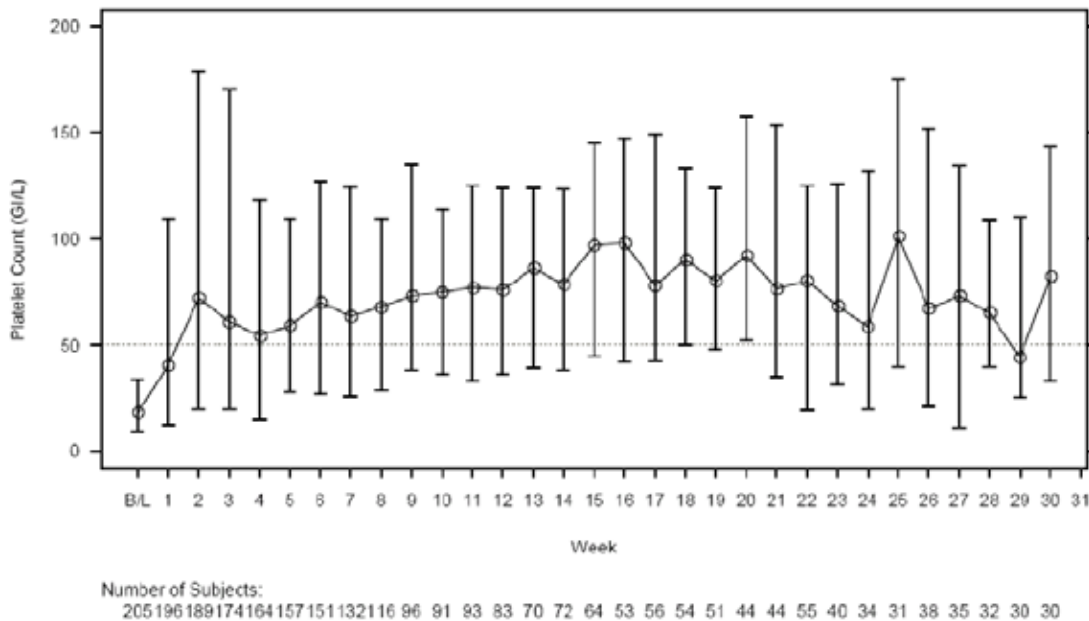
At baseline, 14% of subjects had platelet counts ≥ 50 Gi/L. At the time of data cut-off, 79% of subjects had achieved a platelet count ≥ 50 Gi/L at least once during the study. Thirty-two subjects (16%) achieved platelet counts above 400 Gi/L at least once during the study. The median duration of maximum continuous days of platelet count elevation ≥ 400 Gi/L was 11.5 days (range 7 to 49 days).

Long-term Elevation of Platelet Counts ≥ 50 Gi/L

An important efficacy objective of EXTEND is to assess the ability of eltrombopag to elevate platelet counts above 50 Gi/L and to maintain platelet counts in a safe range (50- 400 Gi/L) during long-term (>6 week) treatment. A similar response to eltrombopag was observed throughout the study regardless of splenectomy status and irrespective of whether or not subjects were taking concomitant ITP medication at baseline. Although the majority of subjects achieved platelet counts ≥ 50 Gi/L regardless of baseline platelet count, subjects with a baseline platelet count < 30 Gi/L had a slower time course and a lower magnitude of median platelet count elevation.

Eltrombopag increased median platelet counts to ≥ 50 Gi/L at the majority of the post-baseline visits on the study, as graphically shown in Figure 8. The median platelet count post-baseline increased to ≥ 50 Gi/L beginning at the second week on study and remained elevated until the end of the observation period presented (that is, 55 weeks), with the exception of weeks 29, 33, and 45 where the median platelet count was 44, 43, and 42 Gi/L, respectively. Just over half of the subjects (51%) experienced ≥ 4 weeks of continuous elevation of platelets ≥ 50 Gi/L and 2x baseline while receiving eltrombopag. Thirty five percent of subjects had a continuous response of ≥ 10 weeks. At approximately 6 months (25 weeks), 24% of subjects who had been in the study for ≥ 25 weeks had continuous elevation ≥ 50 Gi/L and 2x baseline of 25 weeks or longer.

Figure 8: Median Platelet Counts (25th and 75th percentiles) by Week (Weeks 1 – 30)



Data Source: EXTEND Figure 7.16

NOTE: Bars represent the 25th and 75th percentiles. If a subject had more than 1 data point within a week then the average of these points was taken and used in the box plot calculations.

Continuous Elevation of Platelet Counts ≥ 50 Gi/L and ≥ 2 X Baseline by Subject

Because subjects in EXTEND were not required to have platelet counts < 30 Gi/L, a different response criterion was also used in EXTEND (platelet counts ≥ 50 Gi/L and ≥ 2 X baseline at any on-therapy assessment) to control for subjects who started EXTEND with a baseline platelet count already ≥ 50 Gi/L. The maximum number of weeks of continuous platelet count elevations ≥ 50 Gi/L and 2x baseline was assessed for all subjects, taking into consideration the duration of time exposed to eltrombopag. At the time of the data cut-off, subjects had been dosed with eltrombopag for varying periods of time in the ongoing study ranging from 2 to 523 days.

A tabular summary of results is provided in Table 28. The last column shows the number of subjects with a given number of weeks of continuous platelet count elevation (≥ 50 Gi/L and 2x baseline). The denominator includes all subjects known to have been exposed to eltrombopag for the given period of time up to the cut-off date. This includes 42 subjects (21 subjects were in the study ≤ 6 weeks and 21 subjects participated in the study from 7 to 55 weeks) who never achieved a single platelet count ≥ 50 Gi/L. Twenty-five subjects with a baseline platelet count > 50 Gi/L were also included in this analysis.

Just over half of the subjects (51%) experienced ≥ 4 weeks of continuous elevation of platelets ≥ 50 Gi/L and 2x baseline while receiving eltrombopag. In addition, 35% of subjects had a continuous response of ≥ 10 weeks. At approximately 6 months (25 weeks), 24% of subjects who had been in the study for ≥ 25 weeks had continuous elevation ≥ 50 Gi/L and 2x baseline of 25 weeks or longer.

Table 28: Maximum Continuous Weeks of Maintaining Platelet Counts >50 Gi/L and 2x Baseline EXTEND

Number of Continuous Weeks ^a (wks)	Number of Subjects					Total n/N (%) ^b
	≤12 weeks n/N (%) ^b	>12 to ≤24 weeks n/N (%) ^b	>24 to ≤48 weeks n/N (%) ^b	>48 to ≤72 weeks n/N (%) ^b	>72 weeks n/N (%) ^b	
Total	99	33	33	39	3	207
No continuous wks	56/99 (57)	11/33 (33)	6/33 (18)	3/39 (8)	1/3 (33)	77/207 (37)
≥1 wks response	43/93 (46)	22/33 (67)	27/33 (82)	36/39 (92)	2/3 (67)	130/201 (65)
≥4 wks response	17/71 (24)	17/33 (52)	24/33 (73)	32/39 (82)	2/3 (67)	92/179 (51)
≥7 wks response	1/39 (3)	13/33 (39)	19/33 (58)	27/39 (69)	2/3 (67)	62/147 (42)
≥10 wks response	0/17 (0)	6/33 (18)	14/33 (42)	23/39 (59)	1/3 (33)	44/125 (35)
≥13 wks response		3/29 (10)	10/33 (30)	21/39 (54)	1/3 (33)	35/104 (34)
≥16 wks response		1/21 (5)	8/33 (24)	19/39 (49)	1/3 (33)	29/96 (30)
≥19 wks response		1/12 (8)	6/33 (18)	18/39 (46)	1/3 (33)	26/87 (30)
≥22 wks response		0/8 (0)	4/33 (12)	16/39 (41)	1/3 (33)	21/83 (25)
≥25 wks response			3/33 (9)	14/39 (36)	1/3 (33)	18/75 (24)
≥28 wks response			3/28 (11)	12/39 (31)	1/3 (33)	16/70 (23)
≥31 wks response			2/23 (9)	11/39 (28)	1/3 (33)	14/65 (22)
≥34 wks response			1/20 (5)	8/39 (21)	1/3 (33)	10/62 (16)
≥37 wks response			1/17 (6)	5/39 (13)	1/3 (33)	7/59 (12)
≥43 wks response			0/13 (0)	5/39 (13)	0/3 (0)	5/55 (9)
≥52 wks response				2/24 (8)	0/3 (0)	2/27 (7)

Data Source: EXTEND Table 7.71

- Weeks on study in this analysis are determined based on known exposure to eltrombopag up to cut-off date
- n= the number of subjects with continuous elevation of platelet counts of indicated duration, N=the total number of subjects who had been exposed to eltrombopag for the indicated duration up to the cut-off date

Durability of Platelet Count Elevation ≥50 Gi/L

A durable platelet response, excluding subjects who received rescue medication at any time during the first 6 months, was achieved in 56% of subjects treated for ≥ 6 months. An overall platelet response was achieved in 82% of subjects. There was no difference in the percentage of splenectomised and non-splenectomised subjects with a durable platelet response (55% and 57%, respectively) or an overall platelet response (82% and 83%, respectively).

Response in EXTEND Following Response in Prior Study

The majority of subjects who responded in a previous eltrombopag study and received study medication in EXTEND responded again in EXTEND, indicating that a prior response to eltrombopag is predictive of a subsequent rise in platelets when subjects are retreated with eltrombopag.

ITP Medication Dose Reduction

At baseline, 69 subjects (33%) used other ITP medications of which 33 subjects (48%) started to reduce or discontinue concomitant ITP medications during the study. Seventy percent of subjects (23 of 33) permanently discontinued or had a sustained reduction of at least one baseline ITP medication and did not require any subsequent rescue treatment as of the clinical cut-off date. Of these 23 subjects, 15 (65%) maintained this discontinuation or reduction for ≥ 24 weeks. Sixty-one percent of subjects (20 of 33) completely discontinued at least one baseline ITP medication, and 55% of subjects (18 of 33) permanently discontinued all baseline ITP medications, without subsequent rescue treatment.

Use of Rescue Medication

Rescue treatment in EXTEND was defined in the same way as in the RAISE study. As of the cut-off date, 31 subjects (15%) received treatment meeting the definition of rescue while on study.

Analyses of Bleeding

WHO Bleeding Scale

The proportion of subjects with any bleeding (Grade 1–4) and clinically significant bleeding (Grade 2–4) decreased from baseline, beginning as early as Week 2 of treatment with eltrombopag, and continued for all weeks through at least week 47. By Week 48, 13 or fewer subjects had an assessment at each weekly visit. At baseline, 59% of subjects had any bleeding and 18% of subjects reported clinically significant bleeding. During Week 12 on study, 27% of subjects had any bleeding and 4% had clinically significant bleeding. By Weeks 24, 36 and 48, 26%, 8% and 33% of subjects, respectively, had any bleeding and 9%, 4% and 25% of subjects, respectively, had clinically significant bleeding. The apparent increase in proportion of subjects with clinically significant bleeding at Week 48 in comparison to baseline may be due to few subjects having assessments by Week 48: 3 of 12 subjects (25%) at Week 48 had clinically significant bleeding versus 38 of 207 (18%) at baseline. At the majority of time points assessed, WHO Grade 1 bleeding events made up over half of the total bleeding events reported.

Haemostatic Challenges

Twenty-four subjects experienced at least one haemostatic challenge during the study. No subject experienced unexpected bleeding complications related to the procedure while on study.

Subgroup Analyses

Subjects with Baseline Platelet Counts of Less Than or Equal to 15Gi/L

TRA100773A and TRA100773B - Pooled

In more than 50% of subjects, eltrombopag increased platelet counts after up to 6 weeks of dosing, both for subjects who had baseline platelet counts of ≤ 15 Gi/L and for those who had baseline platelet counts >15 Gi/L. A higher percentage of subjects in both treatment groups with baseline platelet counts >15 Gi/L achieved a platelet count ≥ 50 Gi/L compared to subjects with a baseline platelet count ≤ 15 Gi/L. No significant interaction between response and baseline platelet count status was observed (p-value for interaction=0.443).

