25 July 2013
EMA/491212/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of an extension of Marketing Authorisation and variations assessment report

REVOLADE

International non-proprietary name: ELTROMBOPAG

Procedure No. EMEA/H/C/001110/X/0012G

Note

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

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1. Background information on the procedure

1.1. Submission of the dossier

Pursuant to Article 7.2(b) of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Trading Services submitted to the European Medicines Agency (EMA) on 25 May 2012 an application for a group of variations consisting of an Extension, a type II and a type IA variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Revolade	eltrombopag	See Annex A

The group consisted of:

Extension of the Marketing Authorisation for the above mentioned medicinal product

concerning:

new strengths: 75 mg and 100 mg film-coated tablets

and the following variations:

Variation(s) requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
B.I.b.1.b	Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	IA

Extension of the indication of Revolade in the treatment of HCV associated thrombocytopenia and a type IA variation to lower the threshold for drug related impurities.

The application for the strength 100 mg was withdrawn by the MAH on 15th July 2013.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/312/2011 on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH's request for consideration

Additional Data/Market exclusivity

The applicant requested consideration of one year data/market exclusivity in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) No 726/2004.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 March 2006, 22 February 2007, 15 November 2007 and 21 July 2011. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Revolade has been given a Marketing Authorisation in the EU on 11 March 2010.

1.2. Manufacturers

Manufacturers responsible for batch release

GLAXO WELLCOME, S.A.
Avda. Extremadura, 3
Pol. Ind. Allendeduero
Aranda de Duero, Burgos
09400, Spain

Glaxo Operations (UK) Ltd. (trading as Glaxo Wellcome Operations)
Priory Street
Ware, Hertfordshire SG12 0DJ
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Ian Hudson

- The application was received by the EMA on 25 May 2012.
- The procedure started on 20 June 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 September 2012). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 September 2012.
- During the meeting on 18 October 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The consolidated List of Questions was sent to the applicant on 19 October 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 15 March 2013.
- During the CHMP meeting on 21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 26 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 24 May 2013.
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 21 June 2013.
- The Rapporteurs circulated the preliminary Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 8 July 2013.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 19 July 2013.
- During a meeting of a Scientific Advisory Group (SAG) on 2 July 2013, experts were convened to address questions raised by the CHMP.
- The applicant submitted a letter of withdrawal of the application for a change to the marketing authorisation to add a 100 mg film-coated tablet on 15 July 2013.
- During the meeting on 25 July 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting of an extension of the Marketing Authorisation for REVOLADE.
- Furthermore, the CHMP adopted a report on the novelty of the indication in comparison with existing therapies and the significant non-clinical or clinical data in relation to the claimed new indication for REVOLADE.

2. Scientific discussion

2.1. Introduction

More than 2% of the world population is chronically infected with the hepatitis C virus (HCV). The prevalence of HCV in Europe varies geographically, ranging from 0.4% to 3% in Western Europe. Chronic HCV infection is now a leading cause of liver transplantation and has superseded HIV infection as a cause of death in the United States. Furthermore, HCV was associated with more than half of the estimated 18,910 liver cancer deaths in the United States in 2010 and has become the leading cause of primary liver cancer in Europe.

Approximately 20% of HCV-infected individuals develop liver cirrhosis, with thrombocytopenia as a clinical marker of progression to more severe hepatic impairment. Once cirrhosis develops, the outcome is predictable in patients who are not treated with antiviral therapy: patients develop complications of cirrhosis, including hepatic decompensation (ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal bleeding), hepatocellular carcinoma, and death. For patients with chronic HCV and platelet counts <100 Gi/L the prognosis is especially poor, with annualised incidence rates for hepatocellular carcinoma/clinical decompensation, death/liver transplantation, or death alone as high as 7.9%, 7.3%, and 5.3%, respectively. These yearly incidence rates mean that 2 out of 5 patients with chronic HCV and platelet counts <100 Gi/L will have a life threatening complication in the next 5 years and at least 1 out of 4 will die during the same period.

Achieving a sustained virologic response (SVR) is the primary goal of antiviral therapy. It not only represents cure from viral infection, but also provides the prospect of changing the natural history of the disease. The importance of SVR is reflected by a 4-10 fold decrease in mortality and a 2-4 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. Peginterferon and ribavirin form the backbone of approved HCV antiviral therapy. For patients with HCV genotype 1, the addition of a direct-acting antiviral agents (DAA) protease inhibitor such as boceprevir or telaprevir to peginterferon and ribavirin (triple therapy) has led to SVR rates of up to 80% and has redefined the standard of care. Boceprevir and telaprevir are not approved for use in patients with HCV genotype 2 or 3, and their safety and efficacy in patients with marked thrombocytopenia have not been studied.

The etiology of thrombocytopenia in HCV-infected patients is multi-fold and includes impaired production of endogenous thrombopoietin (TPO) in the liver and platelet pooling due to splenomegaly. The severity of thrombocytopenia correlates with the severity of the liver disease. Consequently, low platelet counts are predictive of poorer outcomes.

Thrombocytopenia is also caused, or further aggravated, by interferon-based antiviral therapy due to its myelosuppressive effects. Data from published Phase III studies for peginterferon alfa-2a and peginterferon alfa-2b, which excluded patients with platelet counts <90 Gi/L, and <100 Gi/L, respectively, showed that approximately 20 to 30% experienced thrombocytopenia during treatment with peginterferon plus ribavirin. The current peginterferon labels advise that they should be used with caution in patients with baseline platelet counts <90 Gi/L and should be discontinued in patients who develop severe decreases in platelet counts. It has been estimated that 6% of HCV patients are not eligible for peginterferon and ribavirin antiviral therapy due to thrombocytopenia.

