Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Eltrombopag

Proprietary Product Name: Revolade

Sponsor: GlaxoSmithKline Australia Pty Ltd

22 November 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. Clinical rationale

Eltrombopag olamine 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 works as a supportive care agent to increase the platelet count prior to and throughout interferon-based treatment of HCV infection, to give patients with advanced fibrosis or cirrhosis an opportunity to initiate and help optimize and maintain the dose and duration of their antiviral therapy, thereby improving the likelihood of achieving sustained virologic response (SVR). The importance of SVR is reflected by a 4 to 10 fold decrease in mortality and a 2 to 4 fold decrease in the incidences of decompensated liver disease and hepatocellular carcinoma in HCV patients compared to patients with persistent HCV infection. Even for patients who have developed hepatic decompensation, achieving SVR prior to liver transplantation can improve outcomes after transplantation by avoiding HCV recurrence.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 2 pivotal efficacy/safety studies.
- 1 other efficacy/safety studies.
- Supporting information including pooled analyses and PSURs.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

Information provided by the sponsor indicated that all studies were undertaken in accordance with standard operating procedures of the sponsor, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authorities.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Results from clinical biopharmaceutics studies were provided in the original marketing authorisation application (MAA) to support eltrombopag use in adult patients with chronic idiopathic thrombocytopenic purpura. No additional clinical biopharmaceutics studies were completed for this application. Pharmacokinetic data provided was limited to some information on drug-drug interactions (concurrent administration of peginterferon alfa-2a + ribavirin or

peginterferon alfa-2b + ribavirin) and some information on pharmacokinetics in the target patient population. For the latter, plasma eltrombopag concentration-time data collected in 635 subjects with chronic HCV infection in the Phase II study TPL102357 and the Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from 28 healthy adult subjects (from the Phase I study SB-497115/002, previously submitted) in a population PK analysis.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

3.2.1. Physicochemical characteristics of the active substance

Eltrombopag is achiral but potentially shows *E/Z* isomerism around the hydrazone. It is reported to exist as the hydrogen-bonded, *Z* isomer 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 125ºC; only one morphic form is known. It is not hygroscopic. The solubility of the bis-ethanolamine salt in water is markedly higher. The drug substance is synthetic. Impurity levels are low.

3.2.2. Pharmacokinetics in healthy subjects

3.2.2.1. Absorption

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.

3.2.2.2. Bioavailability

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 %.

3.2.2.3. 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.

3.2.2.4. Metabolism

Eltrombopag is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64 % of plasma radiocarbon are under the plasma concentration time curve ($AUC_{0-\infty}$). 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 3 isozymes responsible for glucuronidation and that bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathways.

3.2.2.5. Excretion

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 to 32 hours in healthy subjects and 26 to35 hours in ITP patients.

3.2.3. Pharmacokinetics in the target population

Plasma eltrombopag concentration-time data collected in 635 subjects with chronic HCV infection in the Phase II study TPL102357 and the Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from 28 healthy adult subjects (from the Phase I study SB-497115/002) in a population PK analysis. Plasma eltrombopag C_{max} and AUC $_{0\text{-}\tau}$ estimates for subjects with HCV enrolled in the Phase III studies are presented for each dose studied below.

Table 1. Plasma eltrombopag C_{max} and AUC $_{0\text{-}\tau}$ estimates for subjects with HCV enrolled in the Phase III studies

Eltrombopag Dose (once daily)	N	Geometric Mean (95% CI)	
		C_{max}, µg/ml	$AUC_{(0\text{-}\tau)}$, µg.h/ml
25 mg	330	6.40 (5.97, 6.86)	118 (109, 128)
50 mg	119	9.08 (7.96, 10.35)	166 (143, 192)
75 mg	45	16.71 (14.26, 19.58)	301 (250, 363)
100 mg	96	19.19 (16.81, 21.91)	354 (304, 411)

Note: AUC (0-τ) and Cmax based on population PK post-hoc estimates at the highest dose in the data for each subject.

A 2-compartment model with absorption lag time, dual sequential first-order absorption and first-order elimination as the final base model adequately described the PK of eltrombopag following oral administration. The model also had correlation between Vc/F and CL/F, inter-individual variability (IIV) on Vc/F and CL/F and inter-occasion variability (IOV) on Ka and CL/F built into the base model. After completion of the covariate model development, eltrombopag Vc/F and Vp/F increased allometrically with body weight. East/Southeast Asian race, female gender, age greater than 60 years, high aspartate aminotransferase (AST), and severity of hepatic impairment, as assessed by Child-Pugh score[1], were associated with lower plasma eltrombopag oral clearance (CL/F). Central/South Asian race was associated with eltrombopag volume of distribution (Vc/F) values 2.3 fold those observed for subjects of other races.

3.2.4. Pharmacokinetics in other special populations

3.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with liver cirrhosis (hepatic impairment). Following the administration of a single 50 mg dose, the AUC $_{0\text{-}\infty}$ of eltrombopag was increased by 41 % (90 % CI: 13 % decrease, 128 % increase) in subjects with mild hepatic impairment, 93 % (90 % CI: 19 %, 213 %) in subjects with moderate hepatic impairment, and 80 % (90 % CI: 11 %, 192 %) in subjects with severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between subjects with hepatic impairment and healthy volunteers.

A similar analysis was also conducted in 28 healthy adults and 635 patients with HCV. A majority of patients had Child-Pugh score of 5-6. Based on estimates from the population pharmacokinetic analysis, patients with HCV had higher plasma eltrombopag $AUC_{(0\text{-}\tau)}$ values as compared to healthy subjects and AUC $_{0\text{-}\tau}$ increased with increasing Child-Pugh score, HCV

[1] The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

patients with mild hepatic impairment had approximately 100-144 % higher plasma eltrombopag AUC $_{0-\tau}$ compared with healthy subjects.

3.2.4.2. Pharmacokinetics in subjects with impaired renal function

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, by 36 % (90 % CI: 66 % decrease, 19 % increase) in patients with moderate renal impairment and by 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.

3.2.4.3. Pharmacokinetics according to age

The age difference of eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects and 635 patients with HCV ranging from 19 to 74 years old. Based on model estimates, elderly (> 60 years) patients had approximately 36% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients.

3.2.4.4. Pharmacokinetics related to ethnicity factors

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 (that is, 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.

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (214 East Asians). On average, East Asian patients had approximately 55 % higher plasma eltrombopag AUC $_{0-\tau}$ values as compared to patients of other races who were predominantly Caucasian.

3.2.4.5. Pharmacokinetics related to 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.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimates, female HCV patients had approximately 41 % higher plasma eltrombopag AUC $_{0-\tau}$ as compared to male patients.

3.2.5. Pharmacokinetic interactions

3.2.5.1. Pharmacokinetic interactions demonstrated in human studies

Information from the previous submission indicated that 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. A clinical drug-drug interaction study between eltrombopag and boceprevir or telaprevir has not been conducted. From the efficacy studies provided, plasma eltrombopag exposure was not altered by concurrent administration of peginterferon alfa-2a + ribavirin or peginterferon alfa-2b + ribavirin, nor were plasma

peginterferon alfa-2a and alfa-2b exposures altered by concurrent administration of eltrombopag.

3.2.5.2. Clinical implications of in vitro findings

In vitro, eltrombopag inhibited the human CYP2C8 and CYP2C9 isozymes with 50% ineffective concentration dose (IC_{50}) 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 IC_{50} 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). As such, eltrombopag is not expected to significantly alter plasma boceprevir or telaprevir exposure because eltrombopag is not an inhibitor of CYP3A4 or P-glycoprotein (Pgp), for which both HCV protease inhibitors are substrates and eltrombopag is not an inducer. Boceprevir and telaprevir are not expected to significantly increase plasma eltrombopag exposure because eltrombopag is not a CYP3A4 or Pgp substrate, for which both HCV PIs are inhibitors and because eltrombopag is metabolised through multiple pathways. The reduced plasma exposures of some drugs co-administered with telaprevir suggest that telaprevir may induce drug metabolising enzymes, which could reduce plasma eltrombopag exposure. Any impact of telaprevir on plasma eltrombopag exposure is clinically manageable because the eltrombopag dose is titrated to platelet response.

3.3. Evaluator's overall conclusions on pharmacokinetics

Eltrombopag was approved for use in Australia in July 2010 (ARTG 158419/158356). As such, the pharmacokinetics for this medication have been extensively characterised and considered previously. In this application, additional information was provided on pharmacokinetics in the target population only. This information was obtained from the clinical efficacy studies and also encompassed the pharmacokinetics of the proposed new strengths, 75 mg and 100 mg.

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52 %. 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. Eltrombopag is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione or cysteine. Minor metabolites, each accounting for < 10 % of the plasma radioactivity, arising from glucuronidation and oxidation were also detected. Based on a human study with radiolabelled eltrombopag, it is estimated that approximately 20 % of a dose is metabolised by oxidation. 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 to 32 hours in healthy subjects and 26-35 hours in ITP patients.

Plasma eltrombopag concentration-time data collected in 635 subjects with chronic HCV infection in the Phase II study TPL102357 and the Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from 28 healthy adult subjects (from the Phase I study SB-497115/002) in a population PK analysis. Plasma eltrombopag concentration over time was accurately predicted for all dosages, including the proposed 75 mg and 100 mg tablets.

Pharmacokinetic data on special populations including renal impairment, hepatic impairment, race, gender and elderly population was provided. This appears to be consistent with previous experience with this medication.

Eltrombopag has the potential to affect the pharmacokinetics of co-administered drugs that are substrates of CYP2C8, CYP2C9, UGTs, OATP1B1 or BCRP. A clinical drug-drug interaction study between eltrombopag and boceprevir or telaprevir has not been conducted. From the efficacy studies provided, plasma eltrombopag exposure was not altered by concurrent administration of peginterferon alfa-2a + ribavirin or peginterferon alfa-2b + ribavirin and plasma peginterferon alfa-2a and alfa-2b exposures were not altered by concurrent administration of eltrombopag.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

No specific pharmacodynamics studies were provided. Information on the pharmacodynamics of Eltrombopag was available from the previous submission. In addition, specific analyses were conducted to characterise the relationship between plasma Eltrombopag exposure and platelet response in subjects with chronic HCV infection and the relationship between plasma Eltrombopag exposure and QTc in patients with chronic HCV infection.

4.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

4.2.1. Mechanism of action

In vitro, eltrombopag demonstrated TPO receptor activation by stimulation of both STAT-based interferon regulatory factor-1 promoter and the megakaryocytic-specific promoter, glycoprotein IIb, with a 50% effective concentration (EC_{50}) 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 EC_{50} 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.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

Primary pharmacodynamics effects were characterised by the relationship between plasma eltrombopag exposure and platelet response in subjects with chronic HCV infection. A 4-compartment life-span model, including three bone marrow compartments (one precursor production and two maturation compartments) and one blood platelet compartment, adequately described the stimulation of platelets by eltrombopag. In accordance with the mechanism of action, eltrombopag increased platelet counts in blood by stimulating the production rate of platelet precursors (KIN). The plasma eltrombopag concentration was related to the increase in KIN through an E_{max} relationship, with 50% of maximum stimulation achieved at the eltrombopag concentration (EC_{50}) of 29 μg/mL. The estimated maximum effect was a 15.4 fold increase in platelet production. Kinetic-pharmacodynamic (KPD) models with first-order absorption and elimination, independently developed for peginterferon alfa-2a and peginterferon alfa-2b, described the inhibition of platelet production by peginterferon. The inhibitory effect of peginterferon on platelet production was linearly associated with peginterferon concentrations. In the clinical studies, rapid platelet count reduction occurred within the first 2 to 3 weeks of initiation of peginterferon + ribavirin therapy, which was then followed by a gradual reduction toward equilibrium in 5-6 weeks. During antiviral therapy, the

model predicted that approximately 50% of subjects would need at least one eltrombopag dose adjustment to maintain platelet counts >50 Gi/L and <200 Gi/L. Subjects were more likely to remain on a lower eltrombopag dose to complete antiviral therapy with biweekly eltrombopag dose adjustment compared to weekly dose adjustment.