RAISE

In RAISE results showed that eltrombopag increased platelet counts compared to placebo irrespective of baseline platelet count (p-value for interaction=0.804).

Use of ITP Medication at Randomisation

TRA100773A and TRA100773B - Pooled

Analysis of responders at the Day 43 Visit showed that eltrombopag increased platelet counts relative to placebo irrespective of whether subjects were using ITP medication or not.

RAISE

Eltrombopag increased platelet counts irrespective of use of baseline ITP medications (p-value for interaction=0.890).

Splenectomy

TRA100773A and TRA100773B - Pooled

Analysis of responders at the Day 43 Visit demonstrated that eltrombopag increased platelet counts compared to placebo after up to 6 weeks of dosing for subjects regardless of splenectomy status. There was no significant interaction between response and splenectomy status (p-value for interaction=0.6610).

RAISE

Eltrombopag increased platelet counts irrespective of splenectomy status (p-value for interaction=0.562).

RAISE Median Platelet Counts by Stratification Variables

Subjects responded to eltrombopag with higher median platelet counts compared to placebo at all on-therapy assessments regardless of whether or not they were taking baseline ITP medication or of splenectomy status; however, the time course of platelet count elevation was slower in splenectomised subjects compared to non-splenectomised subjects. In addition, subjects responded to eltrombopag regardless of baseline platelet count.

Age, Sex and Race

In studies TRA100773A, TRA100773B and RAISE there were no clear clinically important differences in patterns of responses when data were analysed by age, sex and race.

Summary of Efficacy

Efficacy of eltrombopag has been evaluated in 3 double-blind, randomised, placebo-controlled studies in previously-treated adults with chronic idiopathic ITP and platelet levels <30 Gi/L (TRA100773A, TRA100773B, and TRA102537/RAISE). Supportive efficacy data were provided from 2 single arm, open-label studies which provide data on intermittent (TRA108057/REPEAT) and long-term use (TRA105325/EXTEND) of eltrombopag.

The data from these 5 clinical studies showed the following:

- Eltrombopag was consistently superior to placebo in raising and maintaining platelet levels above 50Gi/L for up to 6 months in previously treated subjects with chronic ITP
- Eltrombopag raised platelet counts quickly and predictably. The onset of response in all three studies was rapid with >30% of subjects responding with an increase of platelet counts \geq 50Gi/L by Day 8, and ~50% of subjects responding by Day 15. Platelet levels remained elevated for approximately one week after stopping eltrombopag
- The effectiveness of eltrombopag compared to placebo was observed throughout treatment regardless of baseline platelet counts, use of concomitant ITP medication or splenectomy status
- The dose of eltrombopag can be individualised to maintain platelet counts in the 50- 400 Gi/L range during long term treatment
- The platelet count elevation in eltrombopag-treated subjects was accompanied by a significant reduction in bleeding symptoms (WHO Bleeding Scale) compared to placebo-treated subjects throughout the treatment period
- Subjects treated with eltrombopag were able to master haemostatic challenges without additional treatments to elevate their platelet counts
- Eltrombopag-treated subjects were able to reduce the use of concomitant ITP medications and required less rescue medication than placebo subjects

Comment: The studies submitted for evaluation were appropriately designed and conducted to evaluate efficacy of eltrombopag. Overall the evaluator considered that the data presented for evaluation adequately support that eltrombopag is effective for treatment of patients with chronic

ITP. It has been shown to increase platelet counts and reduce the risk of bleeding in patients who have not responded to corticosteroids, immunoglobulins, or splenectomy.

It is considered that minor amendment should be made to the indication as proposed by the sponsor, in order to accurately reflect the clinical trial population studied and the efficacy results. An indication similar to the following should be considered:

“Revolade is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Revolade has been shown to increase platelet counts and reduce the risk of bleeding. Revolade should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding”.

Safety

The sponsor presented safety data from 3 double-blind placebo-controlled Phase II or III studies (TRA100773A, TRA100773B, TRA102537/RAISE), 2 open-label Phase II or III studies (TRA108057/REPEAT and TRA105325/EXTEND), 1 non-treatment observational Phase III study (TRA108132/LENS), and 13 completed clinical pharmacology studies conducted with eltrombopag. Safety data from TRA100773A and TRA100773B were based on final study results. Data from RAISE and REPEAT were based on final study results including all on-therapy study assessments up through the 4-week follow-up visit (ocular data are being collected from the 3 and 6 month follow-up visits). Safety data from EXTEND included all data up to the clinical data cut-off date of 07 January 2008, and safety data from LENS included all data up to the clinical data cut-off date of 26 February 2008. For all ongoing studies across a range of indications including chronic ITP, as well as for the Compassionate Use/Named Patient program, the cut-off date for reporting serious adverse events (SAEs) was 01 August 2008.

Subject Disposition

In the pooled data analysis of TRA100773A and TRA100773B, a higher proportion of subjects in the eltrombopag 50 mg group (35%) discontinued study medication, compared to subjects in the placebo (PBO) group (22%). This difference was mainly due to the higher number of subjects in the eltrombopag 50 mg treatment group who achieved a platelet count >200 Gi/L and discontinued treatment as required by the protocols. In RAISE, the most common reason for withdrawal from the study was AEs (PBO 6% vs. eltrombopag 10%). In REPEAT, the most common reason for withdrawal from the study was “other” (18%) which included 9 subjects who were non-responsive in Cycle 1 and were not eligible to enter Cycles 2 or 3, 1 subject who relocated, and 2 subjects who withdrew due to a prolonged off-therapy period with platelet counts >50 Gi/L. In EXTEND, the most common reason for withdrawal from study medication was lack of efficacy (6%) followed by subject decision (4%) and adverse event (4%).

Extent of Exposure

The total cumulative exposure of eltrombopag in this patient population is presented by combining the cumulative eltrombopag exposure in EXTEND to the cumulative eltrombopag exposure in the previous study. A tabular summary of exposure is presented in Table 29, and a summary of cumulative exposure to eltrombopag in months is presented in Table 30. The median average daily dose of eltrombopag received was 50.0 mg, and the median number of days of exposure to eltrombopag was 148 days (approximately 5 months). Almost 200 subjects have had a cumulative exposure to eltrombopag of at least 6 months, 41 subjects have been exposed for at least 1 year, and 12 subjects have been exposed for at least 15 months.

Table 29: 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

Data Source: [SDAP Table 8.3](#)

- Number of subjects who received at least one dose of eltrombopag in [TRA100773A](#), [TRA100773B](#), [RAISE](#), [REPEAT](#), or [EXTEND](#).
- Number excludes [RAISE](#) Subject 836 who was dispensed study medication and was subsequently lost to follow-up and [TRA100773A](#) Subject 144 for whom no information was collected by the site regarding the number of tablets taken and/or returned.
- Excludes Subject 836 from [RAISE](#) (see above).
- Subject Months calculated as N x mean days on eltrombopag x (12 / 365.25)

Table 30: Cumulative Exposure to Eltrombopag in Months –ITP Studies (Safety Population)

Duration of Exposure^a	Eltrombopag N=422^b
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

Data Source: [TRA100773A](#) CSR, [Section 8.1](#); [TRA100773B](#) CSR, [Section 8.1](#); [TRA102537](#) CSR, [Section 8.1](#); [TRA105325](#) CSR, [Section 8.1](#); [TRA108057](#) CSR, [Section 8.1](#)

- The categories of exposure incorporate a +/-3 day window.
- [RAISE](#) Subject 836 was dispensed study medication and was subsequently lost to follow-up; however, this subject is included as having at least 1 day of treatment.

A tabular summary of exposure for the double-blind studies is provided in Table 31. The median average daily dose of eltrombopag for the pooled data from the 6-week studies was 50.0mg. The median average daily dose in RAISE was 58.0mg, slightly higher than in the pooled data from TRA100773A and TRA100773B due to the flexibility in dosing in RAISE over a 6 month period of time based on platelet counts. The median duration of treatment was similar for subjects in the placebo and eltrombopag groups in the 6-week and 6-month studies.

Table 31: Summary of Exposure in Double-blind Studies

	773A + 773B (Pooled)		RAISE	
	PBO N=67	Eltrombopag 50 mg N=106	PBO N=61	Eltrombopag N=135
Average Daily Dose (mg), n	NA	105 ^a	NA	134 ^b
Mean (SD)		52.7 (5.67)		55.2 (16.26)
Median (min, max)		50.0 (39 - 65)		58.0 (16 - 72)
Cumulative Dose (mg), n	NA	105	NA	134
Mean (SD)		1868.8 (739.04)		9178.9 (3833.24)
Median (min, max)		2150.0 (350 - 2700)		9450.0 (250 - 14550)
Days on Study Drug, n	67	106	61	134
Mean (SD)	37.7 (11.47)	34.8 (12.61)	169.3 (43.16)	164.7 (45.09)
Median (min, max)	42.0 (5 - 49)	43.0 (8 - 51)	183.0 (7 - 218)	183.0 (5 - 201)
Total Subject Months on Treatment^c	83.0	121.2	339.3	725.1

Data Source: SDAP Table 8.7, CSR TRA102537 Table 8.1

a. Excludes Subject 144 from TRA100773A.

b. Excludes Subject 836 from RAISE.

c. Subject Months calculated as N x mean days on eltrombopag x (12 / 365.25)

In the TRA100773A study, the median cumulative dose for subjects in the 30 mg treatment group was equal to the expected 42 days of treatment; however, the median duration of therapy in the 75 mg treatment group was substantially lower, 22.5 days compared with 42 days in the other treatment groups. In the 75 mg treatment group, the largest proportion of subjects discontinued treatment early due to achieving platelet counts >200 Gi/L (43%).

In the RAISE study, the majority of subjects were exposed to study medication for 6 months. In both REPEAT and EXTEND, the median daily dose of eltrombopag was 50 mg and the median duration of exposure was 80.5 days in REPEAT and 91.5 days in EXTEND. In EXTEND, 106, 75, 58, 27, and 9 subjects were exposed to eltrombopag for at least 3, 6, 9, 12, and 15 months, respectively.

Common Adverse Events

Overall Summary of Adverse Events

Double-blind Studies

A tabular summary of on-therapy adverse events (AEs) of pooled data from TRA100773A and TRA100773B is provided in Table 32. Results showed a slightly higher incidence of AEs among subjects in the pooled 50 mg group as compared with the PBO group during the on-therapy (+1 day) period of the studies. There were no differences observed in the incidence of treatment-related AEs, SAEs and AEs leading to withdrawal between the 2 treatment groups.

Table 32: 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

RAISE

A tabular summary of on-therapy adverse events (AEs) in the RAISE study is provided in Table 33. There were no clear differences observed in the incidence of treatment-related AEs, SAEs and AEs leading to withdrawal between the 2 treatment groups.

Table 33: Overall Summary of On-therapy Adverse Events – 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

Open-label Studies

A tabular summary of on-therapy adverse events (AEs) in the open-label studies is provided in Table 34. There were no clear differences observed in the incidence of treatment-related AEs, SAEs and AEs leading to withdrawal between the 2 treatment groups. However, the majority of subjects in the EXTEND study were exposed to eltrombopag before, which may affect the AE profile in these subjects, and therefore, comparisons between EXTEND and other studies have limitations.

Table 34: Overall Summary of On-therapy Adverse Events – Open-label Studies

	REPEAT (all cycles) Eltrombopag N=66, n (%)		EXTEND Eltrombopag N=207, n (%)
	On	Off	
Any AE	45 (68)	41 (63)	150 (72)
Any SAE	1 (2)	3 (5)	17 (8) ^a
Any treatment-related AE	15 (23)	2 (3)	51 (25)
Any AE leading to withdrawal	1 (2)	0	9 (4) ^b
Any SAE leading to withdrawal	0	0	6 (3) ^b

Data Source: [TRA108057](#) CSR, Section 8.2.1; [TRA105325](#) CSR, Section 8.2.1

- [TRA105325](#) Table 8.6 shows 17 subjects. An SAE in Subject 71 was listed as on-therapy but has been reclassified as post-therapy (eltrombopag had been interrupted due to a platelet count >400 Gi/L, and was not restarted due to SAE). An SAE in Subject 130 occurred after the clinical cut-off date and is included here.
- [TRA105325](#) CSR Table 8.6 shows 8 and 5 subjects with AEs and SAEs, respectively, leading to withdrawal. One additional subject (1272) was dose interrupted due to SAEs and eltrombopag was not restarted. This subject was added to this tabulation.