The current clinical management of HCV-patients with thrombocytopenia receiving antiviral therapy relies primarily on reducing the peginterferon dose. However, such dose reductions, particularly when occurring during the initial 12 weeks of antiviral treatment, are associated with a reduced ability to achieve the desired outcome of antiviral therapy, i.e. SVR. In fact, data suggest that in patients with HCV and advanced fibrosis or cirrhosis, peginterferon dose reductions are particularly detrimental to achieving SVR. The window of opportunity to administer antiviral therapy is relatively short for patients with advanced fibrosis/cirrhosis and significant HCV-associated thrombocytopenia. Most of them are at high risk of transitioning to hepatic decompensation. Once patients have decompensated, initiation of antiviral therapy with peginterferon is contra-indicated due to high rates of treatment- associated side effects and low response rates to currently available antiviral therapies.

The treatment of hepatitis C virus infection is an area of intense current research, with various anticipated improvements to available treatment options emerging. Numerous antiviral agents are currently in various stages of development, most with the ultimate goal of achieving a successful and safe interferon–free treatment regimen. Until interferon-free treatment regimens become available, IFN remains as the backbone of antiviral regimens in HCV.

Eltrombopag is an orally bioavailable thrombopoietin receptor (TPO-R) agonist. It interacts with the TPO-R and induces proliferation and differentiation of megakaryocytes from bone marrow progenitor cells to increase platelet counts.

Eltrombopag is currently indicated in the treatment of adult patients with ITP not candidates or after failure to splenectomy. The recommended dose is 50 mg once daily. For patients of East Asian or South East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily and the maximum allowed is do not exceed a dose of 75 mg daily.

The MAH submitted a variation to extend the indication for the treatment of adult patients with chronic hepatitis C infection for the treatment of thrombocytopenia:
• To enable the initiation of interferon-based therapy; and
• During interferon-based therapy

The proposed starting dose is 25 mg eltrombopag once daily for all patients. After initiating eltrombopag, the dose should be adjusted as necessary to achieve/maintain the minimum target platelet count necessary to maintain full-dose antiviral therapy, up to a maximum dose of 100 mg eltrombopag once daily.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as tablets containing one new strength of eltrombopag olamine equivalent to 75 mg of eltrombopag as active substance.

The Marketing Authorisation Holder applied also for the 100 mg strength; however the application was withdrawn during the evaluation since problems were encountered during the validation process of the 100 mg strength. The Quality information of the withdrawn strength was similar to the one provided for the 75 mg strength.

Other ingredients are: magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone (K30), sodium starch glycolate Type A, hypromellose, iron oxide red (E172), iron oxide black (E172), iron oxide yellow (E172), macrogol 400, and titanium dioxide (E171).

The product is available in aluminium blisters (PA/Alu/PVC/Alu) as the already authorised strengths.

2.2.2. Active Substance

Eltrombopag olamine used for the manufacture of Revolade 75 mg film-coated tablets is of the same quality as the one used for the already authorised strengths. The applicant submitted a Type IA variation to reduce the limit for the potentially genotoxic oxime isomer impurities from 20ppm to 5ppm.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Revolade 75 mg strength was developed to support the additional proposed indication for the treatment of thrombocytopenia in adults with HCV infection.

The Marketing Authorisation Holder applied also for the 100 mg strength; however the application was withdrawn during the evaluation since problems were encountered in the validation process of the 100 mg strength.

All the excipients, except for the colorants, are controlled by the appropriate Ph Eur monograph. The formulae for the colorants mixtures and the specifications applied were provided and considered satisfactory. No compatibility issues were identified between the active substance and the excipients employed in the finished product

The finished product is an immediate release tablet dosage form that employs a common granulation to make tablets of different strengths; therefore, the particle size of the granule will impact the finished product content uniformity and must be controlled. Since the active substance has a low solubility, the active substance particle size will have an impact on tablet dissolution. Granulation is the only critical step identified. For all steps, both quality critical process parameters (QCPP) and quality process parameters (QPP) are defined by an acceptable range of values (defined as the Proven Acceptable Range) or by the desired end point.

The new strength 75mg is manufactured using a common granule as with the 25mg and 50mg tablets, so no new statistical design of experiments was performed on this critical process, but further process validation was performed on the blending and compression processes.

Eltrombopag olamine has a low solubility over the pH range 1 to 7.4. It is considered to have moderate permeability so the bioavailability may be considered to be limited by its dissolution rate. Because of its low solubility, a dissolution method was developed using a surfactant.

The primary packaging used for the 75mg is the same as that used for the 25mg and 50mg tablets, that is polyamide / aluminium foil / polyvinyl chloride (PVC) laminate blister which is

sealed with aluminium foil, nominally 20µm thick with a vinyl acrylic heat seal coating. The product contact materials are the PVC and acrylic coating. Appropriate specifications applied by the product manufacturers have been provided together with supplier documentation indicating that the PVC complies with the PhEur and with the European Directive for contact with food.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of this new strength.

Manufacture of the product

The finished product manufacturing process covers dry mixing of ingredients, granulation, wet milling, drying, milling blending (pre-lubrication and lubrication), compression, coating and packaging and it is the same manufacturing process as the one used for the already authorised strengths.

Product specification

The finished product release specifications are identical to the already authorized strengths and include appropriate tests for description, identification (IR), assay (HPLC), related impurities content (HPLC), uniformity of dosage units (HPLC), dissolution (Ph Eur), and microbiological test (Ph. Eur.).