4.2.2.2. Secondary pharmacodynamic effects

Secondary pharmacodynamics effects included the relationship between plasma Eltrombopag exposure and QTc in patients with chronic HCV infection. Eltrombopag demonstrated no clinically significant effect on cardiac repolarisation in patients with HCV infection. The upper limit of the 90% CI for the mean difference in time-matched QTcF change from baseline with correction for placebo effect (ddQTcF) was below 10 ms at all doses up to 100 mg once a day (QD) and was predicted to be below 10 ms at the supra-therapeutic dose of 200 mg QD.

4.2.3. Time course of pharmacodynamic effects

From the previous submission, the effect of eltrombopag on platelet counts was studied in healthy volunteers. Platelet count increased in a dose-dependent 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.

4.2.4. Relationship between drug concentration and pharmacodynamic effects

Please refer above. Simulations from the final eltrombopag PK/PD model support 25 mg once daily as the initial dose and biweekly dose escalation in 25 mg increments as an effective way for thrombocytopenic HCV patients to raise platelet counts to a sufficient level to allow initiation of antiviral therapy. The same eltrombopag starting dose was regarded as appropriate for all thrombocytopenic HCV patients regardless of race because similar platelet results were predicted across patient subpopulations.

4.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

Pharmacokinetic differences for special populations are noted above. No specific differences in pharmacodynamic response for these groups were noted.

4.2.6. Pharmacodynamic interactions

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 peak plasma concentration (C_{max}) 103 % (90 % CI: 82 %, 126 %) and $AUC_{0-\infty}$ 55 % (90 % CI: 42 %, 69 %). Co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{0-\infty}$ by 17 % (90 % CI: 6.6 %, 26.6 %). 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 $AUC_{0-\infty}$ by 70 % (90 % CI: 64 %, 76 %)and C_{max} by 70 % (90 % CI: 62 %, 76 %). Administration of a single 50 mg dose of eltrombopag with a standard high calorie, high fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{0-\infty}$ by 59 % (90 % CI: 54 %, 64 %) and C_{max} by 65 % (90 % CI: 59 %, 70 %).

4.3. Evaluator's overall conclusions on pharmacodynamics

The mechanism of action of eltrombopag has been well characterised from previous submissions. 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. 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.

To assess the pharmacodynamics of eltrombopag, a population PK/PD model was constructed in a step-wise fashion. Initially, a PK/PD model was developed based on data from eltrombopag mono-therapy to characterise the stimulatory effect of eltrombopag on platelet counts. The model was then extended to incorporate the inhibitory effects of IFN (alfa-2a and alfa-2b) by including data from antiviral therapy in the modelling. Due to a lack of serum concentrations of IFN alfa-2a and IFN alfa-2b in the majority of patients, a kinetic-pharmacodynamic (KPD) modelling approach was used to characterise the inhibitory effect of IFN on platelet counts during antiviral therapy. The plasma eltrombopag concentration was related to the increase in KIN through an E_{max} relationship, with 50% of maximum stimulation achieved at the eltrombopag concentration (EC_{50}) of 29 µg/mL. The estimated maximum effect was a 15.4 to fold increase in platelet production. The inhibitory effect of peginterferon on platelet production was linearly associated with peginterferon concentrations. This modelling allowed for a prediction of required starting dose for eltrombopag and requirement for dose adjustment during treatment. This modelling was then assessed in the pivotal efficacy studies.

Pharmacodynamic interactions were noted with Rosuvastatin, Lopinavir/ritonavir, polyvalent cations and food interactions. Eltrombopag demonstrated no clinically significant effect on cardiac repolarisation in patients with HCV infection.

5. Dosage selection for the pivotal studies

The 25 mg starting dose of eltrombopag administered in ENABLE 1 and ENABLE 2 was based on evidence from the Phase II program (Study TPL102357), in which 75% of HCV-infected subjects receiving the lowest dose of eltrombopag (30 mg) achieved platelet counts >100 Gi/L after the initial 4 week pre-antiviral dosing period. Study TPL102357 used eltrombopag doses of 30, 50 and 75 mg and not the 100 mg dose.

As noted above, pharmacokinetic (PK) and pharmacodynamic (PD) data showed that repeat, once daily dosing led to platelet count increases after 8 days of dosing, and a maximal platelet count response was achieved approximately 2 weeks after the start of dosing. A PK/PD model estimated that 54% of subjects would require an eltrombopag dose of 100 mg to maintain a platelet count >80 Gi/L during peginterferon therapy. Therefore, the 100 mg dose was introduced in the ENABLE 1 and ENABLE 2 studies.

6. Clinical efficacy

6.1. Treatment of thrombocytopenia in adult patients with chronic hepatitis C virus (HCV) infection

6.1.1. Pivotal efficacy studies

6.1.1.1. Study TPL103922 (ENABLE 1)

This study was a randomised, placebo-controlled, multicentre study to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with hepatitis C virus (HCV) infection who were otherwise eligible to initiate antiviral therapy (peginterferon alfa-2a plus ribavirin). The study was conducted between 30 October 2007 and 31 March 2011.

The primary objective of the study was to evaluate the effect of eltrombopag treatment on Sustained Virologic Response (SVR) in thrombocytopenic subjects (platelets <75 Gi/L) with HCV infection.

Secondary Objectives of the study were to evaluate the

- ability of eltrombopag to enable initiation of antiviral therapy in thrombocytopenic subjects with HCV infection.
- effects of eltrombopag treatment on antiviral treatment outcome measures (rapid virologic response [RVR], early virologic response [EVR] and end of treatment response [ETR]) in thrombocytopenic subjects with HCV infection.
- ability of eltrombopag to enable maintenance of antiviral therapy in thrombocytopenic subjects with HCV infection.
- effect of eltrombopag on platelet counts in thrombocytopenic subjects with HCV infection, before and during antiviral therapy.
- safety and tolerability of eltrombopag when administered once daily in thrombocytopenic subjects with HCV infection.
- impact of eltrombopag and interferon-based therapy on reported symptoms and health-related quality of life (HRQoL) using the chronic liver disease questionnaire (CLDQ)-HCV and the Medical Outcomes Study Short-form 36 version 2 acute recall (SF-36v2) before, during, and after completion of therapy,

  and to describe the

- pharmacokinetics (PK) of eltrombopag and explore the relationship between the PK of eltrombopag and relevant safety and efficacy endpoints.
- PK of peginterferon alfa-2a during concomitant dosing with eltrombopag.

The study consisted of an open-label (OL), Pre-Antiviral Treatment Phase (Part 1) and a randomised, double-blind (DB), placebo controlled, Antiviral Treatment Phase (Part 2). Subjects entered the study with a platelet count of <75 Gi/L and were stratified at Baseline (Day 1) by platelet count (<50 Gi/L and ≥50 Gi/L), screening HCV ribonucleic acid (RNA) (<800,000 IU/mL and ≥800,000 IU/mL) and genotype (genotype 2/3, and non-genotype 2/3). In Part 1, all subjects received OL eltrombopag dosed once daily with the objective of increasing platelet counts to ≥90 Gi/L, the recommended platelet count for initiation of peginterferon alfa-2a according to the US and most international labels. Subjects started with a dose of eltrombopag (25 mg once daily) for 2 weeks. If after this time the platelet count was <90 Gi/L, subjects underwent a sequential dose escalation to the next highest dose (50 mg once daily for up to 2 weeks), with further dose escalations to 75 mg once daily (up to 2 weeks) and 100 mg once daily (up to a maximum of 3 weeks) to achieve a platelet count ≥90 Gi/L. Once subjects achieved platelet counts ≥90 Gi/L, they were eligible to enter the randomised part of the study (Part 2) and initiate antiviral therapy (peginterferon alfa-2a plus ribavirin). Subjects with platelet counts <90 Gi/L after the 9 week Pre-Antiviral Treatment Phase were discontinued from eltrombopag and switched to post-treatment follow-up visits.

In Part 2, subjects were randomised 2:1 to either continue on the same dose of eltrombopag from Part 1 or received a matched placebo. Both treatments were given in combination with antiviral therapy for up to 48 weeks. Dose modifications of eltrombopag/matched placebo were permitted to maintain platelet counts at a level that enabled continuation of antiviral therapy, ideally at full dose, by allowing increases in the eltrombopag/matched placebo dose up to 100 mg once daily. Any dose modifications of peginterferon alfa-2a or ribavirin were performed as directed within the product labels.

A total of 716 subjects enrolled in Part 1. Of these, 715 subjects received at least one dose of OL eltrombopag (Safety Population). A total of 682 subjects were randomised to DB treatment (ITT Population), of which 681 subjects received at least one dose of DB study medication (Safety DB Population). Forty-two subjects randomised to DB treatment had protocol deviations and were therefore excluded from the PP Population. Subjects were male or female subjects aged ≥18 years of age with chronic HCV infection, a platelet count <75 Gi/L, and who in the investigator's opinion were appropriate candidates for peginterferon alfa-2a and ribavirin combination antiviral therapy, were eligible for enrolment in the study (Part 1).

For the primary endpoint, SVR rate was defined as the percentage of subjects with undetectable HCV-RNA at end of treatment and all subsequent planned visits up to 24 weeks after completing treatment (generally Week 48 or 72 for genotype 2/3, or Week 72 for non-genotype 2/3). Secondary efficacy endpoints included: Platelet shift from baseline count to ≥90 Gi/L with OL eltrombopag; Assessment of platelet counts throughout the study; proportions of subjects requiring dose reductions and/or dose cessation of peginterferon alfa-2a and/or ribavirin therapy; Proportions of subjects achieving the following antiviral outcome measures

i. undetectable HCV RNA after 12 weeks of antiviral treatment (cEVR)

ii. clinically significant reduction in HCV RNA (≥2 log10 drop or undetectable) after 12 weeks of antiviral treatment (EVR);

iii. undetectable HCV RNA after 4 weeks of antiviral treatment (RVR); and

iv. undetectable HCV RNA at the end of antiviral treatment (ETR). Safety endpoints included: Assessment of safety and tolerability of eltrombopag in comparison with placebo, as measured by the nature and frequency of adverse events (AEs), laboratory abnormalities, ocular examinations, 12-lead electrocardiograms (ECG), and clinical monitoring/observation.

A total of 675 subjects (450 on eltrombopag and 225 on placebo) were required to be randomised to provide a 92.5% power to detect a clinically meaningful absolute difference, assuming a 10% SVR rate for placebo and a two-sided significance level of 5%. The primary analysis compared the proportion of subjects with SVR between eltrombopag and placebo. Stratified Cochran-Mantel-Haenszel (CMH) chi-square test statistics adjusting for HCV genotype, baseline platelet count stratum, and baseline HCV RNA stratum was used to compare SVR rates between treatments. The Wilcoxon rank sum test, adjusting for strata was used to analyse scores between treatment groups.

With regard to efficacy results, six hundred and ninety-one (97%) subjects in the OL Phase achieved a platelet count (≥90 Gi/L) that would allow the initiation of antiviral therapy. The majority of subjects (85%) achieved platelet counts ≥90 Gi/L within the first 4 weeks of treatment. Ninety five percent of subjects who received eltrombopag in the OL phase initiated antiviral therapy in the DB Phase. Of these, 88% were receiving eltrombopag 25 mg or 50 mg at randomisation. At baseline, the median platelet count was 59 Gi/L. Platelet counts began to rise following administration of 25 mg of eltrombopag to a median platelet count of 89 Gi/L by Week 2. Following antiviral treatment in the DB phase, a statistically greater proportion of eltrombopag subjects (23%) achieved SVR than did subjects in the control arm (14%; p=0.0064). EVR, cEVR, ETR and SVR12 were statistically significantly higher in the eltrombopag group compared to the placebo group. A summary of efficacy results appears below.

Table 2. Other Antiviral Endpoints (ITT Population).