Most Common Adverse Events

TRA100773A and TRA100773B (Pooled Data)

Headache, nasopharyngitis, nausea, fatigue and arthralgia were the most common AEs ($\geq 5\%$) reported during the on-therapy (+1 day) period regardless of causality in the eltrombopag 50 mg treatment group. The rates of these common AEs were similar between the PBO and 50 mg treatment groups, with the exception of nausea, which was reported more frequently in the eltrombopag group, and headache and arthralgia, which were reported more frequently in the PBO group.

RAISE

A tabular summary of the most commonly reported on-therapy AEs in RAISE is presented in Table 35. In RAISE, headache was the most commonly reported on-therapy AE in both treatment groups. Diarrhoea, nausea, nasopharyngitis, fatigue and upper respiratory tract infection were reported by \geq

10% of subjects in the eltrombopag group. Two AEs (nausea and vomiting) occurred more frequently ($\geq 5\%$) in eltrombopag-treated subjects compared to PBO-treated subjects.

Table 35: On-therapy AEs Reported by 5% or More of Subjects in Either Treatment Group – RAISE

Preferred Term	Treatment Group, n (%)	
	PBO N=61	Eltrombopag N=135
Subjects with Any AE	56 (92)	118 (87)
Headache	20 (33)	41 (30)
Diarrhea	6 (10)	17 (13)
Nausea	4 (7)	16 (12)
Nasopharyngitis	8 (13)	14 (10)
Upper respiratory tract infection	7 (11)	14 (10)
Fatigue	8 (13)	13 (10)
Pain in extremity	6 (10)	9 (7)
ALT increased	4 (7)	10 (7)
Vomiting	1 (2)	10 (7)
Urinary tract infection	4 (7)	9 (7)
Arthralgia	3 (5)	9 (7)
Pharyngolaryngeal pain	3 (5)	9 (7)
Myalgia	2 (3)	8 (6)
Pharyngitis	1 (2)	8 (6)
AST increased	2 (3)	7 (5)
Epistaxis	6 (10)	7 (5)
Back pain	3 (5)	7 (5)
Influenza	3 (5)	7 (5)
Cough	4 (7)	6 (4)
Abdominal pain upper	5 (8)	6 (4)
Constipation	5 (8)	6 (4)
Dizziness	6 (10)	5 (4)
Pruritus	5 (8)	4 (3)
Cataract	4 (7)	4 (3)
Hypertension	3 (5)	4 (3)
Edema peripheral	6 (10)	2 (1)
Dyspepsia	4 (7)	2 (1)
Ecchymosis	4 (7)	2 (1)
Insomnia	4 (7)	2 (1)
Anxiety	3 (5)	2 (1)
Conjunctival hemorrhage	3 (5)	2 (1)
Contusion	3 (5)	2 (1)
Neck pain	3 (5)	2 (1)
Non-cardiac chest pain	3 (5)	2 (1)
Abdominal distension	3 (5)	1 (<1)
Conjunctivitis	4 (7)	1 (<1)
Fall	3 (5)	1 (<1)
Swelling face	3 (5)	1 (<1)
Cellulitis	4 (7)	0
Eye swelling	3 (5)	0

Open-label Studies

In general, the most common on-therapy AEs reported in the open-label studies were similar to those in the double-blind studies. In REPEAT, headache was the most common on-therapy AE, with 21% of subjects reporting this event during on-therapy periods, followed by diarrhoea (11%), fatigue (9%) and nasopharyngitis (9%). There was no apparent increase in incidence of specific AEs as subjects progressed across the 3 cycles of treatment with eltrombopag. Fatigue (9%), nasopharyngitis (9%), headache (8%) and back pain (8%) were the most common off-therapy AEs reported.

In EXTEND, headache was the most frequently reported on-therapy AE, followed by upper respiratory tract infection and diarrhoea, each reported in at least 10% of subjects.

Treatment-Related AEs

Double-blind Studies

A tabular summary of on-therapy treatment-related AEs for the pooled TRA100773 data is provided in Table 36. Approximately 20% of subjects in both the placebo and eltrombopag 50 mg treatment groups were considered treatment-related. Headache, in the eltrombopag group, was the only treatment-related AE reported in 5% or more subjects in either treatment group. In TRA100773A, there was no dose dependent increase in treatment-related AEs observed upon analysis of the eltrombopag 30, 50 and 75 mg treatment groups.

Table 36: On-therapy Treatment-related AE Reported in 2% or More Subjects-Pooled TRA100773 Data

Preferred Term	Treatment Group, n (%)	
	PBO N=67	Eltrombopag 50 mg N=106
Subject with Any Treatment-related AE	14 (21)	28 (26)
Headache	3 (4)	7 (7)
Nausea	0	4 (4)
Vomiting	0	2 (2)
Fatigue	1 (1)	3 (3)
Myalgia	0	3 (3)
Protein total increased	1 (1)	3 (3)
ALT increased	0	2 (2)
AST increased	0	2 (2)
Arthralgia	2 (3)	1 (<1)
Peripheral edema	2 (3)	1 (<1)
Dysgeusia	2 (3)	0

A tabular summary of on-therapy treatment-related AEs for RAISE is provided in Table 37. In RAISE, AEs considered treatment-related by the investigator were reported in 18 subjects (30%) in the PBO group and in 48 subjects (36%) in the eltrombopag group. Headache was the most frequently reported treatment-related AEs in both treatment groups and occurred at a similar rate in both groups. Treatment-related nausea, diarrhoea, paresthesia, dry mouth and hyperhidrosis were all reported in at least 3 subjects in the eltrombopag group compared to none in the PBO group.

Table 37: On-therapy Treatment-related AE Reported in 2% or More Subjects – RAISE

Preferred Term	Treatment Group, n (%)	
	PBO N=61	Eltrombopag N=135
Subject with Any Treatment-related AE	18 (30)	48 (36)
Headache	5 (8)	15 (11)
Cataract	3 (5)	4 (3)
ALT increased	2 (3)	6 (4)
Nausea	0	6 (4)
Diarrhea	0	4 (3)
Paresthesia	0	3 (2)
Constipation	1 (2)	3 (2)
Dry mouth	0	3 (2)
Hyperhidrosis	0	3 (2)
AST increased	2 (3)	3 (2)
Epistaxis	1 (2)	2 (1)
Fatigue	1 (2)	2 (1)
Myalgia	1 (2)	2 (1)
Dizziness	2 (3)	1 (<1)

Open-label Studies

In REPEAT, on-therapy AEs considered treatment-related by the investigator were reported in 15 (23%) subjects across all cycles for the on-therapy period and in 2 (3%) subjects for the off-therapy period. Headache was the most frequently reported on-therapy treatment-related AE in 9 (14%) subjects in the on-therapy period and 1 (2%) subject in the off-therapy period. The incidence of headaches considered related to study medication did not increase during the on-therapy periods across cycles. Diarrhoea was considered drug related in 3 (5%) subjects in Cycle 1 during the on-therapy period, but no AEs of diarrhoea were considered related in Cycle 2 or Cycle 3.

In EXTEND, on-therapy AEs considered by the investigator to be related to study medication were reported in 25% of subjects. Headache and nausea were the most frequently reported AEs considered treatment-related in 5% and 4% of subjects, respectively. Additionally, 9 subjects experienced one or more hepatobiliary events reported as related to study medication. Five subjects had events of hyperbilirubinemia (2%), 5 subjects had events of increases in ALT (2%), 4 subjects had increased AST (2%) and one had alkaline phosphatase increased.

AEs by Maximum Toxicity Grade

Double-blind Studies

In the pooled TRA100773 data, the majority of subjects had on-therapy AEs with maximum toxicity of Grade 1 or 2. One subject died of cardiopulmonary failure in TRA100773A (Subject 144, eltrombopag 50 mg). Two placebo subjects and 1 eltrombopag subject had a Grade 3 or 4 bleeding AE. Each of these subjects had platelet counts <15 Gi/L proximal to the event. No on-therapy SAEs or deaths were reported in the 30 mg and 75 mg treatment groups.

Similar to the 6-week double-blind studies, the majority of subjects in RAISE had AEs with a maximum toxicity of Grade 1 or Grade 2. Consistent with that seen in the short term studies, the incidence of Grade 3 or greater AEs was similar between the treatment groups (PBO, 11%; eltrombopag 15%). Although there was a similar overall incidence, the pattern of on-therapy Grade 3 or higher AEs was different between the 2 groups. In the PBO group, the majority of the on-therapy Grade 3 or higher events were bleeding events (7%, 11 events in 4 subjects). One PBO-treated subject died from a fatal brain stem haemorrhage, and one PBO-treated subject experienced 7 Grade 3 or greater bleeding AEs and 1 AE of orthostatic hypotension. In contrast, three eltrombopag-treated

subjects had three bleeding AEs (2.2%) of Grade 3 or more severity. All three eltrombopag-treated subjects were non-responders who never achieved platelet counts ≥ 50 Gi/L and had platelet counts <35 Gi/L at the time of the bleeding event.

No subjects in the PBO treatment group had a Grade 3 or higher headache on-therapy, whereas 4 subjects in the eltrombopag treatment group had 8 Grade 3 events of headache (1 subject had 5 AEs of headache and 1 AE of hyperglycaemia-two of the events of headache were reported as serious).

No subject in the PBO treatment group had a thromboembolic event whereas 2 subjects in the eltrombopag treatment group had at least 1 thromboembolic event reported on-therapy. Both subjects were withdrawn from treatment due to these AEs.

No subjects in the PBO treatment group had a Grade 3 or greater gastrointestinal AE on-therapy, whereas 2 subjects in the eltrombopag treatment group had Grade 3 events of nausea (1 of which also experienced Grade 3 events of fatigue and diarrhoea).

Open-label Studies

Similar to the double-blind studies, the majority of subjects had AEs with a maximum toxicity Grade of 1 or 2 in REPEAT and in EXTEND.

In REPEAT, the number and severity of AEs that occurred on-therapy compared to off-therapy were similar in each cycle and overall. No Grade 4 AEs were reported during the study. No events were serious, none led to the withdrawal of study medication, and none were treatment-related.

In EXTEND, 11% and 2% of subjects experienced at least one AE with a maximum toxicity Grade of 3 or 4, respectively. Two subjects died while on therapy. Prior to the clinical cut-off date, Subject 122 died as a passenger in a road traffic accident. After the SAE cut-off date, Subject 127 died suddenly of “acute bleed, acute cerebral haemorrhage versus acute myocardial infarction versus acute arrhythmia and cardiac arrest versus sepsis syndrome in a patient with fever on steroids”, according to the investigator.

In EXTEND, 28 subjects experienced fifty-nine Grade 3 or higher on-therapy AEs. Twenty-five of these events were reported as serious. Six subjects were withdrawn from the study due to nine Grade 3 or higher AEs, and eight were considered by the investigator to be related to study medication.

Six subjects (3%) experienced seven Grade 3 or higher events associated with the disease under study (3 bleeding AEs and 4 AEs of thrombocytopenia). None of the bleeding AEs were serious and none led to withdrawal from study medication. Three subjects (1%) experienced seven hepatobiliary AEs of Grade 3 or higher toxicity. Two of these subjects were withdrawn from study medication due to these AEs.

Analyses by Age, Sex and Race

There were no meaningful differences in the incidence of AEs of eltrombopag with regard to age, sex and race.

Deaths

Deaths have been reported for eight subjects across the ITP program as of 01 August 2008: 1 subject in study TRA100773A, 1 subject in RAISE, 1 subject in REPEAT and 5 subjects in EXTEND. There were no deaths reported in study TRA100773B.

One subject died of cardiopulmonary failure in TRA100773A (eltrombopag 50 mg). This subject had a medical history of pneumonectomy for right lung carcinoma with concomitant medications including prednisone due to asthma and emphysema and experienced SAEs of renal insufficiency and hepatitis which were considered by the investigator as related to study medication. The subject suffered a fatal SAE of cardiopulmonary failure which was assessed as not related to study treatment.