Batch analysis results in 5 full-scale batches confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data was provided for 48 months at 30 °C / 65% RH and 6 months at 40 °C / 75% RH for two commercial scale batches, for the 25mg, 50mg and 75mg strength tablets, in the proposed packaging.

Supporting stability data was provided for 48 months at 30 °C / 65% RH and 6 months at 40 °C / 75% RH for three commercial scale batches, in the proposed packaging.

Based on available stability data, the proposed shelf-life as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of this new strength Revolade 75 mg tablets has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3. Non-clinical aspects

2.3.1. Introduction

A number of additional nonclinical pharmacology, pharmacokinetic and toxicology studies have been completed since the initial marketing application was submitted.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The effects of eltrombopag and TPO recombinant on cell proliferation of hepatocellular cancer (HCC) cell lines (Hep3B, Huh-7 and HepG2) and normal liver samples were investigated. Following treatment with recombinant TPO there was a small, but statically significant proliferative response in the Hep3B and HepG2 cell lines. Treatment with eltrombopag induced a dose-dependent decrease in proliferation with a mean of IC_{50} of 5.6, 26.1 and 15.9 µg/mL for the HepG2, Hep3B and Huh-7 cell lines, respectively.

The expression of the gene which encodes for TPO-R (MPL) mRNA was measured in HCC cell lines, patient-derived HCC and normal liver samples. MPL mRNA expression was very low, but detectable in the Hep3B, Huh-7 and HepG2 cell lines; undetectable in HCV patient liver samples and higher in normal liver samples. TPO-R protein was also detected in the HCC cell lines.

2.3.3. Pharmacokinetics

Three new pharmacokinetic studies have been submitted that are relevant for the treatment of thrombocytopenia in adults with chronic HCV infection:

An in vitro investigation of the role of organic anion transporter polypeptides in the hepatic uptake of [Ring-U-14C]SB-497115 using isolated human hepatocytes.

This study was conducted to investigate eltrombopag uptake into human hepatocytes in vitro. [14C] eltrombopag was incubated with cryopreserved human hepatocyte culture and its uptake by the hepatocytes, as measured by cellular radioactivity content, was determined in the absence and presence of an inhibitor cocktail of uptake transporters (rifamycin, montelukast, cyclosporine A and ketoconazole). This study demonstrated that eltrombopag transport into human hepatocytes was passive and nonsaturable, and that the uptake transporter inhibitors had no effect on the hepatic uptake. These results were consistent with a previous finding that eltrombopag was not a substrate of human OATP1B1. Hepatitis C viral infection has been shown to alter expression of hepatic transporters, including uptake transporters. Because the uptake of eltrombopag into hepatocytes is passive, uptake into hepatocytes of HCV patients should not be affected.

Qualitative investigation of the metabolites of eltrombopag (SB-497115) in human plasma following oral administration of eltrombopag olamine (50 mg) in healthy subjects and in subjects with mild, moderate, or severe renal impairment.

This was a study to qualitatively compare circulating metabolites in patients of renal impairment with healthy subjects. Plasma samples from a clinical study were analysed by LC/MS for eltrombopag and its metabolites. No notable differences were observed in circulating metabolite profiles between healthy and renally impaired subjects. The human radiolabel study indicated that metabolites derived from oxidation and glucuronidation of eltrombopag circulated at low levels in healthy humans. Therefore, renal impairment alone should not notably alter circulating metabolite profiles in HCV patients.

An in vitro investigation into the inhibition by SB-497115 (eltrombopag) of doxorubicin and doxorubicinol transport via human breast cancer resistance protein heterologously expressed in MDCKII cells.

This report described an in vitro study to characterize the effect of eltrombopag on breast cancer resistance protein (BCRP) mediated transport of doxorubicin and doxorubicinol (a metabolite of doxorubicin). Eltrombopag is an inhibitor of BCRP, of which both doxorubicin and doxorubicinol are substrates. In a polarized Madin-Darby canine kidney cell line heterologously expressing human BCRP, eltrombopag up to 30 µM had no effect on BCRP-mediated transport of doxorubicin or doxorubicinol. These results indicated a low potential of clinical interaction of eltrombopag with the anthracycline and its metabolite.

2.3.4. Toxicology

Other toxicity studies

One toxicology study has been conducted with eltrombopag. This study provides an in vitro assessment of the genotoxic potential of the impurities GSK1719938A and SB-433049.

A reassessment of the route of synthesis for eltrombopag identified several potential genotoxins: SB-611855-AAB, SB-601205, SB-564758, GSK560666A, SB-710620-A, GSK1719938A and SB-433049. With the exception of the additional impurities GSK1719938A and SB-433049, these potential genotoxins are the same as those highlighted in the initial marketing application for ITP.

GSK1720079A (a mixture of the isomers GSK1719938A and SB-433049 as pure preparations of these molecules could not be prepared) was evaluated in a screening Ames test using Salmonella typhimurium (TA98, TA100, TA1535 and TA1537) and Escherichia coli (WP2 uvrA pKM101), in both the presence and absence of S9-mix and in concentrations ranging between 50 to 5000 µg/plate.

GSK1720079A induced mutation in strains TA1535, TA1537, TA98 and TA100 when tested in the presence of S9-mix and TA98, TA100 and WP2 uvrA pKM101 when tested in the absence of S9-mix.

Analysis of the eltrombopag drug substance confirmed that the levels of each of these potential impurities at the recommended clinical dose are below 1.5 µg/day, the threshold of toxicological concern (TTC).

2.3.5. Ecotoxicity / environmental risk assessment

For eltrombopag where the maximum recommended daily dosage is 100 mg/day, $PEC_{surface\ water}$ was 0.5 µg/L. Upon CHMP request the $PEC_{SURFACE\ WATER}$ value was refined with information for the sum of all the indications including the sales forecast of Revolade. The refined $PEC_{surface\ water}$ was 0.069 µg/L. This value is greater than the nominal trigger value of 0.01 µg/L and therefore a Phase II environmental was performed.