	Placebo (N=232)	Eltrombopag (N=450)
Rapid virological response (RVR), n (%)	39 (17)	73 (16)
Percentage Difference (95% CI)[a]	1.0 (-2.5, 4.5)	
P-Value[b]	0.7495	
Extended RVR (eRVR), n (%)	28 (12)	68 (15)
Percentage Difference (95% CI)[a]	1.6 (-1.8, 5.1)	
P-Value[b]	0.3006	
Early virological response (EVR), n (%)	115 (50)	297 (66)
Percentage Difference (95% CI)[a]	16.7 (9.2 , 24.1)	
P-Value[b]	<0.0001	
Complete EVR (cEVR), n (%)	60 (26)	187 (42)
Percentage Difference (95% CI)[a]	14.8 (8.6, 21.1)	
P-Value[b]	<0.0001	
End of treatment response (ETR), n (%)	86 (37)	214 (48)
Percentage Difference (95% CI)[a]	10.7 (3.3, 18.1)	
P-Value[b]	0.0080	
SVR at 12 week FU (SVR12), n (%)	36 (16)	103 (23)
Percentage Difference (95% CI)[a]	8.3 (2.7, 13.9)	
P-Value[b]	0.0256	

a. Adjusted for the actual strata: HCV genotype, baseline platelet count and HCV RNA stratum.
b. Stratified CMH Chi-squared test adjusted for the randomisation strata

Adherence to antiviral therapy was defined as receiving at least 80% of the prescribed dose (investigator prescribed) of peginterferon alfa-2a and at least 80% of the prescribed dose (investigator prescribed) of ribavirin, for at least 80% of the planned duration. A higher proportion of eltrombopag subjects (246 subjects, 55%) were adherent to antiviral therapy compared with placebo subjects (102 subjects, 44%) (Treatment difference: 11.7%; 95% CI: 4.2-19.3%; stratified CMH chi-square p=0.0066). Subjects who were adherent to antiviral therapy in both treatment groups were more likely to achieve SVR (p<0.0001). More eltrombopag subjects (43%) had no antiviral dose reductions (peginterferon and/or ribavirin) compared with placebo subjects (28%). Eltrombopag treatment was associated with a significantly lower proportion of antiviral dose reductions. The median time to the first dose reduction was longer for eltrombopag subjects compared to placebo subjects for all dose levels.

With regard to safety results, a similar proportion of subjects in the eltrombopag group reported at least one AE, drug related AE and (S)AE leading to withdrawal during the DB on-treatment+30 days follow-up period compared to the placebo group. A higher proportion of subjects in the eltrombopag group (20%) reported at least one SAE than in the placebo group (15%). Compared to the placebo group (2%), a similar proportion of eltrombopag subjects (2%) died during the DB Phase. A summary of safety results appears below.

Table 3. Overall Summary of Adverse Events During the OL Phase (Safety Population).

	Eltrombopag (N=715)	
	N (%)	Events
Number of subjects with an AE	268 (37)	687
Number of subjects with an SAE	8 (1)	9
Number of subjects with a drug-related AE	107 (15)	206
Number of subjects with an AE leading to withdrawal	5 (<1)	11
Number of subjects with an SAE leading to withdrawal	2 (<1)	2
Number of subjects with an ongoing AE at the end of study/withdrawal	71 (10)	102

Table 4. Overall Summary of Adverse Events on treatment plus 30 days follow-up during the DB Phase (Safety Double-blind Population).

	Placebo (N=232)		Eltrombopag (N=449)	
	n (%)	Events	n (%)	Events
Number of subjects with an AE	226 (97)	2307	430 (96)	5067
Number of subjects with an SAE	35 (15)	52	90 (20)	101
Number of subjects with a fatal AE[a]	4 (2)	7	8 (2)	11
Number of subjects with a drug-related AE	217 (94)	1693	420 (94)	3455
Number of subjects with an AE leading to withdrawal from study	7 (3)	11	11 (2)	23
Number of subjects with an SAE leading to withdrawal	5 (2)	8	8 (2)	16
Number of subjects with an ongoing AE at the end of study/withdrawal	111 (48)	294	137 (53)	659

a. The deaths of 3 additional eltrombopag subjects were reported following completion of the study. Because these 3 subjects died following completion of the study, their deaths are not included in the table.

6.1.1.2. Study TPL108390 (ENABLE 2)

This study was a randomised, placebo-controlled, multicentre study to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with hepatitis C virus (HCV) infection who were otherwise eligible to initiate antiviral therapy (peginterferon alfa-2b plus ribavirin). The study was conducted between 30 October 2007 and 23 August 2011. The primary and secondary objectives were identical to those in study TPL103922 (ENABLE 1). This was a multicentre two-part study, consisting of an open-label (OL),Pre-Antiviral Treatment Phase (Part 1) and a randomised, double-blind (DB), placebo controlled, Antiviral Treatment Phase (Part 2). Subjects entered the study with a platelet count of <75 Gi/L and were stratified at Baseline (Day 1) by platelet count (<50 Gi/L and ≥50 Gi/L), screening HCV RNA (<800,000 IU/mL and ≥800,000 IU/mL) and genotype (genotype 2/3, and genotype non-2/3). With the exception of the antiviral therapy (peginterferon alfa- 2b plus ribavirin), the methodology was exactly the same as for study TPL103922 (ENABLE 1).

A total of 805 subjects enrolled in Part 1. All 805 subjects received at least 1 dose of OL eltrombopag (Safety Population). A total of 759 subjects were randomised to DB treatment (ITT Population), of which 758 subjects received at least one dose of DB study medication (Safety DB Population). Forty-one subjects randomised to DB treatment had protocol deviations and were therefore excluded from the PP Population. Primary, secondary and safety endpoints were the same as for study TPL103922 (ENABLE 1). A total of 675 subjects (450 on eltrombopag and 225 on placebo) were required to be randomised to provide a 92.5% power to detect a clinically meaningful absolute difference of 10%, assuming a 10% SVR rate for placebo and a two-sided significance level of 5%. Statistical methods were otherwise the same as for study TPL103922 (ENABLE 1).

With regard to efficacy results, seven hundred and seventy-three (96%) subjects in the OL Phase achieved a platelet count (≥100 Gi/L) that would allow the initiation of antiviral therapy. The majority of subjects (78%) achieved a platelet count ≥100 Gi/L within the first 4 weeks of treatment.

Ninety-four percent of subjects who received eltrombopag in the OL phase initiated antiviral therapy in the DB Phase. Of these, 81% were receiving eltrombopag 25 mg or 50 mg at randomisation.

At baseline, the median platelet count was 59 Gi/L. Platelet counts began to rise following administration of 25 mg of eltrombopag to a median platelet count of 93 Gi/L by Week 2.

Following antiviral treatment in the DB phase, a statistically greater proportion of eltrombopag subjects (19%) achieved SVR than did placebo subjects (13%; p=0.0202). EVR, cEVR, ETR and SVR12 were statistically higher in the eltrombopag group compared to the placebo group. A summary of efficacy results appears below.

Table 5. Other Antiviral Endpoints (ITT Population).

	Placebo (N=253)	Eltrombopag (N=506)
Rapid virologic response (RVR), n (%)	34 (13)	78 (15)
Percentage Difference (95% CI)[a]	N/A	
Extended RVR (eRVR), n (%)	27 (11)	69 (14)
Percentage Difference (95% CI)[a]	N/A	
Early virologic response (EVR), n (%)	103 (41)	313 (62)
Percentage Difference (95% CI)[a]	20.7 (13.6, 27.8)	
P-value[b]	<0.0001	
Complete EVR (cEVR), n (%)	57 (23)	174 (34)
Percentage Difference (95% CI)[a]	9.1 (3.5, 14.7)	
P-value[b]	0.0003	
End of treatment response (ETR), n (%)	59 (23)	190 (38)
Percentage Difference (95% CI)[a]	13.1 (6.9, 19.4)	
P-value[b]	<0.0001	
SVR at 12 week FU (SVR12), n (%)	29 (11)	106 (21)
Percentage Difference (95% CI)[a]	8.6 (3.7, 13.5)	
P-value[b]	0.0009	

a. Adjusted for the actual strata: HCV genotype, baseline platelet count and HCV RNA stratum
b. Stratified CMH Chi-squared test adjusted for the randomisation strata

Adherence to antiviral therapy was defined as receiving at least 80% of the prescribed dose (investigator prescribed)of peginterferon alfa-2b and at least 80% of the prescribed dose (investigator prescribed)of ribavirin, for at least 80% of the planned duration. A higher proportion of eltrombopag subjects (261 subjects, 52%) were adherent to antiviral therapy compared with placebo subjects (84 subjects, 33%) and this difference was statistically significant (Treatment difference: 17.4%; 95% CI: 10.5, 24.2%; p<0.0001). Subjects who were adherent to antiviral therapy in both treatment groups were more likely to achieve SVR (p<0.0001). A greater proportion of eltrombopag subjects (46%) had no antiviral dose reductions (peginterferon and/or ribavirin) compared with placebo subjects (27%). Eltrombopag treatment was associated with a significantly lower proportion of antiviral dose reduction. A lower proportion of eltrombopag subjects had peginterferon dose reductions (41%) at any dose level than placebo subjects (68%). The median time to the first and second peginterferon alfa-2b dose reductions was longer for eltrombopag subjects.

With regard to safety results, a similar proportion of subjects in the eltrombopag group reported at least one AE, drug related AE and (S)AE leading to withdrawal during the DB on-treatment+30 days follow-up period compared to the placebo group. A higher proportion of subjects in the eltrombopag group (20%) reported at least one SAE than in the placebo group (15%). One percent of placebo subjects and 3% of eltrombopag subjects experienced a fatal event during the DB on-treatment+30 days follow-up period. A summary of the safety results appears below.

Table 6. Overall summary of Adverse Events during the OL Phase (Safety Population).

	Eltrombopag (N=805)	
	N (%)	Events
Number of subjects with an AE	277 (34)	613
Number of subjects with an SAE	9 (1)	9
Number of subjects with a fatal AE	2 (<1)	2
Number of subjects with a drug-related AE	96 (12)	156
Number of subjects with an AE leading to withdrawal from study	2 (<1)	2
Number of subjects with an SAE leading to withdrawal from study	1 (<1)	1
Number of subjects with an ongoing AE at the end of study/withdrawal	63 (8)	88

Table 7. Overall Summary of Adverse Events on treatment plus 30 days follow-up during the DB Phase (Safety Double-blind Population).

	Placebo (N=252)		Eltrombopag (N=506)	
	n (%)	Events	n (%)	Events
Number of subjects with an AE	235 (93)	2077	475 (94)	5109
Number of subjects with an SAE	37 (15)	62	99 (20)	173
Number of subjects with a fatal AE[a]	3 (1)	4	15 (3)	23
Number of subjects with a drug-related AE	225 (89)	1588	453 (90)	3643
Number of subjects with an AE leading to withdrawal from study	9 (4)	10	23 (5)	38
Number of subjects with an SAE leading to withdrawal from study	4 (2)	5	20 (4)	29
Number of subjects with an ongoing AE at the end of study/withdrawal	127 (50)	266	268 (53)	746

a. The death of 2 additional eltrombopag subjects (Subjects 3300, 3500) were reported following completion of the study and were therefore not captured in the eCRF and are not included in the table.

6.1.2. Other efficacy studies

6.1.2.1. Study TPL102357

This study was a double-blind, randomised, placebo-controlled, multi-centre, dose-ranging, parallel group, Phase II study to assess efficacy, safety/tolerability and pharmacokinetics of a thrombopoietin receptor agonist, SB-497115-GR (eltrombopag), when administered as 30, 50, and 75 mg once daily for 16 weeks in subjects with chronic hepatitis C-related thrombocytopenia who are potential candidates for antiviral treatment with pegylated interferon and ribavirin. The study was conducted between 05 Apr2005 and 20 Oct2006. The primary objective was to evaluate the effect of eltrombopag on platelet counts when administered once daily for 4 weeks (Part 1, pre-antiviral phase) to subjects with chronic hepatitis C virus (HCV)-related thrombocytopenia, prior to receiving antiviral therapy.

Secondary objectives of the study were to evaluate the:

- effects of eltrombopag on platelet counts when administered once daily for 12 weeks (Part 2) to subjects with chronic HCV-related thrombocytopenia, during antiviral therapy.
- effects of eltrombopag on markers of thrombopoiesis, when administered once daily for 16 weeks to subjects with chronic HCV-related thrombocytopenia.
- effects of eltrombopag on antiviral treatment outcome measures during and after antiviral therapy in subjects with chronic HCV.
- safety and tolerability of eltrombopag when administered once daily for 16 weeks to subjects with chronic HCV.
- population pharmacokinetic profile of eltrombopag when administered once daily for 16 weeks to subjects with chronic HCV.