In RAISE, one subject in the placebo group suffered a fatal brain stem haemorrhage. The subject was a 43-year old female who had a baseline platelet count of 2 Gi/L and no additional on-therapy platelet counts were recorded for this subject prior to death.

In the REPEAT study, no deaths were reported during the on-therapy period or during the 4-week follow-up period of the study. However, one subject reported a serious adverse event (SAE) of pancreatic carcinoma 6 days following their last dose of eltrombopag, and subsequently died 6 months post-therapy from that cancer. The death occurred following database freeze date and therefore was not captured in the dataset for the study.

There were 5 deaths reported in EXTEND, all reported as unrelated to study medication.

Other Serious Adverse Events

Double Blind Studies

On-therapy SAEs

There was no difference in the incidence of on-therapy SAEs observed between the PBO and eltrombopag 50 mg groups in the pooled data from TRA100773A and TRA100773B. In the PBO group, 5 subjects (7%) reported on-therapy SAEs and 4 eltrombopag subjects (4%) reported on-therapy SAEs. Bleeding complications were the most frequently reported SAEs. Two subjects in the placebo group (3%) and 2 subjects in the eltrombopag 50 mg group (2%) had on-therapy bleeding SAEs. All events occurred in subjects who did not respond to study medication.

In RAISE, 11 subjects (18%) in the PBO group and 15 subjects (11%) in the eltrombopag group experienced on-therapy SAEs. There were four events in four subjects (7%) in the PBO group compared to ten events in seven subjects (5%) in the eltrombopag group reported by the investigator as related to study medication. Although there was a similar overall incidence of SAEs, the pattern of SAEs was different between the two groups. Bleeding SAEs occurred more frequently in the PBO group (7 events in 4 subjects [7%]) compared to the eltrombopag group (1 event in 1 subjects [$<1\%$]). In the PBO group, one subject suffered from a fatal brain stem haemorrhage. One PBO subject experienced four bleeding SAEs, and two subjects experienced one bleeding SAE each. In contrast, one subject treated with eltrombopag had a bleeding SAE of duodenal ulcer haemorrhage. This subject reported a current medical condition of duodenal ulcer at baseline and did not respond to eltrombopag.

Open-label Studies

On-therapy SAEs

One subject (2%) in the REPEAT study had an on-therapy SAE of Grade 2 pneumonia. The event was considered unrelated to eltrombopag and occurred 21 days after the first dose of eltrombopag in Cycle 2 and lasted for 14 days.

In EXTEND, 17 subjects (8%) reported 34 on-therapy SAEs. Of these events, 3 were considered treatment-related. Three subjects (1%) experienced 4 on-therapy SAEs associated with the disease under study (1 bleeding and 3 thrombocytopenia SAEs). Two subjects (1%) experienced 6 hepatobiliary SAEs. Both subjects were withdrawn from study medication due to these AEs. Two subjects (1%) experienced 2 SAEs of cataracts.

Adverse Events of Special Interest

Overall Assessment of Thromboembolic Events

As of the SAE cut-off date for this summary, fourteen of the 422 subjects exposed to eltrombopag had at least one confirmed or suspected thromboembolic event (TEE) for a frequency of 3.3%. These data are in accordance with the literature for the ITP population, 3% (Aledort, 2004¹⁹).

Of the fourteen subjects with a TEE across the program, eight subjects had platelet counts below 100 Gi/L at the time of the event, and of those 8, 4 had platelet counts < 50 Gi/L. Platelet counts proximal to the event ranged between 14 Gi/L and 407 Gi/L. There was no apparent relationship between platelet counts >400 Gi/L and development of thromboembolic events. However, it cannot be ruled out that elevation of platelet counts from baseline, albeit below or within the normal range of platelet counts may be a factor in the development of TEEs.

Cardiac AEs

With the exception of one subject in the eltrombopag 30 mg treatment group of TRA100773A, no subjects in the double-blind or open-label studies experienced AEs related to QTc prolongation. One subject in the eltrombopag 30 mg treatment group experienced a Grade 2 AE of prolonged QTc segment on ECG evaluation. This subject had ECG abnormalities at baseline and a past medical cardiovascular history. No evidence of cardiotoxicity was found as evaluated in AE data from subjects in the 3 double-blind and 2 open-label studies.

Ocular-related Adverse Events

In the 3 placebo-controlled studies, a similar percentage of subjects treated with placebo and eltrombopag had a report of cataract (either incident or progression). In the pooled 6- week studies, 4% of placebo-treated subjects and 5% of eltrombopag-treated subjects with an ocular examination reported either an incident cataract or progression of cataracts. In RAISE, 9% of placebo-treated subjects and 7% of eltrombopag treated subjects had either an incident cataract or progression of cataracts reported. Across these 3 studies, cataracts were reported as SAEs in 4 subjects, 3/128 (2%) of placebo-treated subjects and 1/241 (<1%) of eltrombopag treated subjects. There was no evidence for an increase in the incidence or progression of cataracts in subjects treated with eltrombopag above that which would be expected for a population with chronic corticosteroid use as a risk factor.

The non-treatment observational LENS study was initiated prior to the results from RAISE and in response to a specific request from the Committee for Medicinal Products for Human Use (CHMP) to provide longer-term ocular follow-up of patients enrolled in eltrombopag clinical trials (European Medicines Evaluation Agency (EMA)/110006/2006). To the time of this submission, 54 subjects had been assessed in LENS. The Clinical Events Committee (CEC) review of Long-term Eltrombopag ObservatioNal Study (LENS) data to date suggested that: “Based on the data and the facts that (1) any cataract progression was very limited and (2) the patients were exposed to other possible risk factors for cataract, there does not appear to be [a] recognisable safety concern regarding eltrombopag and cataract formation.”

In the open-label studies, 3% and 4% of subjects had a report of incident or progression of cataract in REPEAT and EXTEND, respectively.

¹⁹ Aledort *et al.*, 2004. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. *American Journal of Hematology*, 76:205 - 213

Malignancies

A similar percentage of malignancies were reported on both treatment arms: 1.2% in eltrombopag- and 1.4% in placebo-treated subjects across the chronic ITP programme.

Clinical Laboratory Evaluations

Haematology

The majority of haematological assessments in all studies were Grade 0, with the exception of platelet counts. The percentage of eltrombopag-treated subjects with a Grade 3 or Grade 4 haematologic toxicity at any time during the double-blind and open-label studies was $\leq 5\%$. There were no significant differences when comparing the eltrombopag-treated subjects with the PBO-treated subjects in the double-blind studies. The frequencies of haematologic abnormalities in the open-label studies were similar to the double-blind studies.

Hepatobiliary Evaluations

There is no clear guidance in Europe regarding clinical evaluation of potential drug induced liver injury (DILI). Therefore the sponsor conducted an analysis using a draft FDA guidance regarding the potential for a drug to cause severe liver injury²⁰. The analysis revealed that elevations of ALT, AST and indirect bilirubin were more common in subjects treated with eltrombopag, compared to placebo.

In the pooled data from TRA100773A and TRA100773B, a total of 5 (8%) of placebo-treated subjects met the DILI screening criteria, compared to 11 (10%) of eltrombopag treated subjects. One subject (eltrombopag 50 mg) had elevated aminotransferases (AT) $>3x$ ULN in conjunction with total bilirubin $>2x$ ULN. This subject died from cardiopulmonary failure, probably following sepsis of pulmonary origin. Except for this subject, all other hepatobiliary laboratory abnormalities (HBLA) in these studies resolved; the majority were not accompanied by clinical symptoms and there were no lasting clinical sequelae. Hepatobiliary SAEs were reported for 1 placebo (1.5%) and 1 eltrombopag-treated subject (1%) in the pooled 6-week study data.

In the RAISE study, more subjects in the eltrombopag group met the DILI screening criteria: four subjects (7%) in the placebo group and seventeen subjects (13%) in the eltrombopag group. No subject in either treatment group had an elevation of aminotransferases (AT) $\geq 3x$ ULN in conjunction with bilirubin elevation $>1.5x$ ULN. In all subjects with hyperbilirubinemia, the elevation was due to indirect bilirubin. Hepatobiliary SAEs were reported for one (2%) placebo and two (2%) eltrombopag-treated subjects in the RAISE study.

In the open-label studies, 3/66 subjects (5%) in REPEAT and 12/207 (6%) subjects in EXTEND met the DILI screening criteria. In REPEAT, no subject had an elevation of AT $\geq 3x$ ULN in conjunction with bilirubin elevation $>1.5x$ ULN. In EXTEND, two subjects had elevations of AT $\geq 3x$ ULN in conjunction with bilirubin elevations $>1.5x$ ULN (Upper Limit of Normal). Both subjects presented with a clinical pattern unusual for DILI, and both had confounding factors and both bilirubin elevations were due to indirect bilirubin. These two subjects (1%) had 6 hepatobiliary SAEs and both were withdrawn from study medication due to these SAEs. The occurrence of HBLA upon re-exposure to eltrombopag provided further evidence that eltrombopag treatment can be associated with HBLA.

Renal Evaluations

In RAISE, REPEAT and EXTEND, enhanced renal monitoring was implemented either after all subjects had been enrolled in the study (RAISE and REPEAT) or near the cut-off date for this report (EXTEND). Given the timing of the implementation of enhanced renal monitoring, the results

²⁰ Guidance for Industry Drug-induced liver injury: Premarketing Clinical Evaluation. Draft October 2007.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072278.pdf>

obtained are limited and inconclusive. However, none of the renal analyses conducted were reported outside the reference range, and no significant trend of clinical concern was demonstrated in the RAISE study. In REPEAT, the results from the majority of the tests were within normal ranges and showed no significant trend of clinical concern. In EXTEND, only limited data were available.

Bone Marrow Abnormalities

There was no apparent evidence of clinically relevant bone marrow alterations or clinical findings in subjects treated with eltrombopag, based on the blood smear; however only limited bone marrow data are available to date.

Vital signs and Physical Findings

No clinically significant abnormalities were reported in the clinical studies.

Overdose, Withdrawal and Rebound

There was one report of eltrombopag overdose in a clinical study (SB497115/003) that was not conducted in ITP subjects. This case was a suspected attempt at suicide. With the exception of a short episode of bradycardia (38 beats per minute, bpm), which was treated with atropine and calcium during the initial treatment for overdose, and mild asthenia, the patient remained asymptomatic.

There is presently no evidence of any potential for abuse or dependency. Transient decreases in platelet counts following discontinuation or interruption of eltrombopag occurred in a minority of patients on both treatment arms, however generally they were not associated with clinically meaningful bleeding events. The incidence of post-therapy bleeding AEs within the 4 weeks following discontinuation of therapy was similar or less in the eltrombopag group compared to the placebo group in all three double-blind studies.

Summary of Safety

In the dose-ranging Phase II study TRA100773A, no dose-dependent pattern of AEs was observed across the eltrombopag 30 mg, 50 mg, and 75 mg treatment groups. In the 6-week studies the most common AEs ($\geq 5\%$) in the eltrombopag 50 mg treatment group were headache, nasopharyngitis, nausea, fatigue and arthralgia. Nausea was reported more frequently in the eltrombopag group and headache and arthralgia were reported more frequently in the placebo group.

In the six month study RAISE, the most common AEs observed in $\geq 10\%$ of subjects in the eltrombopag group were headache, diarrhoea, nausea, nasopharyngitis, fatigue and upper respiratory tract infection. The rates for these AEs were similar in the placebo group. Nausea and vomiting occurred more frequently ($\geq 5\%$) in eltrombopag-treated subjects. The incidence of on-therapy SAEs (18% and 11%) and AEs leading to withdrawal (7% and 9%) was similar in both treatment arms.

Deaths have been reported for eight subjects across the ITP programme: four occurred on-therapy, and four occurred between 42 days and 6 months after discontinuation of treatment with eltrombopag. All eight deaths were reported as unrelated to study medication.