In a phase II Tier A assessment, eltrombopag was investigated for determination of activated sludge sorption isotherm according to OPPTS 835.1110. Due to physico-chemical characteristics of the compound, no determination of the isotherm was possible in this study and a Phase II Tier B assessment was performed. See Table 1 for a summary of the studies performed.

Finally, the distribution coefficient for eltrombopag is 4.52 at ph=7 and it has been screened for persistence, bioaccumulation and toxicity. Eltrombopag has been considered persistent because the degree of ultimate biodegradation has been insignificant (14%, 28 days) and the parent compound has proved recalcitrant to primary degradation (10%, 28 days), but it does not fulfil the criterion for bioaccumulation (BCF=14) in a fish concentration study (OECD 305).

Table 1. Summary of main study results

Substance (INN / Invented Name): Revolade (eltrombopag)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	4.52	Potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.52	B
	BCF	14	not B
Persistence	DT50 or ready biodegradability		P
Toxicity	NOEC or CMR		NA
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$	0.069	µg/L	> 0.01 threshold
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 835.1110	No results due to technical obstacles Estimated log Koc = 5.56	

Ready Biodegradability Test	OECD 302C	Ultimate Biodegradation = 14%, 28 days Primary Biodegradation = 10%, 28 day			Not Inherently biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.45	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>320	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	14	L/kg	%lipids:

In the context of the obligation of the MAH to take due account of technical and scientific progress the CHMP recommends the update of the ERA including the following points for further investigation:

-Tier A: Aerobic and anaerobic transformation in aquatic sediments system (OECD 308), Daphnia sp. reproduction test (OECD 211) and Fish, early life stage toxicity test (OECD 210)

-Tier B: Aerobic transformation in soil (OECD 307), Soil microorganisms, nitrogen transformation test (OECD 216), Terrestrial plants, growth test (OECD 208), Earthworm, acute toxicity test (OECD 207), Collembola reproduction (ISO 11267) and Sediment - water chironomid (OECD 218/219).

In addition, the following standard sentence was added in the Package Leaflet as a precautionary measure until the studies have been performed: “Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.”

2.3.6. Discussion on non-clinical aspects

Eltrombopag is a trombopoietin receptor (TPO-R) agonist that functions in a similar manner to endogenous trombopoietin (TPO). Eltrombopag induces survival, proliferation and megakaryocyte differentiation activities in human bone marrow progenitors. Eltrombopag has no direct effect on in vitro platelet aggregation or activation, nor does it influence agonist-dependent aggregation or activation.

Safety pharmacology studies submitted as part of the initial marketing authorisation application did not reveal any adverse neurobehavioral, respiratory or cardiovascular effects in vivo at the highest doses tested. However, the doses tested did not result in exposure levels in animals compare to humans enough to discard the risk for patients with HCV infection treated with 100 mg of eltrombopag (~3-fold for neurobehavioral or respiratory systems and 1.2 for cardiovascular system). No clinically significant effects on cardiac repolarization were observed in clinical trials in healthy subjects and patients with HCV, but other cardiovascular damage, as thrombotic events and proarrhythmia, have been associated with eltrombopag treatment. Nevertheless the CHMP agreed that additional in vivo non clinical studies with higher doses of eltrombopag were not warranted based on the MAH’s justification that dose higher than 30

mg/kg/day could not be well tolerated by the animals. Further assessment of cardiac repolarization has been performed on a clinical level and the risk of thrombosis is currently adequately addressed in the SmPC.

Taking into account the proposed indication is for patients with hepatic damage, the MAH has discussed the clinical relevance of hepatic effect found in animals in HCV patients and review the available data on possible adverse effects of eltrombopag treatment on liver seen using models with hepatic disease. Hepatotoxicity has been observed in mice and rats generally associated with non-tolerated doses. It was considered a secondary effect of eltrombopag rather than a primary toxicity. In dogs, short treatment (4-14 days) with high doses of eltrombopag (≥60 mg/kg/day) induced hepatocellular degeneration/necrosis and/or apoptosis associated with marked increases from baseline values in serum transaminases, alkaline phosphatase or total bilirubin. No similar findings were observed in dogs after 52 weeks of dosing at a maximum tolerated dose of 30 mg/kg/day. In addition, a review of recent literature on nonclinical models of HCV-related liver disease showed that there are no suitable animal models currently available to evaluate possible effects of eltrombopag treatment on liver.

Since animal models for the study of possible effects of eltrombopag treatment on liver of HCV are not available and the risk in humans is already known and it is included in the current SmPC, the CHMP was of the opinion that further studies were not necessary to characterise the hepatotoxicity associated with eltrombopag treatment from the non-clinical point of view.

According to the data submitted in the initial marketing application, eltrombopag is considered not genotoxic, not carcinogenic, not phototoxic and it does not affect the fertility. However, the doses tested did not allow a safety margin to exclude risk for HCV patients treated with 100 mg/day of eltrombopag. The safety margin was 6.8 (rat bone marrow micronucleus test) for genotoxic potential, below 2 for carcinogenic potential and 1.8 fold in mice/1.9 in rats for photoxicity. In addition low safety margins have been obtained for teratogenic effects in rats and rabbits and the development risk for humans cannot be ruled out. Nevertheless, additional studies were not warranted because higher doses would not be tolerated by the animals. In this regard the SmPC currently describes the risk adequately. It states that mice and rats do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans due to the TPO receptor specificity and safety margins are adequately described (see SmPC section 5.3).