The study was a double-blind, randomised, placebo-controlled, multi-center, dose-ranging, parallel group study in HCV-infected subjects with platelet counts between 20,000 to 70,000 platelets/μL (20 to <70Gi/L) who were eligible to begin treatment with peginterferon and ribavirin. Stratification was according to baseline platelet count (20 to <50Gi/L and ≥50 to <70Gi/L). The study was conducted in two phases, Parts 1 and 2. In Part 1, study subjects were randomised to eltrombopag (30, 50 or 75 mg daily) or placebo for 4 weeks. Subjects who successfully completed Part 1 (achieved a platelet count ≥70Gi/L for Pegasys or platelet count ≥100Gi/L for PEG-Intron at Day 28) proceeded to Part 2. In Part 2, subjects received an additional 8-12 weeks of eltrombopag or placebo administered daily with antiviral therapy (peginterferon and ribavirin). At the completion of Part 2, subjects could continue to receive antiviral therapy per standard of care at the discretion of the investigator. Platelet counts were

measured throughout the study and 4 weeks after the last dose of double-blind study medication.

Subjects were male and female subjects who were ≥18 years of age with chronic HCV (defined as the presence of HCV antibodies and detectable HCV RNA [ribonucleic acid]) who had compensated liver disease and pre-existing thrombocytopenia (defined as a platelet count of 20 to <70Gi/L). Subjects were required to have a liver biopsy indicative of chronic hepatitis or radiographic evidence of cirrhosis or endoscopic evidence of portal hypertension. A total of 74 subjects were randomised to treatment. The primary assessment for efficacy was platelet count. The primary efficacy endpoint was a shift from baseline platelet count (between 20 to <70Gi/L) to ≥100Gi/L after the first 4 weeks of dosing. Secondary endpoints included safety and tolerability, the ability to maintain peginterferon therapy during the antiviral treatment phase, and pharmacokinetic analysis. The planned sample size for the study was 160 subjects, with 40 subjects randomised to each treatment group. The sample size was estimated assuming a placebo response rate of 20% and an active response rate of 60%. The power to detect the anticipated treatment effect was 90% at the overall 5% level of significance (two-sided).

With regard to efficacy results, based on subjects evaluable for efficacy, eltrombopag increased platelet counts to ≥100Gi/L at Week 4 in a dose-dependent manner; 0/18 (0%, placebo), 9/12 (75%, 30 mg), 15/19 (79%, 50 mg), and 20/21 (95%, 75 mg) evaluable subjects achieved the primary endpoint ($p<0.0001$ for treatment effect). The median platelet counts after 4 weeks treatment were 53 Gi/L in the placebo group, 125Gi/L in the 30 mg group, 212Gi/L in the 50 mg group and 204Gi/L in the 75 mg group. The highest response rate was observed in the eltrombopag 75 mg group. Although subjects in both baseline strata responded to treatment with eltrombopag, subjects with a baseline platelet count of 50 to <70Gi/L had higher response rates compared to subjects with a baseline platelet count of 20 to 50Gi/L. At the end of 4 weeks treatment with eltrombopag, the proportion of subjects with platelet levels >200Gi/L increased in a dose-dependent manner and no subject in the placebo group had platelet levels of >200Gi/L.

With regard to safety results, the overall incidence of adverse events for the entire study (including both Parts 1 and 2 and the follow-up period) was higher in the eltrombopag-treatment groups than in the placebo-treatment group. In Part 1, the incidence of adverse events was similar across all 4 treatment groups. The most frequently occurring adverse events occurring with eltrombopag during Part 1 of the study were headache, dry mouth, upper abdominal pain and nausea, which were predominantly of mild severity. None of the adverse events occurred in a dose dependent manner. In the antiviral phase, adverse events were consistent with those associated with peginterferon-based therapy. One death occurred in a subject randomised to treatment with placebo. The death was associated with serious adverse events (SAEs) of abdominal pain and renal failure. The investigator considered the death unrelated to study medication. Other SAEs that occurred during the treatment phase of the study included thrombocytopenia (30 mg treatment group) during the antiviral phase, ascites (30 mg treatment group) during the antiviral phase, and retinal exudates (75 mg treatment group) during the antiviral phase. Neither the ascites nor the retinal exudates were considered by the investigator as related to study medication administration. During the post-treatment follow-up period, 2 subjects had SAEs of cataracts (30 mg and 75 mg treatment groups) and one subject had an SAE of myositis (50 mg treatment group).

6.2. Analyses performed across trials (pooled analyses and meta-analyses)

Pooled data was available for the 2 pivotal studies, TPL103922 (ENABLE 1) and TPL108390 (ENABLE 2). Given the almost identical design of these 2 studies, pooled data was available for both the primary and secondary efficacy endpoints as follows:

For the primary efficacy endpoint, the pooled results demonstrated a clinically meaningful and statistically significantly greater proportion of patients treated with eltrombopag achieved SVR compared to the placebo arm (placebo: 13%; eltrombopag: 21%; p=0.0004). Results are included below.

Table 8. Primary analysis. Sustained Virologic Responses (ITT Population).

	ENABLE 1		ENABLE 2	
	Placebo (N=232)	Eltrombopag (N=450)	Placebo (N=253)	Eltrombopag (N=506)
Sustained Virologic Response, n (%) Yes	33 (14)	104 (23)	32 (13)	97 (19)
Percentage difference[a] (95% CI) [%]	7.9 (2.4, 13.4)		6.0 (1.2, 10.9)	
P-value[b]	0.0064		0.0202	

Data Source: m2.7.3, Section 3.2.2
Note: Primary analysis uses planned HCV RNA assessments within the protocol-specified visit window
a. Adjusted for the actual strata: HCV genotype, baseline platelet count, and HCV RNA. Breslow Day test for homogeneity of treatment effect, p=0.7420 (ENABLE 1) or p=0.5461 (ENABLE 2)
b. Stratified CMH chi-square test adjusted for the randomization strata

Table 9. Univariate Analysis of Sustained Virologic Response for Actual Strata for Subjects with Successful Responses (Pooled Data, ITT Population).

	Placebo (N=485)	Eltrombopag (N=956)	Percentage Difference (95% CI)[a] [%]	P-value for Interaction[b]
Actual HCV RNA Genotype, n (%)				
Genotype 2/3	37 (25)	102 (35)	10.2 (1.4, 19.0)	0.5139
Genotype non 2/3	28 (8)	99 (15)	6.5 (2.5, 10.5)	
Actual Platelet Count, n (%)				
<50 Gi/L	15 (11)	53 (20)	7.6 (1.0, 14.2)	0.4586
≥50 Gi/L	50 (14)	148 (21)	7.0 (2.6, 11.3)	
Actual HCV RNA, n (%)				
<800,000 IU/mL	45 (18)	119 (24)	5.3 (-0.2, 10.8)	0.0593
≥800,000 IU/mL	20 (8)	82 (18)	8.6 (3.8, 13.4)	

Data Source: m2.7.3, Section 3.2.2
a. Adjusted for the study and actual strata: HCV genotype, baseline platelet count, and HCV RNA
b. P-value is a test of the null hypothesis of homogeneity (i.e., no treatment-by-subgroup interaction). Logistic regression including study, treatment, actual strata, and corresponding treatment by stratum interaction

For the secondary efficacy endpoint, the response to eltrombopag during OL treatment (Part 1) was similar in both studies with 97% and 96% of subjects in ENABLE 1 and ENABLE 2, respectively, achieving a platelet count that would allow the initiation of antiviral therapy. Platelet counts began to rise within the first week of treatment with eltrombopag, and the median time to achieve the target platelet count (≥90 Gi/L for ENABLE 1 or ≥100 Gi/L for ENABLE 2) was about 2 weeks, with over 75% of subjects achieving these target platelet counts within the first 4 weeks of treatment.

During the DB phase, there was a statistically significant benefit observed between the treatment groups for other antiviral milestones such as EVR, cEVR, ETR, and SVR12. At the end of treatment, 48% (ENABLE 1) and 38% (ENABLE 2) of subjects randomised to the eltrombopag arm were HCV RNA negative, significantly more than in the respective placebo arms (37% for ENABLE 1and 23% for ENABLE 2). However, due to the limited efficacy of the antiviral regimen, approximately 50% of subjects in both treatment groups had relapsed at the time SVR was assessed 6 months later. In both studies, eltrombopag treatment was associated with a significantly lower proportion of antiviral dose reductions (peginterferon and/or ribavirin) compared with placebo subjects. A greater proportion of eltrombopag-treated subjects had no dose reductions compared with placebo treated subjects. In the pooled analysis, a higher proportion of eltrombopag subjects (45%) completely avoided any antiviral therapy dose reduction compared with placebo subjects (27%), with a treatment difference of 17.1% (95% CI = 12.0, 22.1, p<0.0001).

The median time to the first peginterferon dose reduction was longer for eltrombopag subjects compared to placebo subjects in both studies (hazard ratio of 0.41 [95% CI = 0.33, 0.52] for ENABLE 1 and 0.39 [95% CI = 0.30, 0.49] for ENABLE 2; 2-sided stratified log rank test, p<0.0001). The differences were most pronounced during the first 12 weeks of antiviral therapy in both studies. The proportion of subjects in both studies who prematurely discontinued antiviral therapy (peginterferon and/or ribavirin) was significantly lower in the eltrombopag group (41% and 48%) compared to the placebo group (56% and 65%, respectively; p=0.0001 for ENABLE 1 and p<0.0001 for ENABLE 2). For the pooled data, significantly fewer subjects treated with eltrombopag prematurely discontinued antiviral therapy compared to the placebo group (45% versus 60%, p<0.0001). The median platelet counts at the start of antiviral therapy were similar in both treatment groups for both studies (128 to 140 Gi/L) and the same overall pattern of platelet response was observed in both studies. Median platelet counts began falling after initiation of antiviral therapy and stabilizing within approximately 4 weeks. Median platelet counts remained near the Week 4 values (placebo: 48 Gi/L; eltrombopag: 97 Gi/L) for the remainder of DB treatment in both studies.

Results for secondary efficacy endpoints are included below.

Table 10. Initiation of Antiviral Therapy (Safety population).

	ENABLE 1	ENABLE 2
	Eltrombopag (N=715)	Eltrombopag (N=805)
Initiation of Antiviral Therapy, n (%)		
Yes	680 (95)	759 (94)
95% CI [%][a]	(93, 97)	(92, 96)
Dose of Eltrombopag Enabling Initiation of Antiviral Therapy, n (%)		
25 mg	451 (63)	443 (55)
50 mg	176 (25)	208 (26)
75 mg	39 (5)	77 (10)
100 mg	14 (2)	31 (4)
Did not initiate antiviral therapy[b,c]	35 (5)	46 (6)

Data Source: m2.7.3, Section 3.2.1

a. Exact 95% CI based on binomial distribution

b. 11 subjects in ENABLE 1 had insufficient platelet response (<90 Gi/L), 9 subjects experienced an AE, 7 subjects withdrew due to investigator discretion, 3 subjects withdrew consent, 2, subjects were lost to follow-up, and 1 subject had a protocol deviation; 2 subjects were randomized but withdrew consent prior to receiving antiviral treatment

c. 13 subjects in ENABLE 2 had insufficient platelet response (<100 Gi/L), 5 subjects experienced an AE, 8 subjects withdrew due to investigator discretion, 3 subjects withdrew consent, 12 subjects were lost to follow-up, and 5 subjects had a protocol deviation

Table 11. Other Antiviral Endpoints (ITT Population).

	ENABLE 1		ENABLE 2	
	Placebo (N=232)	Eltrombopag (N=450)	Placebo (N=253)	Eltrombopag (N=506)
Early Virologic Response (EVR), n (%)	115 (50)	297 (66)	103 (41)	313 (62)
Percentage difference (95% CI)[a] [%]	16.7 (9.2 , 24.1)		20.7 (13.6, 27.8)	
P-value[b]	<0.0001		<0.0001	
End of Treatment Response (ETR), n (%)	86 (37)	214 (48)	59 (23)	190 (38)
Percentage difference (95% CI)[a] [%]	10.7 (3.3, 18.1)		13.1 (6.9, 19.4)	
P-value[b]	0.0080		<0.0001	

Data Source: m2.7.3, Section 3.2.2

a. Adjusted for the actual strata: HCV genotype, baseline platelet count and HCV RNA stratum.

b. Stratified CMH Chi-squared test adjusted for the randomization strata

Table 12. Summary of Antiviral Therapy Dose Reductions (ITT Population).