Hepatobiliary laboratory abnormalities occurred more frequently in ITP patients in the eltrombopag group compared to the placebo group. More hepatobiliary AEs were observed in the eltrombopag group compared to the placebo group in the double-blind studies [6% vs. 4% in the 6 weeks studies, and 12% vs. 8% in RAISE]. Thromboembolic events were observed in 3.3% of eltrombopag-treated subjects during the observation period of 228 patient-years. No thromboembolic events were seen in placebo-treated subjects during the observation period of 26 patient-years.

There was no clinical confirmation of non-clinical signals such as QTc prolongation, phototoxicity, or renal toxicity.

Comment: Overall eltrombopag had a well-defined safety profile with consistent findings across all ITP studies irrespective of treatment duration. The safety database supports a positive benefit/risk profile for the treatment of previously-treated subjects with chronic ITP.

Clinical Summary and Conclusions

In this submission the sponsor is seeking to register eltrombopag olamine (Revolade) 25 mg and 50 mg film-coated tablets for the treatment of chronic idiopathic thrombocytopenic purpura. The application included efficacy and safety data of eltrombopag for the treatment of chronic ITP, based principally on the results of 3 double-blind, placebo-controlled clinical studies (TRA102537/RAISE, TRA100773A and TRA100773B) and 2 open-label studies (TRA108057/REPEAT and TRA105325/EXTEND).

The studies submitted for evaluation were appropriately designed and conducted to evaluate efficacy of eltrombopag. Efficacy data from the clinical studies showed the following:

- Eltrombopag was consistently superior to placebo in raising and maintaining platelet levels above 50 Gi/L for up to 6 months in previously treated subjects with chronic ITP.
- Eltrombopag raised platelet counts quickly and predictably. The onset of response in all 3 studies was rapid with >30% of subjects responding with an increase of platelet counts ≥ 50 Gi/L by Day 8, and ~50% of subjects responding by Day 15. Platelet levels remained elevated for approximately 1 week after stopping eltrombopag.
- The effectiveness of eltrombopag compared to placebo was observed throughout treatment regardless of baseline platelet counts, use of concomitant ITP medication or splenectomy status.
- The dose of eltrombopag can be individualised to maintain platelet counts in the 50- 400 Gi/L range during long term treatment.
- The platelet count elevation in eltrombopag-treated subjects was accompanied by a significant reduction in bleeding symptoms (WHO Bleeding Scale) compared to placebo-treated subjects throughout the treatment period.
- Subjects treated with eltrombopag were able to master haemostatic challenges without additional treatments to elevate their platelet counts.
- Eltrombopag-treated subjects were able to reduce the use of concomitant ITP medications and required less rescue medication than placebo subjects.
- The effect of eltrombopag has been maintained for up to 15 months and there is no evidence of tolerance upon repeat or long-term administration.

Overall the evaluator considered that the data presented for evaluation adequately support that eltrombopag is effective for treatment of patients with chronic ITP. It has been shown to increase platelet counts and reduce the risk of bleeding in patients who have not responded to corticosteroids, immunoglobulins, or splenectomy.

It was considered that minor amendment should be made to the indication as proposed by the sponsor, in order to accurately reflect the clinical trial population studied and the efficacy results. An indication similar to the following could be considered:

“Revolade is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Revolade has been shown to increase platelet counts and reduce the risk of bleeding. Revolade should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding”.

In the dose-ranging Phase II study TRA100773A, no dose-dependent pattern of AEs was observed across the eltrombopag 30 mg, 50 mg, and 75 mg treatment groups. In the 6-week studies the most common AEs ($\geq 5\%$) in the eltrombopag 50 mg treatment group were headache, nasopharyngitis,

nausea, fatigue and arthralgia. Nausea was reported more frequently in the eltrombopag group and headache and arthralgia were reported more frequently in the placebo group.

In the six month study RAISE, the most common AEs observed in $\geq 10\%$ of subjects in the eltrombopag group were headache, diarrhoea, nausea, nasopharyngitis, fatigue and upper respiratory tract infection. The rates for these AEs were similar in the placebo group. Nausea and vomiting occurred more frequently ($\geq 5\%$) in eltrombopag-treated subjects. The incidence of on-therapy SAEs (18% and 11%) and AEs leading to withdrawal (7% and 9%) was similar in both treatment arms.

Hepatobiliary laboratory abnormalities occurred more frequently in ITP patients in the eltrombopag group compared to the placebo group. More hepatobiliary AEs were observed in the eltrombopag group compared to the placebo group in the double-blind studies [6% versus 4% in the 6 weeks studies, and 12% versus 8% in RAISE]. Thromboembolic events were observed in 3.3% of eltrombopag-treated subjects during the observation period of 228 patient-years. No thromboembolic events were seen in placebo-treated subjects during the observation period of 26 patient-years.

Overall eltrombopag had a well-defined safety profile with consistent findings across all ITP studies irrespective of treatment duration. The safety database supports a positive benefit: risk profile for the treatment of previously-treated subjects with chronic ITP.

Recommendation: It was recommended that the application for registration of eltrombopag olamine (Revolade) 25 mg and 50 mg film-coated tablets for the treatment of chronic idiopathic thrombocytopenic purpura *should be approved*.

The data submitted for evaluation would support an indication similar to the following:

“Revolade is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Revolade has been shown to increase platelet counts and reduce the risk of bleeding. Revolade should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding”.

V. Pharmacovigilance Findings

Risk Management Plan

The TGA has not undertaken a formal evaluation of the sponsor’s proposed risk management plan (RMP) as, at the time this application was lodged, sponsors were not required to submit these documents. The safety concerns identified in the EU RMP included

- Hepatotoxicity,
- Thromboembolic events,
- Post Therapy Reoccurrence of thrombocytopenia,
- Potential for Increase in Bone Marrow Reticulin Formation,
- Haematological Malignancies,
- Cataracts,
- Renal Tubular Toxicity,
- Phototoxicity,
- Potential for Haematological Changes,

- Potential for Endosteal Hyperostosis,
- Paediatric Population and
- Pregnant or lactating females.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no quality objections to registration.

Nonclinical

The Nonclinical evaluator considers that the nonclinical data have not demonstrated an acceptable safety profile. A major issue was that the drug has been tested in animals species (rodents, dogs) in which eltrombopag is not pharmacologically active. Hence any potential toxicities in humans due to the interaction between the drug and the TPO receptor would not be identified in the nonclinical studies.

- The toxicity studies also demonstrated several "off-target" toxicities including:
- Evidence of cardiotoxicity from *in vitro* studies;
- Hepatotoxicity in all species;
- Cataracts in rodents;
- Renal toxicity in mice.

These toxicities are discussed further below.

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacodynamics

The effect of eltrombopag on platelet counts was studied in healthy volunteers. Platelet count increased in a dose-dependant manner after repeated doses. After 10 days of dosing, peak values were reached on Day 16 and counts returned to normal by Day 22.

Platelet function tests (levels of activated GPIIb/IIIa, P-selectin, GPIb and formation of leukocyte aggregates) suggested no increased or decreased platelet activation in eltrombopag-treated ITP subjects compared to untreated ITP subjects or normal volunteers. Platelets of eltrombopag-treated subjects responded normally to stimulation with ADP.

Eltrombopag at doses up to 150 mg for five days was found to have no effect on QT interval.

Pharmacokinetics

Absolute bioavailability has not been determined due to inability to develop an intravenous (IV) formulation. Following oral administration T_{max} occurs at approximately 3 hours. Co-administration with a cation-containing antacid resulted in a 70% reduction in AUC. However, administration with non-dairy food with a low calcium content did not result in substantial changes in bioavailability.

As IV administration has not been studied, volume of distribution and clearance have not been determined. Following oral administration of a radiolabelled dose, eltrombopag accounted for most (64%) of the radioactivity circulating in plasma. Protein binding is > 99%.

Following oral administration of a radiolabelled dose, approximately 31% of the radioactivity is excreted in the urine, with none as unchanged drug, indicating that the drug is cleared through

metabolic mechanisms. *In vitro* data indicated that the drug is metabolised by CYP1A2 and 2C8 and through conjugation with glucuronic acid. Half-life is 21 – 32 hours. After oral dosing, excretion is predominantly through the faeces.

Eltrombopag AUC was increased by up to 93% in subjects with hepatic impairment. Renal impairment did not result in increased eltrombopag levels.

A population PK analysis indicated that subjects of East Asian ethnicity had an 87% increase in eltrombopag AUC.

Eltrombopag is an inhibitor of the transporter proteins OATP-1B1 and BCRP. Rosuvastatin is a substrate for these transporters, and co-administration of the two drugs resulted in a 55% increase in rosuvastatin AUC. *In vitro* data and one clinical interaction study indicated that eltrombopag did not induce or inhibit CYP450 enzymes.

Efficacy

Evidence for efficacy comes from three randomised, double-blind placebo controlled trials. Two studies (-773A and -773B) were of six weeks duration, and the third (RAISE) lasted for 6 months. The two 6-week studies have been published (in *NEJM*²¹ 2007 and *Lancet* 2009²²). The RAISE study appears not to have been published other than in abstract form. All three studies enrolled subjects with chronic ITP (> 6 months), age ≥18 years, with platelet counts at baseline of < 30 x 10⁹/L, and who had received at least one prior therapy.

Study -773A was a dose ranging study in which subjects were randomised to receive eltrombopag 30, 50 or 75 mg daily or placebo. The primary endpoint for the 6-week studies was the percentage of subjects who were responders (that is, in whom platelet count increased from <30 to >50). The 50 mg dose was superior to placebo whereas the 30 mg dose was not. The 75 mg dose appeared no more effective.

Study -773B compared the 50 mg dose with placebo. Eltrombopag significantly increased the proportion of patients who responded (62% versus 14%; Odds ratio: 12.40; 95%CI: 5.2 – 29.7; p<0.001). Multiple secondary endpoints, based on improvements in platelet count, also indicated superiority of eltrombopag over placebo. Analysis of bleeding events in the two studies suggested a lower incidence in the eltrombopag 50 mg groups compared to placebo.

In the RAISE study, subjects were randomised (2:1) to receive eltrombopag 50 mg or placebo. The primary endpoint was the percentage of subjects who achieved a response (that is, in whom platelet count increased to between 50 and 400). Numerical results are summarised in Table 38 below.

²¹ Bussel, JB *et al.* (2007). Eltrombopag, an Oral Platelet Growth Factor, for the Treatment of Patients with Chronic Idiopathic Thrombocytopenic Purpura. *N Engl J Med* 357(22): 2237-224.

²² Bussel JB *et al.* (2009). Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *Lancet* 373:641-8.

Table 38: Summary of responders-Primary Dataset (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)

Data Source: [Table 7.1](#)

Evaluable = Subject attended the visit and had a non-missing result. If a subject did not have an assessment at the nominal visit (defined as Weeks 1 to 6 inclusive, Week 10 and every 4 weeks thereafter) due to receiving a dose adjustment, platelet count data from the immediately preceding visit (non-nominal) was used.

a. Subject 137 (placebo) had a missing baseling platelet count.

b. At baseline (Day 1), Subject 584 (placebo) had a platelet count of 87 Gi/L, and Subject 1115 (eltrombopag) had a platelet count of 78 Gi/L.

The Odds Ratio for responders was 8.2 (95%CI 3.59 – 18.73; $p < 0.001$). A variety of secondary endpoints based on platelet count also supported the superiority of eltrombopag over placebo. Analysis of bleeding events also indicated superiority. Eltrombopag patients required fewer rescue treatments (18% versus 40%) and were more likely to discontinue ITP medications (59% versus 32%).

The submission also included an open label, single arm extension study (**EXTEND**) in which patients could continue to receive eltrombopag indefinitely. The results for median platelet count over an additional 30 weeks of treatment suggest that efficacy is maintained during long term treatment.

The submission also included another open single-arm study (**REPEAT**) which used cyclical dosing (Weeks 1 to 6) of a 10 week cycle. This dosage regimen is not being proposed for registration.

Safety

A total of 422 ITP subjects were treated with eltrombopag in Phase II and III studies. Of these, 192 received treatment for at least 6 months and only 41 for at least 12 months.