Eltrombopag is not a PBT substance. The refined PEC surface water calculated for the maximum daily dose of 100mg exceeds the trigger value for a Phase II environmental fate and effects analysis. An activated sludge sorption isotherm was not determined for eltrombopag due to instability problems, but a QSAR (PCKOC) evaluation of eltrombopag predicts that Koc will be significantly greater than 10,000 (Log Koc = 5.66). The CHMP was of the opinion that the risk to the environment has been properly assessed.

2.3.7. Conclusion on the non-clinical aspects

Eltrombopag has been well characterised in a comprehensive battery of nonclinical studies that support the clinical use of eltrombopag in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the

main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

GSK Study Number	Study Design / Primary Objective	Dosing and Administration	Enrolled/ Randomized
Pivotal Phase III Studies			
TPL103922 (ENABLE 1) and 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 IP.	Part 1: Eltrombopag 25 mg, 50 mg, 75 mg and 100 mg; once daily oral dosing until platelets ≥ 90 Gi/L (TPL103922) or ≥100 Gi/L (TPL108390) Part 2: Eltrombopag dose from Part 1 or matching placebo; once daily oral dosing in conjunction with pegIFN (TPL103922: alfa 2a; TPL108390: alfa 2b)+ribavirin antiviral therapy for up to 48 weeks	TPL103922: OL Phase: Eltrombopag 716 DB Phase: Placebo:232 Eltrombopag: 450 TPL108390: OL Phase: Eltrombopag 805 DB Phase: Placebo:253 Eltrombopag: 506
Supportive Phase II Study			
TPL102357	Part 1: DB, randomized, placebo controlled parallel group study, Increase in platelets to ≥70 Gi/L by Week 4.	Part 1: Eltrombopag 30 mg, 50 mg, 75 mg or matching placebo; once daily oral dosing for 4 weeks Part 2: Eltrombopag 30 mg, 50 mg, 75 mg or matching placebo; once daily oral dosing in conjunction with pegIFN+ribavirin (alfa 2a or alfa 2b) antiviral therapy for 12 weeks	Part 1: Placebo: 18 Eltrombopag: 56 Part 2: Placebo: 4 Eltrombopag: 45

2.4.2. Pharmacokinetics

The effect of the co-administration of eltrombopag and IFN alfa-2a plus ribavirin or IFN alfa-2b plus ribavirin was studied by performing population PK analyses. An eltrombopag population PK model was developed using eltrombopag plasma concentration-time, dosing, demographic and covariate data collected from one Phase II pilot study in subjects with HCV infection (TPL102357)

and two Phase III studies (TPL103922 [ENABLE I] and TPL108390 [ENABLE II]) in subjects with HCV infection, combined with data from a healthy subject study (SB497115/002, N=28).

Population PK model

Of the 663 subjects included in the population PK analysis, 28 were healthy subjects and 635 were HCV patients. The median (range) age across the 663 subjects was 52.0 (19.0-74.0) years, and 403 subjects (61%) were male. There were 144 elderly (>60 years) subjects (22%) in the population. The median (range) body weight was 75.0 (41.0-164.0) kg. Of the 663 individuals, 362 subjects (55%) were White, 12 (2%) were Black or African-American, 145 (22%) were East Asian, 69 (10%) were South East Asian, 74 (11%) were Central/South Asian and 1 (<1%) were classified as Other.

Of the 635 HCV patients included in the population PK and PK/PD analyses, 605 subjects (95%) were classified as Child-Pugh Class A (Child-Pugh score of 5-6, mild hepatic impairment), 27 (4%) as Child-Pugh Class B (Child-Pugh score of 7-9, moderate hepatic impairment) and none as Child-Pugh Class C (Child-Pugh score of 10-15, severe hepatic impairment).

The parameter estimates of the final PK model are presented in Table 2. There were a number of significant covariates identified. CL/F of eltrombopag was, on average, 29% lower in female subjects compared to males, 27% lower in elderly (>60 years) compared to younger subjects, and on average, 36% lower in East/Southeast Asian subjects compared to other races who are predominantly Caucasian. CL/F in subjects with a Child-Pugh score of 5 was estimated to be, on average, 50% lower than healthy subjects. As the severity of the hepatic impairment increased there was a further reduction in CL/F. For a patient with Child-Pugh score of 9, CL/F was estimated to be 71% lower compared to a patient with a Child-Pugh score of 5. CL/F was negatively correlated to AST levels. Vc/F was estimated to be 2.3-fold higher in Central/South Asians compared to all other races. For the range of weights in the analysis population (41-164 kg), Vc/F and Vp/F ranged from 7.1- 28.3 L and 12.7-50.6 L, respectively. For an average AST level in the HCV population of the current analysis (102 IU/L), CL/F value was estimated to decrease by 18% compared to HCV patients with normal AST (20 IU/L). All of the fixed effect parameters were estimated with good precision (%RSE <24%). The inter-individual and inter-occasional random effects were also estimated with reasonable precision, with %RSE less than 12%.

The final model was evaluated by performing a VPC stratified by study and dose. Only 9% of the observed concentrations fell outside the 90% prediction intervals, supporting the conclusion that the final model adequately describes the observed data.