	ENABLE 1		ENABLE 2	
	Placebo (N=232)	Eltrombopag (N=450)	Placebo (N=253)	Eltrombopag (N=506)
Any Antiviral Therapy Dose Reductions[a], n (%)	n=232	n=450	n=253	n=506
0	65 (28)	195 (43)	68 (27)	231 (46)
1	57 (25)	93 (21)	76 (30)	101 (20)
2	55 (24)	56 (12)	40 (16)	75 (15)
3	26 (11)	49 (11)	34 (13)	47 (9)
>3	29 (13)	57 (13)	35 (14)	52 (10)
P-value[b]	0.0029		<0.0001	

Data Source: m2.7.3, Section 3.2.2

a. Dose reduction of peginterferon and/or ribavirin; interferon and ribavirin reduced at the same time for a subject was counted as 2 dose reductions

b. Wilcoxon rank p-value

Figure 1. Median Time to First Peginterferon Dose Reduction (Pooled data, ITT Population).

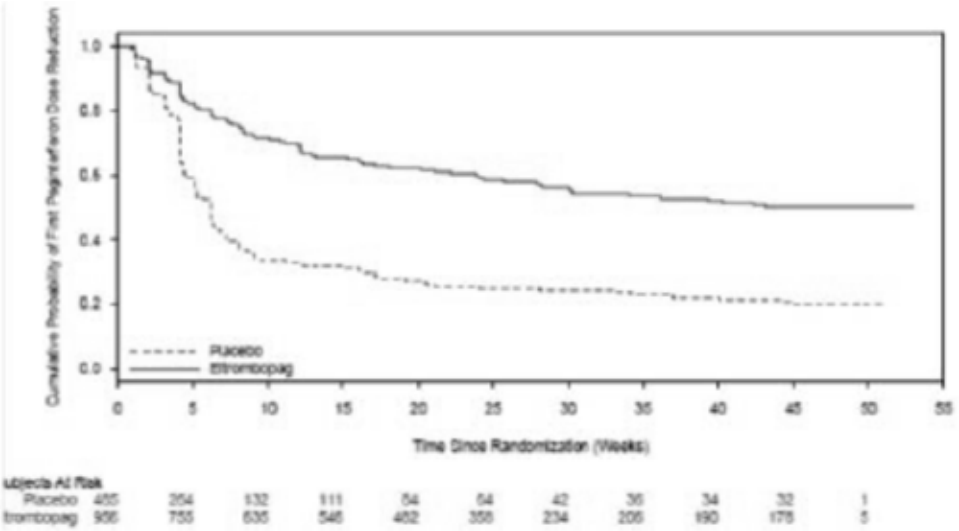
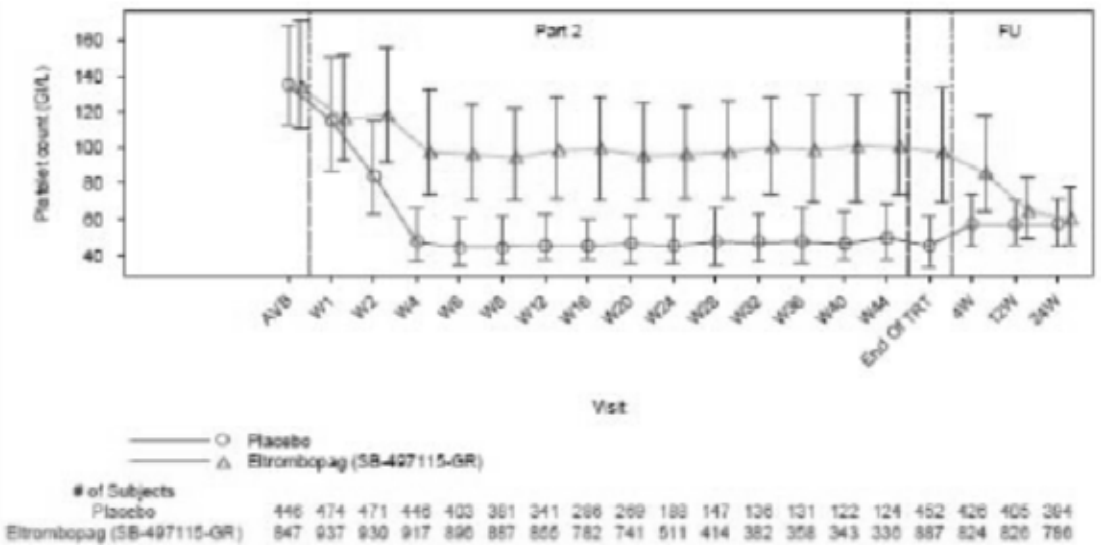


Figure 2. Median Platelet Counts during DB eltrombopag Treatment (Pooled data, ITT Population).



6.3. Evaluator's conclusions on clinical efficacy

Information on clinical efficacy for the proposed indication was provided by 2 pivotal studies, ENABLE 1 and ENABLE 2, as well as one supporting study, TPL102357. The pivotal studies had identical study designs and differed only in the pegylated interferon (peginterferon) used. They were global, multicenter, two-part studies that used a randomised withdrawal design. They consisted of an open-label (OL), Pre-Antiviral Treatment Phase (Part 1) and a randomised, double-blind (DB), placebo-controlled, Antiviral Treatment Phase (Part 2). Subjects entered the studies with a platelet count of <75 Gi/L and were stratified at baseline by platelet count, level of HCV RNA at screening and HCV genotype.

During Part 1, all subjects in ENABLE 1 and ENABLE 2 received eltrombopag dosed once daily with the objective of increasing platelet counts to the required threshold to initiate antiviral therapy (≥90 Gi/L to initiate peginterferon alfa-2a plus ribavirin in ENABLE 1 and ≥100 Gi/L to initiate peginterferon alfa-2b plus ribavirin in ENABLE 2). The starting dose of eltrombopag was 25 mg once daily for 2 weeks. Dose escalations could occur every 2 weeks up to a maximum of 100 mg eltrombopag. The maximal time subjects could receive open-label eltrombopag was 9 weeks. Subjects not randomised to Part 2 were withdrawn from OL eltrombopag and asked to attend the post-treatment follow-up visits. Once eligible for Part 2, subjects in ENABLE 1 and ENABLE 2 were randomised 2:1 to either continue on the same dose of eltrombopag from OL treatment or receive a matched placebo. These DB treatments were given in combination with antiviral therapy for up to 48 weeks (dependent on HCV genotype). All subjects in ENABLE 1 and ENABLE 2 were to attend post-treatment follow-up visits up to 24 weeks. At the 24 week follow-up visit, SVR was assessed to determine the benefit of the completed treatment regimen.

Guidance on assessment of treatment regimes for chronic hepatitis C is provided in the European Union *Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C*.[2] While there is no specific guidance on supportive agents such as eltrombopag , the overall principles in terms of response of HCV to treatment are applicable. The design of the pivotal studies was consistent with these guidelines. As such, sustained virologic response (SVR) was chosen as the primary endpoint for the pivotal studies. A subject was classified as having achieved SVR only if the subject was a responder at the end of treatment and all subsequent planned visits through to 24 weeks follow-up after completing treatment (for HCV genotype subgroups, 24 weeks after completing treatment corresponds to Week 48 for genotype 2/3, and Week 72 for genotype non 2/3 or genotype 2/3 who received 48 weeks of treatment) and if a subject had a positive HCV RNA ("blip") between two visits with undetectable HCV RNA, the subject was considered a sustained virologic responder provided that the detectable HCV RNA was of the same order of magnitude as the limit of detection. Both pivotal studies were adequately powered to provide statistically meaningful results.

Both studies demonstrated that a greater proportion of eltrombopag subjects achieved SVR than did placebo subjects and this result was statistically significant. In the pooled results, a clinically meaningful and statistically significantly greater proportion of patients treated with eltrombopag achieved SVR compared to the placebo arm (placebo: 13%; eltrombopag: 21%; p=0.0004). The response to eltrombopag during OL treatment (Part 1) was similar in both studies with 97% and 96% of subjects in ENABLE 1 and ENABLE 2, respectively, achieving a platelet count that would allow the initiation of antiviral therapy. Platelet counts began to rise within the first week of treatment with eltrombopag and the median time to achieve the target platelet count (≥90 Gi/L for ENABLE 1 or ≥100 Gi/L for ENABLE 2) was about 2 weeks, with over 75% of subjects achieving these target platelet counts within the first 4 weeks of treatment. At the end of treatment, 48% (ENABLE 1) and 38% (ENABLE 2) of subjects

[2]EMEA/CHMP/51240/2011.
<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500102109.pdf>

randomised to the eltrombopag arm were HCV RNA negative, significantly more than in the respective placebo arms (37% for ENABLE 1and 23% for ENABLE 2).

TPL102357 was a double-blind, randomised, placebo-controlled, multi-centre, dose-ranging, parallel group, Phase II study to assess efficacy, safety/tolerability, and pharmacokinetics of a thrombopoietin receptor agonist, SB-497115-GR (eltrombopag), when administered as 30, 50, and 75 mg once daily for 16 weeks in subjects with chronic hepatitis C-related thrombocytopenia who are potential candidates for antiviral treatment with pegylated interferon and ribavirin. A total of 74 subjects were enrolled, despite the statistical plan allowing for 160 subjects. No rationale for this was stated and only limited information on this study was provided. Eltrombopag increased platelet counts to ≥100Gi/L at Week 4 in a dose-dependent manner; 0/18 (0%, placebo), 9/12 (75%, 30 mg), 15/19 (79%, 50 mg) and 20/21 (95%, 75 mg) evaluable subjects achieved the primary endpoint ($p<0.0001$ for treatment effect). Given the above statistical limitations, this should be interpreted with caution.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

· Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

Assessment of safety and tolerability of eltrombopag in comparison with placebo, as measured by the nature and frequency of adverse events (AEs), laboratory abnormalities, ocular examinations, 12-lead electrocardiograms (ECG).

· Pivotal studies that assessed safety as a primary outcome

Not applicable.

· Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

Study TPL 102357 provided data on monitoring of adverse events and laboratory analyses performed throughout the course of the study, including complete blood counts with differentials, blood chemistries, urinalysis, electrocardiograms, vital signs, spleen examinations and qualitative and quantitative toxicities associated with this treatment regimen. Ocular examinations were completed throughout the study. Subjects completed a follow-up visit 4 weeks after the last eltrombopag dose. Subjects were also followed up 6 months post last dose of study medication for assessment of any ocular changes. In addition, blood samples were collected for pharmacokinetic analysis.

· Other studies evaluable for safety only

Not applicable.

7.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

7.3. Patient exposure

Table 13. Tabulation of subjects contributing to the Safety Analysis of eltrombopag.

GSK Study Number	Open-label Study Treatment	Double-Blind Study Treatment	
		Placebo	Eltrombopag
TPL103922 (ENABLE 1)	715	232	449
TPL108390 (ENABLE 2)	805	252	506
TPL102357 Part1	NA	18	56
TPL102357 Part2	NA	2	45

Table 14. Description and dosing of studies evaluating eltrombopag therapy in HCV.