In the placebo-controlled studies there was an increase in the overall incidence of adverse events and treatment-related adverse events, but no increase in overall incidence of deaths, serious adverse events or withdrawals due to adverse events. Specific common adverse events that were observed more frequently in the eltrombopag arms of the studies included the following:

- GIT effects - nausea, vomiting, diarrhoea;
- Arthralgia and myalgia;
- Headache;
- Fatigue

Liver function test abnormalities. These adverse effects were mainly Grade 1 or 2 in severity.

Thromboembolic adverse events: A total of fourteen eltrombopag subjects developed thromboembolic adverse events. The events were not associated with abnormally elevated platelet counts. Of concern is the finding that, in the placebo-controlled trials, there were four eltrombopag-treated patients who developed such events, compared to no placebo-treated patients. The exclusion criteria for these studies excluded many subjects who would be at an increased risk of such adverse events, so the observed incidence may be below that which will occur in the post-market setting.

Hepatotoxicity: One of the safety concerns raised by the nonclinical evaluator was that of liver toxicity. In the clinical studies, eltrombopag treatment was associated with an increased incidence of abnormal Liver function tests (LFTs) compared to placebo. These are summarised in tabular format in Tables 39-41 below.

Liver Function Test abnormalities – placebo-controlled studies

Table 39: Summary of Subjects meeting the DILI Screening criteria for HBLA-pooled data from TRA100773A and TRA100773B.

Laboratory Criteria	773A + 773B ^a	
	PBO N=67	Eltrombopag, 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)

Table 40: 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)

Liver Function Test abnormalities – open-label studies

Table 41: Summary of Subjects meeting the DILI Screening criteria for HBLA-Open-label studies.

Laboratory Criteria	REPEAT Eltrombopag N=66	EXTEND Eltrombopag N=207
Subjects, n (%)	3 (5)	12 (6)
>3x ULN AT and >2.0x ULN Total Bilirubin	0	2 (<1)
>3x ULN AT and >1.5x ULN Total Bilirubin	0	2 (<1)
≥20x ULN ALT and AST	0	0
≥10x ULN ALT and AST	0	1 (<1)
≥5x ULN ALT and AST	0	1 (<1)
≥3x ULN ALT and AST	0	3 (1)
≥20x ULN ALT	0	0
≥10x ULN ALT	0	1 (<1)
≥5x ULN ALT	0	2 (<1)
≥3x ULN ALT	1 (2)	4 (2)
≥20x ULN AST	0	0
≥10x ULN AST	0	1 (<1)
≥5x ULN AST	0	2 (<1)
≥3x ULN AST	0	3 (1)
>2x ULN Total Bilirubin	0	5 (2)
>1.5x ULN Total Bilirubin	1 (2)	7 (3)
>1.5x ULN Alkaline Phosphatase	2 (3)	3 (1)

Data Source: SDAP 8.200; TRA108057 CSR Section 8.11, TRA105325 CSR Section 8.10

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

Note: Subjects are counted in more than one category if they fulfill multiple criteria.

The FDA has published a guideline²³ on assessing the potential for drugs to cause serious drug-induced liver injury (DILI) – that is, irreversible liver failure that is fatal or requires liver transplantation. The guideline describes “Hy’s Law”. A patient who:

- develops hepatocellular damage as evidenced by a 3-fold increase above upper limit of normal (ULN) in ALT; and

²³<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

- has impairment of liver *function* as evidenced by a 2-fold increase above ULN in total bilirubin; and
 - has no evidence of cholestasis as evidenced by an increase above ULN in serum ALP; and
 - has no other reason to explain these findings;
- is referred to as a “Hy’s Law case”. The expected incidence of severe DILI is approximately 1/10 of the incidence of Hy’s law cases.

The FDA guideline states that “...*the finding of two Hy’s law cases, and probably even one, is a strong predictor of a significant risk of severe liver injury.*” In the submitted studies, there were 3 patients who developed a 3-fold increase in ALT or AST together with a 2-fold increase in bilirubin (one in 773A/B and two in EXTEND). For all three patients there were other causes documented for the elevated LFTs and/or the pattern of LFT abnormalities was not consistent with drug-induced injury. Therefore, on the basis of the FDA guideline, the available data do not indicate that the drug is likely to be associated with serious DILI.

Cataracts: The formation of cataracts was observed in rodents in nonclinical studies, at exposure levels similar to those achieved in patients. However, in the placebo-controlled clinical studies there was no apparent increase in the incidence of cataracts with up to 6 months treatment. This safety issue could be adequately addressed through precautionary statements in the PI.

Renal toxicity: The nonclinical evaluator has also raised concerns regarding renal toxicity, which was observed in mice at exposure levels similar to those achieved in patients. In the placebo controlled studies there was no increased incidence of raised creatinine levels compared to placebo. There were no cases of Grade 3 or 4 creatinine elevations in these studies.

Cardiac toxicity: The nonclinical evaluator raised concerns regarding potential cardiotoxicity based on *in vitro* studies. However, a clinical study in healthy volunteers demonstrated no effects on QT interval or ECG parameters, and there was no excess of ECG abnormalities among eltrombopag-treated subjects in the placebo controlled trials.

Risk-Benefit Analysis

1 Overall risk-benefit

The submitted data have adequately demonstrated efficacy with three placebo-controlled studies showing clinically significant elevations in platelet count. The limited data available suggest that efficacy is maintained in the long term.

There are some safety concerns with the drug, in particular:

- An apparent increase in the incidence of thromboembolic adverse events compared to placebo. The mechanism of such a finding is unclear, as the events were not associated with elevated platelet counts and pharmacodynamic data suggest that platelets produced by eltrombopag function normally.
- The drug is associated with some hepatotoxicity. Although the available data do not suggest that the drug will result in serious DILI, long term safety data are very limited. Given that another agent in this class (romiplostim) is registered in Australia, the Delegate considered it would be unnecessary to expose patients to these potential risks, and it would be prudent to await resolution of these concerns through the generation of further safety data, before registering the product.

2. Indication

If the Committee considers that registration is appropriate, the indication will require amendment. The wording proposed by the sponsor is as follows:

“... for the treatment of previously treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce bleeding.”

- The drug has not been studied in children, and efficacy in paediatric ITP cannot be extrapolated from adults;
- Most patients included in the pivotal efficacy studies had received at least 2 prior therapies. In view of the limited safety data available for eltrombopag, it would be prudent to restrict its use to patients who have failed both corticosteroids and IVIg.
- Claims regarding effects on platelet counts and bleeding should be moved to the clinical trials section of the PI to ensure a concise indication.

An appropriate indication would therefore read:

*“...for the treatment of adult patients with chronic idiopathic thrombocytopenic purpura (ITP) who have had an inadequate response or are intolerant to corticosteroids **and** immunoglobulins.”*

The Delegate proposed to reject the application on safety grounds, specifically:

- A risk of thromboembolic adverse events;
- Limited long-term safety data, particularly in relation to hepatotoxicity.

ACPM, having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, recommended approval of the submission from GlaxoSmithKline Australia Pty Ltd to register the new chemical entity eltrombopag olamine (REVOLADE) tablets 25 mg and 50 mg for the indication:

Treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an inadequate response or are intolerant to corticosteroids and immunoglobulins.

In making this recommendation the ACPM considered the risk of thromboembolic events (TEES) and noted that the evidence indicates that the thromboembolism risk appears similar to that observed with romiplostim. The ACPM had concerns regarding the risk of bone marrow fibrosis and requested that the Delegate review the available evidence to ensure this risk had been adequately assessed. However, the ACPM was satisfied that a positive overall risk benefit ratio had been established and that safety concerns regarding TEEs and liver abnormalities were adequately addressed by the proposed risk management plan.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Revolade (25-50 mg tablets as eltrombopag free acid), at 50-75 mg/day, indicated for:

“Treatment of adult patients with chronic immune (idiopathic) thrombocytopaenic purpura (ITP) who have had an inadequate response, or are intolerant, to corticosteroids and immunoglobulins.”

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

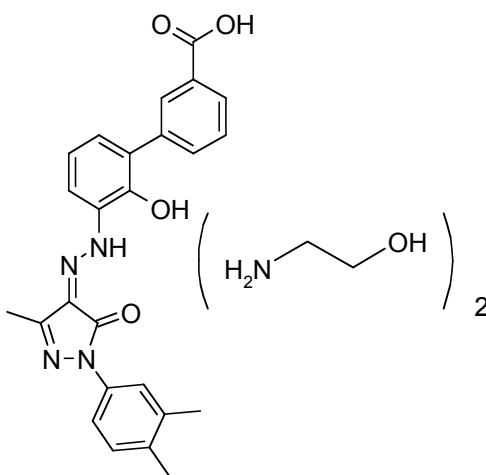
REVOLADE[®] TABLETS

NAME OF THE MEDICINE

REVOLADE[®] (Eltrombopag olamine)

REVOLADE film-coated tablets contain eltrombopag olamine. Eltrombopag olamine is an oral small molecule, thrombopoietin receptor (TPO-R) agonist. The chemical name for eltrombopag olamine is 3'-{(2Z)-2-[1-(3,4-dimethyl-phenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid-2-aminoethanol (1:2).

The structural formula is:



Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

Molecular formula: C₂₅ H₂₂ N₄ O₄ · 2 (C₂ H₇ N O)

Molecular weight: 564.65.

CAS number: 496775-62-3

DESCRIPTION

Each film-coated tablet contains eltrombopag olamine equivalent to either 25 mg or 50 mg of eltrombopag as eltrombopag free acid.

Each film-coated tablet also contains magnesium stearate, mannitol, cellulose - microcrystalline, povidone, sodium starch glycolate, hypromellose, macrogol 400, titanium dioxide, polysorbate 80 (25 mg tablet only), iron oxide red CI77491 (50 mg tablet only) and iron oxide yellow CI77492 (50 mg tablet only).

PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamic Effects

Eltrombopag differs from TPO with respect to the effects on platelet aggregation. Unlike TPO, eltrombopag treatment of normal human platelets does not enhance adenosine diphosphate (ADP)-induced aggregation or induce P-selectin expression. Eltrombopag does not antagonise platelet aggregation induced by ADP or collagen.

Pharmacokinetics

The pharmacokinetic parameters of eltrombopag after administration of eltrombopag to patients with ITP are shown in Table 1.

Table 1 Geometric Mean (95 % CI) Steady-State Plasma Eltrombopag Pharmacokinetic Parameters in Adults with Idiopathic Thrombocytopenic Purpura

Regimen of eltrombopag	C _{max} (µg/ml)	AUC _(0-τ) (µg.hr/ml)
50 mg once daily (n=34)	8.01 (6.73, 9.53)	108 (88, 134)
75 mg once daily (n=26)	12.7 (11.0, 14.5)	168 (143, 198)

Absorption and Bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see *Dosage and Administration, Interactions*). The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites

eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52 %.

Distribution

Eltrombopag is highly bound to human plasma proteins (> 99.9 %). Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Metabolism

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64 % of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites, each accounting for < 10 % of the plasma radioactivity, arising from glucuronidation and oxidation were also detected. Based on a human study with radiolabel eltrombopag, it is estimated that approximately 20 % of a dose is metabolised by oxidation. *In vitro* studies identified CYP1A2 and CYP2C8 as the isoenzymes responsible for oxidative metabolism, uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 as the isozymes responsible for glucuronidation, and that bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathways.

Elimination

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59 %) with 31 % of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20 % of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours in healthy subjects and 26-35 hours in ITP patients.

Special Patient Populations

Renal Impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult patients with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-\infty}$ of eltrombopag was decreased by 32 % (90 % CI: 63 % decrease, 26 % increase) in patients with mild renal impairment, 36 % (90 % CI: 66 % decrease, 19 % increase) in patients with moderate renal impairment, and 60 % (90 % CI: 18 % decrease, 80 % decrease) in patients with severe renal impairment compared with healthy volunteers. There was a trend for reduced plasma eltrombopag exposure in patients with renal impairment, but there was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Patients with impaired renal function should use eltrombopag with caution and close monitoring.