Table 2. Parameter estimates of final eltrombopag population PK model

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	Bootstrap
CL/F [L/hr]	0.938	23.5	0.507-1.37	0.944 (0.816 – 1.09)
Vc/F [L]	12.1	4.65	11.0-13.2	11.9 (10.8 – 13.0)
Vp/F [L]	21.6	3.81	20.0-23.2	21.8 (17.2 – 26.3)
Q/F [L/hr]	0.615	5.04	0.554- 0.676	0.622 (0.527 – 0.718)
Ka1 [hr^{-1}]	0.356	9.47	0.290-0.422	0.363 (0.253 – 0.592)
Ka2 [hr^{-1}]	4.10	12.7	3.08-5.12	4.53 (1.64 – 13.4)
ALAG1 [hr]	0.442	1.51	0.429-0.455	0.449 (0.412 – 0.477)
MTIME [hr]	1.42	1.31	1.38-1.46	1.89 (1.01 – 1.95)
σProp ~HCV	0.642	4.70	0.583-0.701	0.646 (0.495 – 0.821)
σProp ~TAD<4hr	1.34	2.87	1.26-1.42	1.36 (1.14 – 1.63)
CL/F ~Females	0.710	5.20	0.638-0.782	0.708 (0.644 – 0.774)
CL/F~AST[a]	-0.0476	20.2	-0.0665- -0.0287	-0.0487 (-0.0652 - -0.0343)
CL/F~Age (>60 years)	0.734	6.65	0.638- 0.830	0.737 (0.667 – 0.811)
CL/F ~CP Score 5	0.498	24.3	0.261-0.735	0.503 (0.429 – 0.588)
CL/F ~ East/Southeast Asians	0.645	5.80	0.572-0.718	0.648 (0.589 – 0.708)
CL/F ~ CP Score > 5[b]	-0.178	12.1	-0.220--0.136	-0.186 (-0.241 - -0.140)
Vc/F ~Central/South Asians	2.27	9.12	1.86-2.68	2.29 (1.75 – 3.02)
Vc/F and Vp/F ~WT[c]	1 FIX	-	-	-
Inter-individual or inter-occasion variability				**CV% or R**
ω^2_{CL}	0.295	9.15	0.242-0.348	54.3%
Covar ω_{CL}, ω_{Vc}	0.239	8.83	0.198-0.280	0.608
ω^2_{Vc}	0.524	8.51	0.437-0.611	72.4%
IOV CL/F	0.191	8.01	0.161-0.221	43.7%
IOV Ka	1.41	11.1	1.10-1.72	119%
Residual variability				**CV% or SD**
σ^2_{prop}	0.0222	10.0	0.0178-0.0266	14.9%
σ^2_{add}	2.81×10^{4}	8.43	2.35×10^{4}-3.27×10^{4}	168

a. A proportional function was used to evaluate AST (See Equation 2, with COV_{ST}=20)
b. A coefficient for each unit increase in Child-Pugh Score from CP Score 5, such that the fractional change of CL/F by CPS is expressed as 0.498*[1-0.178*(CPS-5)] in the final PK model.
c. Both Vc/F and Vp/F increased allometrically with both weight as described by $(WT/70)^{1.0}$.
Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; 95% CI= 95% confidence interval on the parameter; CL/F = apparent clearance, Vc/F = volume of central compartment, Vp/F = volume of peripheral compartment, Q/F = inter-compartmental exchange flow rate, Ka1 = absorption rate constant prior to MTIME, Ka2 = absorption rate constant after MTIME, MTIME = Time at which absorption rate changes, ALAG1 = lag-time, σProp ~HCV = factor of proportional error for HCV patients; σProp ~TAD<4hr = factor of proportional error for TAD < 4 hr (absorption time); R= correlation coefficient; ω^2_{CL} and ω^2_{Vc} = variance of random effect of CL/F and Vc/F, respectively; Covar ω_{CL}, ω_{Vc} = correlation between random effect of CL/F and Vc/F; IOV = inter-occasion variability; CV = Coefficient of variation of proportional error (=[σ^2prop]$^{0.5}$*100); SD=standard deviation of additive error (=[σ^2add]$^{0.5}$); σ^2prop = proportional component of the residual error model, σ^2add = additive component of the residual error model.

Source: Model 104.res

The individual post-hoc parameter estimates were derived for all subjects in the PK dataset and to further characterize the difference in eltrombopag PK across various sub-populations, individual predicted steady state CL/F, Cmax, AUC(0-τ), and half-life (t1/2) were derived following repeat dosing of once daily 50 mg eltrombopag, and summarized by population in this model. Consistent with the final PK model, plasma eltrombopag exposure is higher in subjects with HCV compared to healthy subjects. For repeat daily dose of 50 mg eltrombopag, the geometric mean AUC(0-τ) and steady state Cmax in all HCV patients were 3.1 and 2.3-fold higher, respectively, than healthy subjects. The elimination half-life (t1/2) of eltrombopag was also significantly longer in HCV patients due to their reduced clearance (CL/F). Within HCV patients, exposure is higher in both females and East/Southeast Asians, and elderly subjects (>60 years) due to their lower CL/F. The terminal half-life of eltrombopag derived from the final PK model for both healthy subjects and HCV patients (52.2 and 122 h, respectively) was longer than that previously reported for both healthy subjects and subjects with CLD (21.1 and 76.4 h, respectively). The estimates of the typical values of both CL/F and Q/F from Model 104 were in

close agreement with those previously reported (0.938 vs. 0.953 L/h; 0.615 and 0.633 L/h). However, the estimates of the typical values for both volume terms (Vc/F and Vp/F) from the present analysis were higher than those previously reported, particularly for the peripheral volume term which was double the estimate from the CLD analysis (21.6 vs. 9.41 L).

A summary of eltrombopag PK parameter estimates by population is shown in Table 3.