GSK Study Number	Study Design / Primary Objective	Dosing and Administration	Randomized
Pivotal Phase III Studies			
TPL103922 (ENABLE 1)	Part 1: OL pre-antiviral treatment phase Part 2: DB, randomized, placebo controlled antiviral treatment phase, Improvement in SVR for eltrombopag compared to placebo, measured 6 months post last dose of all investigational products.	Part 1: Eltrombopag 25 mg, 50 mg, 75 mg and 100 mg; daily oral dosing until platelets ≥90Gi/L, with dose escalation every 2 weeks up to a maximum 9 weeks of treatment Part 2: Eltrombopag dose from Part 1 or matching placebo; daily oral dosing in conjunction with pegIFN (alfa-2a)+ribavirin antiviral therapy for up to 48 weeks	OL phase: Eltrombopag 716[a] DB phase: Placebo:232 Eltrombopag: 450[b]
TPL108390 (ENABLE 2)	Part 1: OL pre-antiviral treatment phase Part 2: DB, randomized, placebo controlled antiviral treatment phase, Improvement in SVR for eltrombopag compared to placebo, measured 6 months post last dose of all investigational products.	Part 1: Eltrombopag 25 mg, 50 mg, 75 mg and 100 mg; daily oral dosing until platelets ≥100Gi/L, with dose escalation every 2 weeks up to a maximum 9 weeks of treatment Part 2: Eltrombopag dose from Part 1 or matching placebo; daily oral dosing in conjunction with pegIFN (alfa-2b)+ribavirin antiviral therapy for up to 48 weeks.	OL phase: Eltrombopag:805 DB phase: Placebo:253[b] Eltrombopag: 506
Supportive Phase II Study			
TPL102357	Part 1: DB, randomized, placebo controlled parallel group study, Increase in platelets to ≥70Gi/L or ≥ 100Gi/L by Week 4.	Part 1: Eltrombopag 30 mg, 50 mg, 75 mg or matching placebo; daily oral dosing for 4 weeks Part 2: Eltrombopag 30 mg, 50 mg, 75 mg or matching placebo; daily oral dosing in conjunction with pegIFN (alfa 2a or alfa 2b) +ribavirin antiviral therapy for 12 weeks	Part 1: Placebo: 18 Eltrombopag: 56 Part 2: Placebo: 4[c] Eltrombopag: 45

a. One subject in ENABLE 1 randomized to Part 1 did not receive OL treatment. This subject is not included in the Safety OL Population.

b. One subject in each of the ENABLE 1 and ENABLE 2 studies randomized to Part 2 did not receive DB treatment. These 2 subjects are not included in the Safety DB Population but are included in the ITT Population.

c. Two placebo subjects in TPL102357 were enrolled in Part 2 in error and were withdrawn.

Table 15. Safety populations

Study Population	TPL103922 (ENABLE 1)		TPL108390 (ENABLE 2)		TPL102357		Total
	Part 1	Part 2	Part 1	Part 2	Part 1	Part 2	
Safety OL Population	715	--	805	--	--	--	1520
Safety DB Population	--	681	--	758	--	--	1439
Safety Phase II/III Population	--	681	--	758	--	47	1486
Overall Safety Population	715	--	805	--	56[a]	--	1576
Intent-to-Treat Population	--	682	--	759	--	--	1441

a. 74 subjects were enrolled in Part 1 of study TPL102357 but only the 56 subjects who received eltrombopag are included in the Overall Safety Population

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Pivotal studies

In the OL Phase, headache was the only AE that occurred in ≥5% of subjects. The incidence of AEs in the on-treatment plus 30 days follow-up period was similar between the treatment groups. The most common AEs included anaemia, neutropaenia, pyrexia, fatigue, headache, nausea, diarrhoea, decreased appetite and influenza like illness. The distribution of AEs by maximum Division of Acquired Immunodeficiency Syndrome (DAIDS) Grade was similar between treatment groups, although the proportion of subjects reporting maximum Grade 3/Grade 4 AEs up to 30 days post-treatment was 5% higher on placebo (54%) than on eltrombopag (49%). This difference was mainly due to Grade 3/Grade 4 events of thrombocytopenia (placebo: 27%; eltrombopag: 5%) Results are included below.

Table 16. Adverse events on-treatment plus 30 days follow-up occurring in 10% or more subjects in the eltrombopag group and higher than placebo group (Safety DB population).

Preferred term	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	461 (95)	905 (95)
Anaemia	168 (35)	384 (40)
Pyrexia	114 (24)	284 (30)
Fatigue	113 (23)	263 (28)
Headache	97 (20)	202 (21)
Nausea	69 (14)	179 (19)
Diarrhoea	51 (11)	178 (19)
Decreased appetite	67 (14)	172 (18)
Influenza like illness	76 (16)	170 (18)
Asthenia	63 (13)	153 (16)
Insomnia	72 (15)	151 (16)
Cough	60 (12)	141 (15)
Pruritus	61 (13)	139 (15)
Chills	44 (9)	130 (14)
Myalgia	48 (10)	116 (12)
Alopecia	27 (6)	100 (10)
Oedema peripheral	23 (5)	92 (10)

7.4.1.2. Other studies

The overall incidence of adverse events for TPL102357 (including both Parts 1 and 2 and the follow-up period) was higher in the eltrombopag treatment groups than in the placebo treatment group. In Part 1, the incidence of adverse events was similar across all 4 treatment groups. The most frequently occurring adverse events occurring with eltrombopag during Part 1 of the study were headache, dry mouth, upper abdominal pain and nausea, which were predominantly of mild severity. None of the adverse events occurred in a dose-dependent

manner. In the antiviral phase, adverse events were consistent with those associated with peginterferon-based therapy.

7.4.2. Deaths and other serious adverse events

7.4.2.1. Pivotal studies

There were 2 AEs reported during the OL Phase with a fatal outcome: one subject with hepatorenal syndrome died on Day 46 of treatment and one subject died from a hepatic neoplasm more than one year after study completion. Both events were considered unrelated to eltrombopag.

In the DB phase, there was a 3% incidence of death in the placebo group in ENABLE 1, compared to 2% in the eltrombopag arm. In ENABLE 2, there was a 2% incidence of death in the placebo group, compared to 4% in the eltrombopag group. For the pooled data from the 2 Phase III studies, 39 subjects (3%) with 57 fatal AEs died during the on-treatment plus 6 months follow-up period: 10 (2%) in the placebo group and 29 (3%) in the eltrombopag group. Of these, 8 of the subjects in the placebo group (80%) and 22 of the subjects in the eltrombopag group (76%) had a baseline MELD score ≥10. The most common causes of death in both treatment groups for both studies were events suggestive of hepatic decompensation, such as hepatic failure, variceal bleeding, ascites, gastrointestinal (GI) bleeding and infections. Seven placebo treated subjects (1%) and 23 eltrombopag treated subjects (2%) had AEs with fatal outcome that started during the on-treatment plus 30 days timeframe. Most of these deaths (62%) were not related to any IP and only 1 death was considered related solely to DB treatment. The incidence of deaths, taking into account the observation time, was similar between both treatment arms (placebo: 2.3/100 patient years, 95% CI [0.88,3.72]; eltrombopag: 2.93/100 patient years, 95% CI [1.86,4.00]). Furthermore, in the HCV genotype 2/3 subgroup, for which the treatment duration was very similar between the treatment groups (about 6 months), the death rates were similar (placebo: 3%; eltrombopag: 2%).

For other SAE, seventeen subjects (1%) reported 18 SAEs during the OL Phase. The only SAEs that occurred in more than 1 subject were malignant hepatic neoplasm (3 subjects) and pneumonia (2 subjects).There was a 5% higher incidence of SAEs in the eltrombopag group (20%) compared with the placebo group (15%) in the on-treatment plus 30 days follow-up period, for both of the ENABLE studies and also for the pooled data set. The most common SAE in both treatment groups was hepatic neoplasms. SAEs related to the Gastrointestinal (GI) and Hepatobiliary disorders system organ classes (SOC) occurred ≥2% more frequently in the eltrombopag group compared with the placebo group. SAEs related to GI disorders occurred in 6% of eltrombopag subjects and 4% of placebo subjects; SAEs related to Hepatobiliary disorders occurred in 3% of eltrombopag subjects and <1% of placebo subjects. All other SAEs by SOC occurred at differences of 1% or less between treatment groups. When SAEs were analysed based on observation time (on-treatment plus 30 days), the incidence rates (IR) were similar between the treatment groups (placebo: 28.76/100 PY, CI [22.12, 35.40]; eltrombopag: 31.47/100 PY, CI [26.98, 35.96]). A summary of SAE appears below.

Table 17. Serious Adverse Events on-treatment plus 30 days follow-up during DB Phase in 0.5% or more if subjects in either treatment group (Safety DB Population).

Preferred term	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	72 (15)	189 (20)
Hepatic neoplasm malignant	6 (1)	20 (2)
Hepatic encephalopathy	0	12 (1)
Ascites	4 (<1)	10 (1)
Cataract	2 (<1)	10 (1)
Hepatic failure	1 (<1)	10 (1)
Oesophageal varices haemorrhage	4 (<1)	10 (1)
Pneumonia	6 (1)	10 (1)
Gastrointestinal haemorrhage	0	7 (<1)
Anaemia	3 (<1)	6 (<1)
Upper gastrointestinal haemorrhage	0	6 (<1)
Peritonitis bacterial	2 (<1)	5 (<1)
Pyrexia	1 (<1)	5 (<1)
Cellulitis	3 (<1)	3 (<1)

7.4.2.2. Other studies

In TPL102357, one death occurred in a subject randomised to treatment with placebo. The death was associated with serious adverse events (SAEs) of abdominal pain and renal failure. The investigator considered the death unrelated to study medication. Other SAEs that occurred during the treatment phase of the study included thrombocytopenia (30 mg treatment group) during the antiviral phase, ascites (30 mg treatment group) during the antiviral phase and retinal exudates (75 mg treatment group) during the antiviral phase. Neither the ascites nor the retinal exudates were considered by the investigator as related to study medication administration. During the post-treatment follow-up period, 2 subjects had SAEs of cataracts (30 mg and 75 mg treatment groups) and one subject had an SAE of myositis (50 mg treatment group).

7.4.3. Discontinuation due to adverse events

7.4.3.1. Pivotal studies

Fourteen subjects (<1%) reported 27 AEs leading to permanent discontinuation of eltrombopag during the OL Phase. The only events occurring in 2 or more subjects were increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST) and peripheral oedema. During the DB phase, a greater proportion of placebo subjects (29%) discontinued investigational product due to an AE compared with eltrombopag treated subjects (22%). The difference was mainly due to events of thrombocytopenia. Other haematological toxicities, which are expected with antiviral treatment, were the most common reasons for discontinuation in both treatment groups and the incidences were similar across the treatment groups. The Phase III studies followed the approved labels for peginterferon and ribavirin for therapy discontinuation due to hematologic toxicities (anaemia, thrombocytopenia, and neutropaenia).

7.4.3.2. Other studies

Limited information only was provided.

7.5. Laboratory tests

7.5.1. Liver function

7.5.1.1. Pivotal studies

There was a frequent occurrence of indirect bilirubin elevations observed in ENABLE study participants receiving eltrombopag. Eltrombopag is known to inhibit UGT1A1, the enzyme responsible for glucuronidation of bilirubin in humans. Eltrombopag is also an inhibitor of OATP1B1, which is one of the hepatic transporters for bilirubin. Indirect hyperbilirubinaemia is likely to be exacerbated by co-administration of ribavirin, which also induces haemolytic anaemia in up to 40% of HCV patients receiving antiviral therapy. Consequently, a higher incidence of bilirubin elevations occurred in the eltrombopag group compared to the placebo group. Elevations of direct bilirubin in conjunction with ALT occurred more often in placebo subjects than in the eltrombopag group.

There was no evidence to indicate eltrombopag as a cause for drug-induced liver toxicity (DILI). With the exception of bilirubin abnormalities (largely due to increases in indirect bilirubin) the distribution of all other combinations of laboratory abnormalities and the pattern of liver chemistry abnormalities were similar in the treatment groups, despite the longer observation period and the higher doses of antiviral therapy with peginterferon and ribavirin for eltrombopag-treated subjects. Few subjects in either treatment group met the protocol specified criteria for discontinuation of study medication due to liver chemistry elevations during the on-treatment plus 30 days followup period (placebo: 3 subjects; eltrombopag: 3 subjects). Results are included below.

Table 18. Hepatobiliary parameters on-treatment plus 30 days follow-up during DB Phase (Safety DB Phase).

	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
ALT or AST >3x ULN and total bilirubin >2x ULN and (Alkaline Phosphatase <2x ULN or missing)	31 (6)	96 (10)
With fractionated bilirubin ≥35% direct	15 (3)	22 (2)
ALT or AST >3x ULN and total bilirubin >2x ULN	35 (7)	96 (10)
With fractionated bilirubin ≥35% direct	20 (4)	22 (2)
ALT or AST >3x ULN and total bilirubin >1.5x ULN	61 (13)	166 (17)
With fractionated bilirubin ≥35% direct	30 (6)	36 (4)
ALT or AST >20x ULN	0	0
ALT or AST >10x ULN	4 (<1)	4 (<1)
ALT or AST >5x ULN	43 (9)	74 (8)
ALT or AST >3x ULN	182 (38)	327 (34)
ALT >20x ULN	0	0
ALT >10x ULN	2 (<1)	1 (<1)
ALT >5x ULN	13 (3)	28 (3)
ALT >3x ULN	83 (17)	143 (15)
AST >20x ULN	0	0
AST >10x ULN	4 (<1)	3 (<1)
AST >5x ULN	40 (8)	67 (7)
AST >3x ULN	172 (36)	305 (32)
Total bilirubin >2x ULN	120 (25)	518 (54)
Total bilirubin >1.5x ULN	243 (50)	730 (76)
Alkaline Phosphatase >1.5x ULN	66 (14)	173 (18)

A 6% higher proportion of subjects experienced an event suggestive of hepatic decompensation in the eltrombopag treatment group compared with the placebo group, particularly events of ascites and hepatic encephalopathy. Compared with the placebo group, a lower proportion of the events in the eltrombopag group were fatal, led to withdrawal of study medication or led to withdrawal from study. A higher proportion of events suggestive of hepatic decompensation were reported as resolved in the eltrombopag group.