Hepatic Impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult patients with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was increased by 41 % (90 % CI: 13 % decrease, 128 % increase) in patients with mild hepatic impairment, 93 % (90 % CI: 19 %, 213 %) in patients with moderate hepatic impairment, and 80 % (90 % CI: 11 %, 192 %) in patients with severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Patients with hepatic impairment should use eltrombopag with caution and close monitoring (see *Precautions*). For patients with moderate and severe hepatic impairment, initiate eltrombopag at a reduced dose of 25 mg once daily (see *Dosage and Administration*).

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). 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 (see *Dosage and Administration*).

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.

CLINICAL TRIALS

The safety and efficacy of REVOLADE has been demonstrated in two, randomised, double-blind, placebo-controlled studies (**TRA102537 RAISE** and **TRA100773B**) and one open label study (**EXTEND TRA105325**) in adult patients with previously treated chronic ITP.

Double-Blind Placebo-Controlled Studies

TRA102537: In RAISE, the primary efficacy endpoint was the odds of achieving a platelet count $\geq 50,000/\mu\text{l}$ and $\leq 400,000/\mu\text{l}$, during the 6 month treatment period, for subjects receiving REVOLADE relative to placebo. One hundred and ninety seven subjects were randomized 2:1, REVOLADE (n=135) to placebo (n=62), and were

stratified based upon splenectomy status, use of ITP medication at baseline and baseline platelet count. Subjects received study medication for up to 6 months, during which time the dose of REVOLADE could be adjusted based on individual platelet counts. In addition, subjects could have tapered off concomitant ITP medications and received rescue treatments as dictated by local standard of care.

The odds of achieving a platelet count between 50,000/ μ l and 400,000/ μ l during the 6 month treatment period were 8 times higher for REVOLADE treated subjects than for placebo-treated subjects (Odds Ratio: 8.2 [99 % CI: 3.59, 18.73] $p = < 0.001$). Median platelet counts were maintained above 50,000/ μ l at all on-therapy visits starting at Day 15 in the REVOLADE group; in contrast, median platelet counts in the placebo group remained below 30,000/ μ l throughout the study.

At baseline, 77 % of subjects in the placebo group and 73 % of subjects in the REVOLADE group reported any bleeding (WHO Grades 1-4); clinically significant bleeding (WHO Grades 2-4) at baseline was reported in 28 % and 22 % of subjects in the placebo and REVOLADE groups, respectively. The proportion of subjects with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% throughout the 6 month treatment period in REVOLADE-treated subjects. When compared to the placebo group, the odds of any bleeding (Grades 1-4) and the odds of clinically significant bleeding (Grades 2-4) were 76 % and 65 % lower in the REVOLADE-treated subjects compared to the placebo-treated subjects ($p < 0.001$).

REVOLADE therapy allowed significantly more subjects to reduce or discontinue baseline ITP therapies compared to placebo (59 % vs. 32 %; $p < 0.016$).

Significantly fewer REVOLADE-treated subjects required rescue treatment compared to placebo-treated subjects [18 % vs. 40 %; $p = 0.001$].

Four placebo and 14 REVOLADE subjects had at least 1 haemostatic challenge (defined as an invasive diagnostic or surgical procedure) during the study. Fewer REVOLADE-treated subjects (29 %) required rescue treatment to manage their haemostatic challenge, compared to placebo-treated subjects (50 %).

In terms of improvements in health related quality of life, statistically significant improvements from baseline were observed in the REVOLADE group in fatigue, including severity and impact on thrombocytopenia-impacted daily activities and concerns [as measured by the vitality subscale of the SF36, the motivation and energy inventory, and the 6-item extract from the thrombocytopenia subscale of the FACIT-Th]. Comparing the REVOLADE group to the placebo group, statistically significant improvements were observed with thrombocytopenia impacted activities and concerns specifically regarding motivation, energy and fatigue, as well as physical and emotional

role and overall mental health. The odds of meaningful improvement in health related quality of life while on therapy was significantly greater among patients treated with REVOLADE than placebo.

TRA100773B: In TRA100773B, the primary efficacy endpoint was the proportion of responders, defined as patients who had an increase in platelet counts to $\geq 50,000/\mu\text{l}$ at Day 43 from a baseline $< 30,000/\mu\text{l}$; patients who withdrew prematurely due to a platelet count $> 200,000/\mu\text{l}$ were considered responders, those discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 subjects with previously treated chronic ITP were randomised 2:1 into the study, with 76 randomised to REVOLADE and 38 randomized to placebo.

Fifty-nine percent of subjects on REVOLADE responded, compared to 16 % of subjects on placebo. The odds of responding were 9 times higher for REVOLADE treated subjects compared to placebo (Odds Ratio: 9.6 [95 % CI: 3.31, 27.86] $p < 0.001$). At baseline, 61 % of subjects in the REVOLADE group and 66 % of subjects in the placebo group reported any bleeding (Grade 1-4). At Day 43, 39 % of subjects in the REVOLADE treatment group had bleeding compared with 60 % in the placebo group. Analysis over the treatment period using a repeated measures model for binary data confirmed that a lower proportion of REVOLADE subjects had bleeding (Grade 1-4) at any point in time over the course of their treatment (Day 8 up to Day 43) compared to subjects in the placebo group (OR=0.49, 95 % CI=[0.26,0.89], $p = 0.021$). Two placebo and one REVOLADE subject had at least one haemostatic challenge during the study.

In both RAISE and TRA100773B the response to REVOLADE relative to placebo was similar irrespective of ITP medication use, splenectomy status and baseline platelet count ($\leq 15,000/\mu\text{l}$, $> 15,000/\mu\text{l}$) at randomization.

Open Label Studies

TRA105325: EXTEND is an open label extension study which has evaluated the safety and efficacy of REVOLADE in subjects with chronic ITP who were previously enrolled in a REVOLADE trial. In this study, subjects were permitted to modify their dose of study medication as well as decrease or eliminate concomitant ITP medications.

REVOLADE was administered to 207 patients; 104 completed 3 months of treatment, 74 completed 6 months and 27 patients completed 1 year of therapy. The median baseline platelet count was $18,000/\mu\text{l}$ prior to REVOLADE administration. REVOLADE increased median platelet counts to $\geq 50,000/\mu\text{l}$ at the majority of the post-baseline visits on the study. The median count post-baseline increased to $\geq 50,000/\mu\text{l}$ beginning at the second week on study and remained elevated until the end of the observation period presented (i.e., 55 weeks), with the exception of weeks 29, 33 and 45 where the median platelet count was 44,000 43,000 and 42,000/ μl , respectively. Just over half of the subjects

(51%) experienced ≥ 4 weeks of continuous elevation of platelets $\geq 50,000/\mu\text{l}$ and 2 x baseline while receiving REVOLADE.

At baseline, 59 % of subjects had any bleeding (WHO Bleeding Grades 1–4) and 18 % had clinically significant bleeding. By weeks 24, 36 and 48, 26%, 8% and 33% of subjects, respectively, had any bleeding and 9%, 4% and 25% of subjects, respectively, had clinically significant bleeding. The apparent increase in proportion of subjects with clinically significant bleeding at week 48 in comparison to baseline may be due to few subjects having assessments by week 48.

Seventy percent of subjects who reduced a baseline medication permanently discontinued or had a sustained reduction of their baseline ITP medication and did not require any subsequent rescue treatment. Sixty-five percent of these subjects maintained this discontinuation or reduction for at least 24 weeks. Sixty-one percent of subjects completely discontinued at least one baseline ITP medication, and 55 % of subjects permanently discontinued all baseline ITP medications, without subsequent rescue treatment.

Twenty-four subjects experienced at least one haemostatic challenge during the study. No subject experienced unexpected bleeding complications related to the procedure while on study.

INDICATIONS

REVOLADE is indicated for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an inadequate response or are intolerant to corticosteroids and immunoglobulins.

CONTRAINDICATIONS

REVOLADE is contraindicated in patients with hypersensitivity to the active substance eltrombopag olamine or to any of the excipients (*see DESCRIPTION*).

PRECAUTIONS

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

Hepatic monitoring: REVOLADE administration can cause hepatobiliary laboratory abnormalities. In clinical trials with REVOLADE, increases in serum alanine

aminotransferase (ALT), aspartate aminotransferase (AST) and indirect bilirubin were observed (see *Adverse Events*).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate impaired liver function. In two placebo controlled studies, adverse events of ALT increase were reported in 5.7 % and 4.0 % of eltrombopag and placebo treated patients respectively.

Measure serum ALT, AST and bilirubin prior to initiation of REVOLADE, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests until the abnormality(ies) resolve, stabilize, or return to baseline levels. Discontinue REVOLADE if ALT levels increase $\geq 5X$ the upper limit of normal [ULN] or to $\geq 3X$ ULN and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

If the potential benefit for reinitiating REVOLADE treatment is considered to outweigh the risk for hepatotoxicity, then cautiously reintroduce REVOLADE and measure serum liver tests weekly during the dose adjusted phase. If liver test abnormalities persist, worsen or recur, then permanently discontinue REVOLADE.

Thrombotic/Thromboembolic Complications: Thromboembolic events may occur in patients with ITP. Platelet counts above the normal range present a theoretical risk for thrombotic/thromboembolic complications. In clinical trials with REVOLADE thromboembolic events were observed at low and normal platelet counts. In ITP studies, 21 thromboembolic/thrombotic events were observed in 17 out of 446 subjects (3.8%). The TEE events included: embolism including pulmonary embolism, deep vein thrombosis, transient ischaemic attack, myocardial infarction, ischaemic stroke, and suspected PRIND (prolonged reversible ischemic neurologic deficiency). Patients who had a prior history of thrombosis AND at least 2 additional proven risk factors for TEE were excluded from the pivotal studies and therefore the safety of the drug in such patients has not been established. Use caution when administering REVOLADE to patients with known risk factors for thromboembolism (e.g., advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity, smoking, Factor V Leiden, ATIII deficiency, and antiphospholipid syndrome). Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing REVOLADE treatment if the platelet count exceeds the target levels (see *Dosage and Administration*).

In a controlled study in thrombocytopenic patients with chronic liver disease (n = 288) undergoing elective invasive procedures, the risk of thrombotic events was increased in patients treated with 75 mg REVOLADE once daily for 14 days. Six thrombotic complications were reported within the group that received REVOLADE and one within the placebo group. All of the thrombotic complications reported within the REVOLADE group were of the portal venous system.

Bleeding Following Discontinuation of REVOLADE: Following discontinuation of REVOLADE, platelet counts return to baseline levels within 2 weeks in the majority of patients (see *Clinical Trials*), which increases the bleeding risk and in some cases may lead to bleeding. Platelet counts must be monitored weekly for 4 weeks following discontinuation of REVOLADE.

Bone Marrow Reticulin Formation and Risk of Bone Marrow Fibrosis: Thrombopoietin (TPO) receptor agonists, including REVOLADE, may increase the risk for development or progression of reticulin fibers within the bone marrow. Clinical studies have not excluded a risk of bone marrow fibrosis with cytopaenias.

Prior to initiation of REVOLADE, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of REVOLADE, perform complete blood count (CBC) with white blood cell count (WBC) differential monthly. If immature or dysplastic cells are observed, examine peripheral blood smears for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with REVOLADE and consider a bone marrow biopsy, including staining for fibrosis. Cytogenetic analysis of the bone marrow sample for clonal abnormality should also be considered.

Malignancies and progression of malignancies: There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS (see *Carcinogenicity*). Across the clinical trials in ITP (n = 493) no difference in the incidence of malignancies or haematological malignancies was demonstrated between placebo- and REVOLADE treated patients.

Cataracts:

Treatment related cataracts were detected in rodents; an effect that was both dose- and time-dependent. Cataract formation was observed after 6 weeks of treatment at systemic exposure ≥ 6 times that anticipated in humans (based on plasma AUC). This effect was also evident during long-term (2 years) treatment at systemic exposure 4-5 times the anticipated clinical exposure, with the no-effect-dose level being similar to or only slightly higher than the anticipated clinical exposure level. Cataract formation

progressed even after the cessation of treatment. Cataracts have not been observed in dogs after 52 weeks of dosing at 3 times the anticipated clinical exposure based on plasma AUC. The clinical relevance of these findings is unknown.