Table 3. Summary of individual posterior eltrombopag PK parameter estimates by population

Population	N	CL/F (L/h)	t1/2 (h)	Cmax[a] (µg/mL)	AUC(0-τ)[a] (µg.h/mL)
Healthy Subjects	28	0.796 0.660-0.961	52.2 47.7-57.2	4.68 4.07-5.38	62.8 52.0 – 75.8
Overall HCV[b]	602	0.259 0.243-0.276	122 117-127	10.6 10.0-11.2	193 181 – 206
HCV (Males)	353	0.325 0.302-0.350	112 106-117	8.98 8.33-9.67	154 143 - 166
HCV (Females)	249	0.188 0.171-0.207	138 129-148	13.4 12.4-14.6	266 242 - 293
HCV (Non-East/Southeast Asians)	389	0.313 0.289-0.338	116 110-123	9.31 8.66-10.0	160 148 – 173
HCV (East/Southeast Asians)	213	0.183 0.168-0.200	133 125-142	13.5 12.4-14.6	273 250 - 297
HCV (Non- South/Central Asians)	535	0.252 0.236-0.269	122 117-128	10.7 10.1-11.3	199 186-212
HCV (South/Central Asians)	67	0.323 0.262-0.397	122 107-140	10.1 8.44-12.2	155 126-191
HCV (Non-Elderly [≤ 60 years])	488	0.290 0.271-0.310	115 110-121	9.84 9.23-10.5	173 161 – 185
HCV (Elderly [> 60 years])	114	0.160 0.140-0.183	156 141-172	14.6 13.1-16.3	312 274 - 356

a. Dose-normalized to 50 mg; Results expressed as geometric means and 95% confidence interval.
b. HCV subjects with Part 1 PK samples were included in the summary (N=602).

A statistical analysis was undertaken to evaluate the effect of IFN alfa-2a and IFN alfa-2b on eltrombopag CL/F using a mixed effects model approach (Treatment as a fixed effect and Subject as a random effect) which showed that there was an estimated 9% and 11% drop in the CL/F of eltrombopag when IFN alfa-2a and alfa-2b were co-administered with eltrombopag, respectively. The ratios (90% CI) for the effect of IFN alfa-2a and IFN alfa-2b were estimated to be 0.910 (0.851-0.974) and 0.887 (0.823-0.956) (Table 4). The 90% CI for both the comparisons were within the 80 to 125% limit of the standard bioequivalence criteria suggesting that there were no clinically meaningful differences in the CL/F of eltrombopag with and without administration of IFNs.

Table 4. Summary of statistical analysis to assess impact of antiviral therapy on eltrombopag Cl/F

		LSMeans			
IFN	Parameter	Reference	Test	Ratio	90% CI
IFN-alfa-2a	Ln(CL/F)	0.2723	0.2479	0.910	0.851 – 0.974
IFN-alfa-2b	Ln(CL/F)	0.2465	0.2186	0.887	0.823 – 0.956

In order to further assess the impact of more severe hepatic impairment on eltrombopag clearance (CL/F) and to test the impact of age on CL/F, the MAH provided upon CHMP request a combined PK population analysis including data from the previous HCV (ENABLE-based) and the CLD (ELEVATE-based) population PK analyses.

A total of 742 subjects were included in the combined PK dataset (28 healthy volunteers, 635 patients form the HCV studies and 79 patients from the CLD studies [38 of which were HCV patients]). Most of the subjects were males (61%), Child-Pugh Class A (90%) and the mean age was 52 years (range 19-81 years). Eleven percent (n=79) of the subjects were 65 years old or above, with very few subjects ≥75 years of age (n=4).

The combined model confirmed both, age and hepatic impairment, as significant covariates. The previously identified covariates remained significant as well. With regards to hepatic impairment, simulations performed with the combined model indicate that eltrombopag CL/F decreases with increasing degrees of hepatic impairment, assessed by Child-Pugh Scores. Therefore, the combined model confirmed that exposure increases with increasing hepatic impairment, as previously predicted. The estimated increase in exposure, compared to healthy subjects, was 111-183%, for subjects with mild and moderate hepatic impairment, respectively.

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the Phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag Cmax AUC(0-τ) estimates for patients with HCV enrolled in the Phase 3 studies are presented for each dose studied in Table 5.

Table 5. Geometric mean (95 % CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

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

Data presented as geometric mean (95 % CI).
AUC (0-τ) and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

2.4.3. Pharmacodynamics

An eltrombopag population PK/PD model was developed using platelet count over time and eltrombopag dosing from the Phase II (Study TPL102357) and the Phase III (ENABLE 1 and ENABLE 2) studies were combined with the individual PK parameters obtained from the population PK model. The population PK/PD model was built using a non-linear mixed-effect modeling approach with NONMEM program version VII.

Population PK/PD Model for Eltrombopag without and with Interferon

The final dataset for the eltrombopag PK/PD model consisted of 1567 platelet observations from 633 subjects. The structural PK/PD model for eltrombopag was the same as that previously developed for subjects with CLD. As higher dose levels were used in this study, this allows the relationship between plasma eltrombopag concentrations and the stimulation of platelet production in the thrombocytopenic HCV subjects to be described by the Emax model. The parameter estimates are shown in Table 6.