7.5.1.2. Other studies

Limited information only was provided.

7.5.2. Kidney function

7.5.2.1. Pivotal studies

Based upon AE, electrolyte and renal monitoring data, there was no evidence for clinically relevant eltrombopag-related renal toxicity.

7.5.2.2. Other studies

Limited information only was provided.

7.5.3. Other clinical chemistry

7.5.3.1. Pivotal studies

No significant trends were identified.

7.5.3.2. Other studies

Limited information only was provided.

7.5.4. Haematology

7.5.4.1. Pivotal studies

No significant new trends were identified. Overall, abnormalities in the haematology parameters were balanced between treatment groups with the exception of increases to Division of AIDS (DAIDS) Grade 4 lymphocytes, which occurred more frequently with eltrombopag than placebo subjects.

7.5.4.2. Other studies

Limited information only was provided.

7.5.5. Electrocardiograph

7.5.5.1. Pivotal studies

During the DB Phase of the study, subjects were instructed to have a 12-lead electrocardiogram (ECG) at antiviral baseline, every 12 weeks during treatment, at their end-of-treatment/withdrawal visit and 24 week follow-up visit. There were 3 possible results regarding the interpretation of the ECGs: "Normal", or "Abnormal - not clinically significant", or "Abnormal - clinically significant". Whether or not a finding was clinically significant was determined by the investigator. Most subjects who had an ECG recorded at antiviral baseline had normal or abnormal, not clinically significant results. The pattern of ECG results during the DB Phase was similar between the treatment groups, with most subjects having a worst post baseline ECG reading of 'normal' or 'abnormal – not clinically significant' (82% for both placebo and eltrombopag subjects).

From information provided by the sponsor, eltrombopag had no effect on cardiac repolarisation in a previous Thorough QTc study conducted in healthy subjects receiving eltrombopag doses of 50 mg and 150 mg once daily for 5 days. Because patients with HCV infection achieve higher plasma eltrombopag exposure than healthy subjects and patients with liver disease are more susceptible to QTc prolongation, assessment of the potential impact of eltrombopag on the QTc interval in subjects with HCV was incorporated into the Phase III clinical trials (TPL103922 and TPL108390). Based on the final Cp-ddQTcF model, simulations were performed to predict ddQTcF at maximum plasma concentration (C_{max}) for therapeutic and supratherapeutic eltrombopag doses. The results of simulation, indicated that the upper bound of the 90% CI for the mean ddQTcF was <10 ms at therapeutic doses from 25 mg to 100 mg QD, and at dose of 200 mg QD, a supratherapeutic dose that is twice the maximum eltrombopag dose

administrated in subjects with HCV. These results suggest that eltrombopag will not have a clinically significant effect on ddQTcF at a dose up to 200 mg QD.

7.5.5.2. Other studies

Limited information only was provided.

7.5.6. Vital signs

7.5.6.1. Pivotal studies

No significant trends were identified.

7.5.6.2. Other studies

Limited information only was provided.

7.5.7. Thromboembolic events

7.5.7.1. Pivotal studies

There were more TEEs (both arterial and venous) reported in the eltrombopag group compared to the placebo group. During the on-treatment plus 30 days follow-up period, 5 placebo subjects (1%) experienced events compared to 31 subjects (3%) in the eltrombopag group. Portal vein thrombosis was the most common TEE in both treatment groups (placebo: 2 subjects; eltrombopag: 12 subjects). Approximately 40% of all TEEs were detected as part of scheduled regular surveillance (Doppler of portal vein, ocular surveillance), and were not associated with clinical symptoms. The majority of TEEs in eltrombopag subjects resolved and most on-treatment events did not lead to discontinuation from antiviral treatment. Approximately one-third of the events in both treatment groups were reported as SAEs; there was 1 fatal event in the placebo group and 2 fatal events in the eltrombopag group due to suspected or confirmed TEEs. No specific relationship between the TEE event and time on-treatment or high proximal platelet counts was observed. Some subjects had additional risk factors for TEEs such as coronary or peripheral artery disease and tobacco use; in others the events were associated with other underlying disease or treatment factors such as hepatic coma, recent diuretic treatment, severe diarrhoea or vascular catheter placement. Subjects with baseline MELD score ≥10 or albumin ≤35 g/L had a higher incidence of thrombotic events compared to subjects with baseline MELD score <10 or albumin >35 g/L. Portal vein thrombosis events were the largest contributor to this higher incidence of thrombotic events in patients with poor baseline liver function.

7.5.7.2. Other studies

No TEEs occurred at any time during the open-label or antiviral parts of the Phase II study.

7.5.8. Cataracts

7.5.8.1. Pivotal studies

There was a higher overall occurrence of cataract events in the eltrombopag group (8%) compared with the placebo group (5%). Similar results were seen for the genotype non-2/3 subgroup for bilateral incidence (placebo: <1%; eltrombopag: 3%) and bilateral progression (placebo: <1%; eltrombopag: 2%). However, no meaningful difference was observed in the occurrence of cataract events for the genotype 2/3 subgroup, in which there was a similar duration of treatment between the placebo group and the eltrombopag group.

7.5.8.2. Other studies

Ocular examinations identified 4 subjects with cataracts. Three of these subjects had cataracts prior to the first ocular examination (in one subject a pre-existing cataract was observed post treatment) and 1 subject had a post-baseline report of cataract. In general, no pattern was observed in regard to the relationship to dose or duration of treatment with study medication.

All four subjects with reports of cataract had documented risk factors for cataract development. Of the 3 cataract cases that were identified prior to initiation of study medication, cataracts were reported to progress in two subjects (30 mg and 75 mg treatment groups) over the duration of the assessment period.

7.6. Postmarketing experience

Eltrombopag was first approved for marketing in the US on 20 November 2008 for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP). Based on latest data available from IMS (Intercontinental Medical Statistics) Health data, it is estimated that approximately 6,664 patient years of eltrombopag treatment have been prescribed worldwide as of December 2011. This calculation is based on available sales information volume and assumes a once-daily dose of 12.5 mg, 25 mg, 50 mg, or 75 mg tablets.

As of 31 March 2012, there were 2261 spontaneous and post marketing cases received from marketed use of eltrombopag. A total of 5215 spontaneous and post marketing AEs (serious and non serious) have been received from the marketed use of eltrombopag (2261 cases). A summary of adverse events appears below.

Table 19. Ten most frequent reported adverse events from spontaneous and postmarketing surveillance cases.

MedDRA Preferred Term	Adverse Events n(%)
All Preferred Terms	5215 (100)
Drug ineffective	865 (16.6)
Death	162 (3.1)
Platelet count decreased	152 (2.9)
Thrombocytopenia	73 (1.4)
Fatigue	65 (1.2)
Platelet count increased	64 (1.2)
Nausea[a]	63 (1.2)
Deep vein thrombosis[a]	61 (1.2)
Headache	56 (1.1)
Liver function test abnormal[a]	51 (1.0)
Idiopathic thrombocytopenic purpura	50 (1.0)

a. Adverse events included in the eltrombopag Core Safety Information.

As of 31 March 2012, there were 489 cases with a fatal outcome out of the 2261 cases reported from marketed usage of eltrombopag. A review of these cases of death reveals no significant new safety findings associated with the use of eltrombopag. In terms of hepatotoxicity, there were 206 cases identified in this search of the worldwide clinical safety database from 20 November 2008 through 31 March 2012. In general, most cases describe mild and transient elevations in liver function parameters, which resolved or improved following eltrombopag discontinuation or dose reduction. Some cases were of severe liver injury or liver failure in the setting of other co-morbid conditions such as sepsis leading to multi-organ failure or worsening liver function in patients with pre-existing liver disease (hepatitis, cirrhosis).

There were 210 cases reviewed that pertained to thromboembolic events from first approval of eltrombopag for chronic ITP in 20 November 2008 through 31 March 2012. The most frequently reported events in these 210 cases were deep vein thrombosis (58), pulmonary embolism (48), myocardial infarction (22), thrombosis (20), cerebrovascular accident (15), acute myocardial infarction (9), and portal vein thrombosis (9). The outcomes of the 210 cases were improved/resolved (81), resolved with sequelae (3), unresolved (24), worse (1), fatal (34), and unknown (67). The patients with a fatal thromboembolic event had multiple co morbidities including congestive heart failure, leukemia, diabetes, hypertension, coronary

artery disease, carotid arterial stenosis, and hyperlipidemia. In conclusion, an overall review of cases of thromboembolic events does not suggest any new trends or changes in incidence or severity of TEEs.

7.7. Safety issues with the potential for major regulatory impact

7.7.1. Liver toxicity

During the DB Phase on-treatment plus 30 day follow-up period, a higher proportion of eltrombopag subjects reported hepatobiliary events compared with placebo subjects. However, the proportion of AEs that led to withdrawal or were considered serious were similar for eltrombopag treated and placebo treated subjects. In addition, the majority of AEs resolved in both treatment groups.

In this patient population, 2 types of hepatobiliary events were noted to be of particular relevance: DILI and events suggestive of hepatic decompensation. The data do not indicate eltrombopag as a cause for DILI in this study. DILI requires evidence of hepatocellular injury (that is, greater incidence of ALT >3xULN in the treatment group than in the control group. A greater incidence of ALT >3x ULN was observed in the placebo group than in the eltrombopag group.

The safety results from this section show that hepatobiliary adverse events, events suggestive of hepatic decompensation and hepatobiliary laboratory abnormalities are common in the patient population studied, as expected for patients with HCV-induced liver cirrhosis. Safety findings reported more frequently on the eltrombopag-treatment group included events suggestive of hepatic decompensation, such as ascites and hepatic encephalopathy. The incidence of other events suggestive of hepatic decompensation (HCC and death), was similar between the treatment groups. It should be noted, however, that hepatic decompensation is a known risk in cirrhotic HCV patients receiving pegylated interferon and that subjects in the eltrombopag group received ≥60% more peginterferon and the median observation time for the eltrombopag group is longer than for subjects in the placebo-treatment group. In addition, events showing a higher frequency in the eltrombopag-treatment group can be observed as a complication of antiviral treatment with peginterferon and ribavirin and represent known complications of chronic HCV-infections occurring over time in patients with HCV-induced liver cirrhosis.

Overall, eltrombopag treated subjects were similar to placebo treated subjects with respect to several measures of hepatic function and prognosis, including Child-Pugh (CP) score, serum albumin values, INR (prothrombin time ratio) values, total bilirubin values and model for end-stage liver disease (MELD[3]) score.

7.7.2. Haematological toxicity

No significant haematological toxicity was noted for eltrombopag.

7.7.3. Serious skin reactions

No significant trend of skin reactions was noted.

7.7.4. Cardiovascular safety

Most subjects who had an ECG recorded at antiviral baseline had normal or abnormal, not clinically significant results. The pattern of ECG results during the DB Phase was similar between the treatment groups, with most subjects having a worst post baseline ECG reading of 'normal' or 'abnormal – not clinically significant' (82% for both placebo and eltrombopag

[3] A score that is used to rank the urgency for liver transplant. The worse your liver works, the higher your MELD score and the higher your position on the transplant list.

subjects). A greater proportion of eltrombopag subjects were considered to have a clinically significant change from baseline compared with placebo subjects.

Assessment of the potential impact of eltrombopag on the QTc interval in subjects with HCV was incorporated into the Phase III clinical trials (TPL103922 and TPL108390). As a result, eltrombopag is predicted to have no clinically significant effect on QTc intervals at either therapeutic or supratherapeutic dose in HCV subjects.