In the 3 controlled clinical studies, cataracts developed or worsened in 15 (7%) of patients who received 50 mg REVOLADE daily and 8% (7%) placebo-group patients. Perform a baseline ocular examination prior to administration of REVOLADE and, during therapy with REVOLADE, regularly monitor patients for signs and symptoms of cataracts.

Photosensitivity: Eltrombopag is phototoxic and photoclastogenic *in vitro*. *In vitro* photoclastogenic effects were observed only at drug concentrations that were cytotoxic ($\geq 15 \mu\text{g/ml}$) in the presence of high ultraviolet (UV) light exposures (700 mJ/cm²). There was no evidence of *in vivo* cutaneous phototoxicity in mice at exposures up to 10 times the human clinical exposure based on AUC or photo-ocular toxicity in rats at exposures up to 10 times the human clinical exposure based on AUC. The clinical relevance of these findings is unknown. A study of skin responses to UV and visible radiation has not been conducted in humans treated with REVOLADE. As a precaution, patients receiving REVOLADE should avoid being in strong direct sunlight and/or UV exposure or use protective clothing, sunscreen and sun glasses.”

Effects on Fertility

Eltrombopag did not affect female or male fertility in rats at doses 2 to 4 times the human clinical exposure based on AUC. However, due to differences in TPO receptor specificity, data from nonclinical species do not fully model effects in humans.

Use in Pregnancy (Category B3)

Eltrombopag was not teratogenic in rats or rabbits at doses up to 20 mg/kg/day and 150 mg/kg/day respectively. The doses resulted in exposures 2 and 0.5 fold the expected clinical AUC. At the maternally toxic dose of 60 mg/kg/day in rats, fetal weights were significantly reduced and there was an increase in fetal variation, cervical rib, when administered during the period of organogenesis. Eltrombopag treatment during early embryogenesis was associated with an increase in pre-and post-implantation loss (or embryonic death). Due to the fact that eltrombopag is not pharmacologically active in rats or rabbits, the potential teratogenicity of eltrombopag may not have been fully revealed in the studies with these animal species.

There are no adequate and well-controlled studies of REVOLADE in pregnant woman. The effect of REVOLADE on human pregnancy is unknown. REVOLADE should not be used during pregnancy unless the expected benefit clearly out-weighs the potential risk to the fetus.

Use in Lactation

It is not known whether REVOLADE is excreted in human milk. Eltrombopag was detected in the pups of lactating rats 10 days post-partum suggesting the potential for transfer during lactation. REVOLADE is not recommended for nursing mothers unless the expected benefit justifies the potential risk to the infant.

Ability to perform tasks that require judgement, motor or cognitive skills

There have been no studies to investigate the effect of REVOLADE on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of REVOLADE. The clinical status of the patient and the adverse event profile of REVOLADE should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

Carcinogenicity

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 greater than 3 times the anticipated clinical exposure based on plasma AUC). Eltrombopag activates TPO receptors on the surface of haematopoietic cells and has been shown to stimulate the proliferation of megakaryocytic leukaemia cells *in vitro*. There is therefore a theoretical possibility that eltrombopag may increase the risk for haematologic malignancies.

Genotoxicity

Eltrombopag was not mutagenic in a bacterial mutation assay or clastogenic in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 8 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). The clinical significance of the *in vitro* finding remains unclear.

Interactions with other medicines

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. *In vitro* studies demonstrate that eltrombopag is an inhibitor of UGT1A1 UGT1A3 UGT1A4 UGT1A6 UGT1A9 UGT2B7 and UGT2B15 (IC_{50} values 3-33 μ M; 1.3-14.6 μ g/mL). Clinically significant drug interactions involving glucuronidation are not anticipated due to

limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag and potential co-medications.

Based on a human study with radiolabelled eltrombopag, approximately 21 % of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. *In vitro* eltrombopag was an inhibitor of CYP2C8 and CYP2C9 (IC₅₀ 20-25 µM; 8.9-11 µg/mL), but eltrombopag did not inhibit or induce the metabolism of the CYP2C9 probe substrate flurbiprofen in a clinical drug interaction study when eltrombopag was administered as 75 mg once daily for 7 days to 24 healthy adult subjects. In the same study, eltrombopag also did not inhibit or induce the metabolism of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole) or CYP3A3 (midazolam). No clinically significant interactions are expected when eltrombopag and CYP450 substrates, inducers, or inhibitors are co-administered.

Rosuvastatin: *In vitro* studies demonstrated that REVOLADE is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter with an IC₅₀ value of 2.7 µM (1.2 µg/mL). *In vitro* studies also demonstrated that REVOLADE is a breast cancer resistance protein (BCRP) substrate and inhibitor with an IC₅₀ value of 2.7 µM (1.2 µg/mL). Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103 % (90 % CI: 82 %, 126 %) and AUC_{0-∞} 55 % (90 % CI: 42 %, 69 %). When co-administered with REVOLADE, a reduced dose of rosuvastatin should be considered and careful monitoring should be undertaken. In clinical trials with REVOLADE, a dose reduction of rosuvastatin by 50 % was recommended for co-administration of rosuvastatin and REVOLADE. Concomitant administration of REVOLADE and other OATP1B1 and BCRP substrates should be undertaken with caution.

Polyvalent Cations (Chelation): REVOLADE chelates with polyvalent cations such as aluminium, calcium, iron, magnesium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag AUC_{0-∞} by 70 % (90 % CI: 64 %, 76 %) and C_{max} by 70 % (90 % CI: 62 %, 76 %). Antacids, dairy products and other products containing polyvalent cations such as mineral supplements should be administered at least four hours apart from REVOLADE dosing to avoid significant reduction in REVOLADE absorption (see *Dosage and Administration*).

Food Interaction: Administration of a single 50 mg-dose of REVOLADE with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag AUC_{0-∞} by 59 % (90 % CI: 54 %, 64 %) and C_{max} by 65 % (90 % CI: 59 %, 70 %). Food low in calcium [<50 mg calcium] including fruit, lean ham, beef and unfortified (no added

calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see *Dosage and Administration*).

ADVERSE EVENTS

Clinical Trial Data

The safety and efficacy of REVOLADE has been demonstrated in two randomised, double-blind, placebo controlled studies (TRA102537 RAISE and TRA100773B) in adults with previously treated chronic ITP. In the RAISE study 197 subjects were randomised 2:1, REVOLADE (n=135) to placebo (n=62). Subjects received study medication for up to 6 months.

Table 2 On-therapy Adverse Events reported by 5% or More of Subjects in Either Treatment Group in RAISE

Preferred Term	Treatment Group, n (%)	
	Placebo N=61	REVOLADE N=135
Subjects with Any AE	56 (92)	118 (87)
Diarrhoea	6 (10)	17 (13)
Nausea	4 (7)	16 (12)
Vomiting	1 (2)	10 (7)
Pharyngolaryngeal pain	3 (5)	9 (7)
Myalgia	2 (3)	8 (6)
Pharyngitis	1 (2)	8 (6)
AST increased	2 (3)	7 (5)

Adverse reactions considered as possibly related to REVOLADE are listed below by MedDRA body system organ class and by frequency. The frequency categories used are:

Very common	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100
Rare	≥ 1 in 10,000 and < 1 in 1,000

The adverse reactions identified in subjects treated with REVOLADE are presented below (pooled data from RAISE and TRA100773B).

Infections and infestations

Common Pharyngitis
 Urinary tract infection

Gastrointestinal disorders

Very Common Nausea
 Diarrhoea

Common Dry mouth
 Vomiting

Hepatobiliary disorders

Common Increased aspartate aminotransferase
 Increased alanine aminotransferase

Skin and subcutaneous tissue disorders

Common Alopecia
 Rash

Musculoskeletal and connective tissue disorders

Common Back pain
 Musculoskeletal chest pain
 Musculoskeletal pain
 Myalgia

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving REVOLADE (n = 446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n = 6), pulmonary embolism (n = 6), acute myocardial infarction (n = 2), cerebral infarction (n = 2), embolism (n = 1) (see *Precautions*).

Post marketing data

No post-marketing data are currently available.

DOSAGE AND ADMINISTRATION

REVOLADE dosing regimens must be individualised based on the patient's platelet counts. Use the lowest effective dosing regimen to maintain platelet counts, as clinically indicated.

In most patients, measurable elevations in platelet counts take 1-2 weeks (*see Clinical Trials*).

Adults

The recommended starting dose of REVOLADE is 50 mg once daily.

Monitoring and dose adjustment

After initiating REVOLADE, adjust the dose to achieve and maintain a platelet count $\geq 50,000/\mu\text{l}$ as necessary to reduce the risk for bleeding (*see Table 3*). Do not exceed a dose of 75 mg daily.

Clinical haematology and liver function tests should be monitored regularly throughout therapy with REVOLADE and the dose regimen of REVOLADE modified based on platelet counts as outlined in Table 3. During therapy with REVOLADE complete blood counts (CBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count ($\geq 50,000/\mu\text{l}$ for at least 4 weeks) has been achieved. CBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

Table 3 Dose adjustments for REVOLADE

Platelet count	Dose adjustment or response
< 50,000/ μ l following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
\geq 200,000/ μ l to \leq 400,000/ μ l	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 400,000/ μ l	Stop <u>REVOLADE</u> ; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150,000/ μ l, reinstate therapy at a lower daily dose.

The standard dose adjustment, either decrease or increase, would be 25 mg once daily. However, in a few patients a combination of different tablet strengths on different days may be required.

After any REVOLADE dose adjustment, platelet counts should be monitored at least weekly for 2 to 3 weeks. Wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

REVOLADE should be taken at least **four hours** before or after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations (e.g. aluminium, calcium, iron, magnesium, selenium and zinc) (see *Interactions, Pharmacokinetics – Absorption*).

REVOLADE may be taken with food containing little (< 50 mg) or preferably no calcium (see *Interactions, Pharmacokinetics*).

Discontinuation

Treatment with REVOLADE should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of REVOLADE therapy at 75 mg once daily.

Populations

Children

The safety and efficacy of REVOLADE in children have not been established.

Elderly

There are limited data on the use of REVOLADE in patients aged 65 years and older. In the clinical studies of REVOLADE, overall no clinically significant differences in efficacy and safety of REVOLADE were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

Administration of REVOLADE to patients with hepatic impairment should be undertaken with caution and close monitoring (see *Precautions*). In patients with moderate or severe hepatic impairment, REVOLADE should be initiated at a reduced dose of 25 mg once daily.

REVOLADE 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.

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

East Asian Patients

For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese or Korean), REVOLADE should be initiated at a reduced dose of 25 mg once daily (see *PHARMACOLOGY*). Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

OVERDOSAGE

Symptoms and Signs

In the clinical trials there was one report of overdose where the subject ingested 5000 mg of REVOLADE. Reported adverse events included mild rash, transient bradycardia, fatigue and elevated transaminases. Liver enzymes measured between Days 2 and 18 after ingestion peaked at 1.6-fold ULN in AST, 3.9-fold ULN in ALT, and 2.4-fold ULN in total bilirubin. The platelet counts were 672,000/ μ l on day 18 after ingestion and the

maximum platelet count was 929,000/ μ l. All events resolved without sequelae following treatment.

Treatment

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with REVOLADE in accordance with dosing and administration recommendations (*see Dosage and Administration*).

Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, hemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

PRESENTATION AND STORAGE CONDITIONS

The 25 mg tablets are round, biconvex, white, and film-coated, debossed with 'GS NX3' and '25' on one side.

The 50 mg tablets are round, biconvex, brown, and film-coated, debossed with 'GS UFU' and '50' on one side.

Shelf-Life

36 months.

Storage

Store below 30°C.

Nature and Contents of Container

REVOLADE film-coated tablets are supplied in aluminium-aluminium foil blisters in packs of 14, 28 or 84 tablets*.

* not all pack sizes may be marketed

NAME AND ADDRESS OF THE SPONSOR:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

POISON SCHEDULE OF THE MEDICINE - S4

This document was approved by the Therapeutic Goods Administration on: 2 July 2010.

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Version 1.0