7.7.5. Unwanted immunological events

No significant trend of unwanted immunological events was noted.

7.8. Other safety issues

7.8.1. Safety in special populations

The pooled safety analyses were evaluated for the impact of intrinsic factors on AE incidence. Subgroup analyses were performed for the on-treatment plus 30 days post-treatment follow-up period for subjects in the Safety DB Population for the following:

- HCV Genotype: non-2/3 (n=990, 69%), 2/3 (n=445, 31%)
- Baseline MELD Score: <10 (n=805, 56%), ≥10 (n=613, 43%)
- Baseline albumin: ≤35 g/L (n=414, 29%), >35 g/L (n=1025, 71%)
- Fibrosis Score: F0/F1/F2 (n=125, 9%), F3/F4 (n=1141, 79%)
- Age: <65 years (n=1340, 93%), ≥65 years (n=99, 7%)
- Gender: Female (n=537, 37%), Male (n=902, 63%)
- Race: Eastern Asian heritage (n=145, 10%), other Asian heritage (n=186, 13%),
- White and other (n=1108, 77%)
- Body mass index (BMI): <30 (n=1026, 71%), ≥30 (n=406, 28%)

Subgroup analyses for the intrinsic factors age, gender, race, fibrosis score, and BMI did not show any meaningful differences from the overall Safety DB Population results. Patients with poor liver function at baseline (that is, MELD score ≥10 or albumin ≤35 g/L) were noted to be at an increased risk for adverse events.

Subjects with HCV genotype non-2/3 showed a safety profile very similar to the overall Safety DB Population but had a generally worse overall safety profile when compared with subjects with HCV genotype 2/3. For genotype 2/3 subjects, there were no clinically meaningful differences in the overall safety profile between the 2 treatment groups. The overall incidence of AEs was higher in the HCV genotype non-2/3 subgroup (97%) compared with the HCV genotype 2/3 subgroup (91%). Anaemia, pyrexia, fatigue, nausea, diarrhoea, oedema peripheral and blood bilirubin increased were reported more frequently (≥5% difference in treatment incidence) in the eltrombopag group compared with the placebo group for the HCV genotype non-2/3 group. For the HCV genotype 2/3 group, influenza-like illness, diarrhoea, and asthenia were reported more frequently (≥5% difference in treatment incidence) in the eltrombopag group compared with the placebo group. In the HCV genotype non-2/3 subgroup, more subjects died in the eltrombopag group (17 subjects, 3%) than in the placebo group (2 subjects, <1%). The incidence of deaths was similar between treatment groups for subjects with HCV genotype 2/3 (eltrombopag 2%, placebo 3%).

7.8.2. Safety related to drug-drug interactions and other interactions

When eltrombopag and rosuvastatin were coadministered in a clinical drug interaction study, there was increased plasma rosuvastatin exposure. Eltrombopag chelates with polyvalent

cations such as aluminium, calcium, iron, magnesium, selenium and zinc. Administration of a single 50 mg dose of eltrombopag with a standard high calorie, high fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{0-\infty}$ by 59% (90% CI: 54%, 64%)and C_{max} by 65% (90% CI: 59%, 70%).

7.8.3. Thromboembolic events

A 2% higher incidence of TEEs was observed in subjects treated in the eltrombopag treatment group compared with the placebo group. No specific temporal relationship between start of treatment and event of TEE was observed. Some subjects had additional risk factors for TEE such as coronary or peripheral artery disease and tobacco use, in others the events were associated with other underlying disease or treatment factors such as hepatic coma, recent diuretic treatment, severe diarrhoea or catheter placement. The majority of TEEs resolved and did not lead to discontinuation from antiviral treatment.

7.8.4. Cataracts

There was a higher incidence of progression of pre-existing baseline cataracts in the eltrombopag treatment group (4%) compared with the placebo group (2%), and a higher incidence of subjects with incident cataracts in the eltrombopag group (4%) compared with the placebo group (2%). Similar results were seen for the genotype non-2/3 subgroup (bilateral incidence (eltrombopag: 3%, placebo: <1%) and bilateral progression (eltrombopag: 2%, placebo: <1%), but this was not seen for the genotype 2/3 subgroup, in which there was a similar duration of treatment between the placebo group and the eltrombopag group.

7.9. Evaluator's overall conclusions on clinical safety

Information on clinical safety was available from the pivotal efficacy studies, supporting efficacy study, information previously submitted to TGA and post-marketing surveillance data submitted by the sponsor. There were no specific safety studies submitted.

Interpretation of the safety profile was complicated by the overall health status of the target population, especially those subjects with more severe baseline liver impairment and requiring more intensive therapy (and hence with more side-effects of treatment). In addition, the results from the efficacy studies indicated a proportion of patients who would have been unable to be treated previously because of low platelet counts, who could now be treated more aggressively. Given the role of eltrombopag, as a supportive care agent, patients would tend to receive more intensive anti-viral treatment and hence be more prone to side-effects.

The incidence of AEs in the on-treatment plus 30 days follow-up period was similar between the treatment groups. The most common AEs included anaemia, neutropaenia, pyrexia, fatigue, headache, nausea, diarrhoea, decreased appetite and influenza like illness. In terms of SAE, there was a 5% higher incidence of SAEs in the eltrombopag group (20%) compared with the placebo group (15%) in the on-treatment plus 30 days follow-up period, for both of the ENABLE studies and also for the pooled data set. The most common SAE in both treatment groups was hepatic neoplasms. SAEs related to the GI and Hepatobiliary disorders system organ classes (SOC) occurred ≥2% more frequently in the eltrombopag group compared with the placebo group.

With regard to deaths, for the pooled data from the 2 Phase III studies, 39 subjects (3%) with 57 fatal AEs died during the on-treatment plus 6 months follow-up period: 10 (2%) in the placebo group and 29 (3%) in the eltrombopag group. Of these, 8 of the subjects in the placebo group (80%) and 22 of the subjects in the eltrombopag group (76%) had a baseline MELD score ≥10. The most common causes of death in both treatment groups for both studies were events suggestive of hepatic decompensation, such as hepatic failure, variceal bleeding, ascites, GI bleeding, and infections.

Thromboembolic/thrombotic complications were observed more frequently in the eltrombopag treatment group than in the placebo treatment group. Reported TEEs included both arterial and venous events, including portal vein thrombosis. The majority of TEEs in eltrombopag subjects resolved and most on-treatment events did not lead to discontinuation from antiviral treatment.

Events suggestive of hepatic decompensation were observed in the ENABLE study population, and more commonly in eltrombopag-treated subjects. Subjects with poor liver function at baseline had a greater risk of hepatic decompensation. Given that hepatic decompensation is a known risk in cirrhotic HCV patients receiving peginterferon therapy, this result is not unexpected.

The incidence and progression of cataracts occurred more frequently in the eltrombopag treatment group compared to the placebo treatment group. This has previously been recognised in the original application.

In terms of postmarketing surveillance, approximately 6,664 patient years of eltrombopag treatment have been prescribed worldwide as of December 2011. A total of 5215 spontaneous and post marketing AEs (serious and nonserious) have been received from the marketed use of eltrombopag (2261 cases). No significant trends were identified that would impact on the safety profile of eltrombopag.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of eltrombopag in the proposed usage are:

Eltrombopag enabled the introduction of antiviral therapy in 95% of study subjects who would otherwise have been ineligible or poor candidates for peginterferon-based therapy. Both ENABLE studies met the primary endpoint: the pooled ENABLE data showed that the addition of eltrombopag to standard antiviral therapy resulted in a statistically significant and clinically meaningful improvement in SVR (21%) compared with standard antiviral therapy + placebo (13%) (p=0.0004). The benefit offered by eltrombopag treatment is that 1 out of 5 patients who were previously ineligible or poor candidates for antiviral therapy achieved SVR and now have the opportunity to experience the long-term benefits of SVR.

The results were robust and similar across all 3 stratification factors (baseline platelet count, HCV genotype, viral load). There was no meaningful difference in the SVR rates for subjects with <50 Gi/L compared to subjects ≥50 Gi/L. As expected, the SVR rates were higher for HCV genotype 2/3 compared to HCV genotype non-2/3. However, eltrombopag-supported antiviral therapy nearly doubled the SVR rate from 8% to 15% for HCV genotype non-2/3 subjects.

8.2. First round assessment of risks

The risks of eltrombopag in the proposed usage are:

The safety profile observed in the ENABLE studies is consistent with the peginterferon/ribavirin safety profile and the established safety profile of eltrombopag. Thrombotic/thromboembolic events, including portal vein thrombosis and occurrence of cataracts are already described in the eltrombopag label. Thrombotic events were reported 2% more frequently in the eltrombopag group compared to the placebo group. There was no clear correlation between platelet counts, duration of treatment with eltrombopag or other direct eltrombopag-specific risk factors and reports of thrombotic events.

Hepatic decompensation is a known side effect of interferon therapy in patients with cirrhosis and was observed in the pivotal studies.

The safety profile was largely influenced by the degree of liver impairment prior to initiating treatment. Subjects with more severe baseline liver impairment had a higher incidence of hepatic decompensation and thromboembolic events.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of eltrombopag, given the proposed usage, was considered to be favourable.

9. First round recommendation regarding authorisation

Eltrombopag was approved for use in Australia in July 2010 (ARTG 158419/158356) 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. This application seeks to extend the application to the treatment of thrombocytopenia adult patients with chronic hepatitis C virus (HCV) infection to enable the initiation of interferon-based therapy and also during interferon-based therapy. As such, eltrombopag treatment would raise platelet counts to allow thrombocytopenic HCV subjects to become eligible for the initiation of interferon-based antiviral therapy; and would allow continuation of antiviral therapy at higher doses with less need for thrombocytopenia-induced dose reductions of interferon, thereby increasing the likelihood of achieving SVR .

The pharmacokinetics and pharmacodynamics of eltrombopag have previously been well characterised. Additional information was provided on pharmacokinetics in the target population, including the proposed new dosage strengths of 75 mg and 100 mg as well as pharmacodynamic modelling in HCV. There were no unexpected trends or adverse findings.

There is no specific European Medicines Agency (EMA) guidance on thrombopoietin agonists, although the need for this has been recognised. EMA guidance does exist on the clinical evaluation of medicinal products for the treatment of chronic hepatitis C. The pivotal efficacy studies reflected this guidance and were appropriately designed and powered to be clinically meaningful. Both studies demonstrated that a greater proportion of eltrombopag subjects achieved SVR than did placebo subjects and this result was statistically significant. The response to eltrombopag during OL treatment was similar in both studies with 97% and 96% of subjects in ENABLE 1 and ENABLE 2, respectively, achieving a platelet count that would allow the initiation of antiviral therapy. Platelet counts began to rise within the first week of treatment with eltrombopag, and the median time to achieve the target platelet count was about 2 weeks, with over 75% of subjects achieving these target platelet counts within the first 4 weeks of treatment. At the end of treatment, 48% (ENABLE 1) and 38% (ENABLE 2) of subjects randomised to the eltrombopag arm were HCV RNA negative, significantly more than in the respective placebo arms (37% for ENABLE 1and 23% for ENABLE 2).

Interpretation of safety results was complicated by the nature of the target population and the impact of a supportive agent (eltrombopag), allowing for more intensive anti-viral treatment than would otherwise be possible. Nonetheless, the safety profile was comparable between treatment and placebo groups. Thromboembolic/thrombotic complications were observed more frequently in the eltrombopag treatment group than in the placebo treatment group. Events suggestive of hepatic decompensation were observed more commonly in eltrombopag treated subjects. Subjects with poor liver function at baseline had a greater risk of hepatic decompensation. The incidence and progression of cataracts occurred more frequently in the eltrombopag treatment group compared to the placebo treatment group. None of these issues were unexpected and surveillance for these conditions is recommended during treatment. Given the nature of the target population, all patients undergoing this treatment for this

condition will require close surveillance to reduce morbidity and mortality from both the condition itself and any medication-related effects.

Overall, this medication has an acceptable benefit-risk profile, and registration was recommended for the proposed indication.

10. Clinical questions

No questions were raised by the evaluator.

11. Second round evaluation of clinical data submitted in response to questions

No second round evaluation was conducted.

12. References

Nil.

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