Table 6. Parameter estimates of eltrombopag population PK model

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	
KIN [Gi/L/day]	10.6	17.8	6.90 – 14.3	
KT [day^{-1}]	0.667	9.67	0.541 – 0.793	
EMAX [fold]	15.4	12.9	11.5 – 19.3	
EC50 (µg/mL)	29.0	17.5	19.1 – 38.9	
Inter-individual Variability				**CV%**
ω^2_{KIN}	0.185	41.4	0.0351 – 0.335	43.0
ω^2_{EC50}	0.654	6.07	0.576 – 0.732	80.9
Residual variability				**CV% or SD**
σ_{prop}	0.0188	7.07	0.0162 – 0.0214	13.7
σ_{add}	61.2	8.22	51.3 – 71.1	7.82

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; EMAX: max effect of eltrombopag concentration on platelet production; EC50: eltrombopag concentration eliciting 50% of maximum effect; ; KIN: production rate of platelet precursors; KT: maturation rate of platelet precursors; ω^2_{EC50} and ω^2_{KT} = variance of random effect of EC50 and KT, respectively; CV = coefficient of variation of proportional error (=[σ^2prop]$^{0.5}$*100); SD=standard deviation of additive error (=[σ^2add]$^{0.5}$); σ^2_{prop} = proportional component of the residual error model; σ^2add = additive component of the residual error model.

Source: 003emax2.res

The typical estimates for KIN and KT were 10.6 Gi/L/day and 0.667 day-1, respectively. The maximal stimulatory effect was 15.4 and the associated EC50 was 29 µg/mL. The IIV for KIN and EC50 was 43.0 and 80.9%, respectively. The structural parameters for the model were estimated with reasonable precision, with %RSE less than 30%. The diagnostic plots for the final model indicated that the model adequately described the platelet count data for the thrombocytopenic subjects with HCV during the eltrombopag dose escalation phase of the studies, although there was a slight under-prediction of the higher observed platelet count data. The distribution of the random effects was close to normal and no strong unexplained covariate-parameter relationships were noticeable.

The eltrombopag PK/PD model was evaluated by performing a VPC, only 8% of the observed platelet concentrations fell outside the 90% prediction intervals.

The simulations of the eltrombopag dose escalation phase of the ENABLE 1 and 2 underestimated the percentage of subjects who would qualify for initiation of antiviral therapy after two weeks of receiving 25 mg eltrombopag QD. However, the subsequent predictions at Weeks 4, 6 and 9 were closer to the observed data. The simulations also predicted that, on average, only 3 and

5% of the HCV subjects would have failed to initiate antiviral therapy in ENABLE 1 and 2, respectively, which is almost identical to the actual study results.

The final model included separate models for the inhibitory effects of IFN alfa-2a and 2b therapy on platelet counts. Due to a lack of PK data for IFN, a KPD modelling approach was used (see Figure1). As with the eltrombopag PK/PD model, there was an under-prediction of the higher platelet counts.

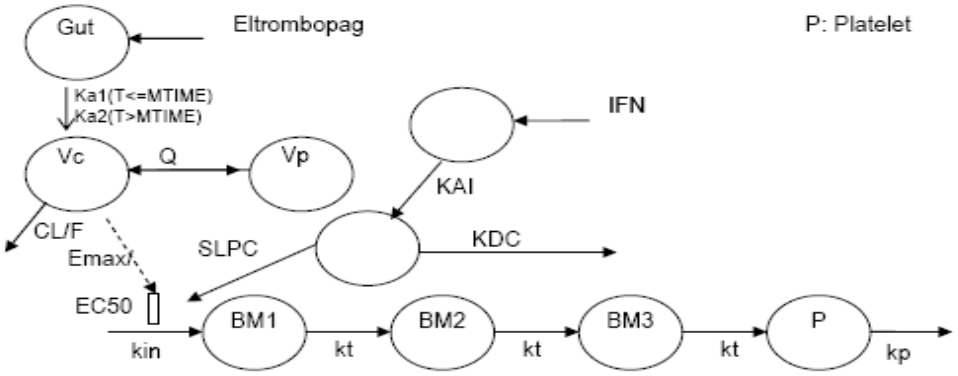


Figure 1. Schematic representation of the KPD model for eltrombopag and Peg-IFN in thrombocytopenic patients with HCV

The parameters estimates of PEG-INF alfa-2a and 2b population KPD model are shown in Tables 7 and 8.

Table 7. Parameter estimates of PEG-IFN alfa-2a population KPD model

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	
KDC [day^{-1}]	9.64	68.7	-3.34 – 22.6	
SLPC (μg^{-1})	0.524	69.5	-0.189 – 1.24	
KAI (day^{-1})	0.0789	8.66	0.0655 – 0.0923	
Inter-individual Variability				**CV%**
ω^2_{SLPC}	1.80	8.50	1.50 – 2.10	134
ω^2_{KAI}	1.20	13.5	0.882 – 1.52	110
Residual variability				**CV% or SD**
σ_{prop}	0.0427	1.56	0.0414 – 0.0440	20.7
σ_{add}	178	1.42	173 - 183	13.3

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; SLPC: slope for the linear effect of IFN alfa-2a concentrations on platelet production; KDC: hypothetical elimination rate constant for IFN; KAI: hypothetical absorption rate constant for IFN; ω^2_{SLPC} and ω^2_{KAI} = variance of random effect of SLPC and KAI, respectively; SD=standard deviation of additive error (=$[\sigma^2 add]^{0.5}$); σ^2_{prop} = proportional component of the residual error model; $\sigma^2 add$ = additive component of the residual error model.

Source: kpd401f.res

Table 8. Parameter estimates of PEG-IFN alfa-2b population KPD model

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	
KDC (day^{-1})	0.133	2.57	0.126 – 0.140	
SLPC (μg^{-1})	0.00727	9.04	0.00598 – 0.00856	
KAI (day^{-1})	0.922 (fixed)	-	-	
Inter-individual Variability				**CV%**
ω^2_{SLPC}	1.54	10.7	1.22 – 1.86	124
Residual variability				**CV% or SD**
σ_{prop}	0.0528	1.73	0.0501 – 0.0546	23.0
σ_{add}	156	2.97	147 - 165	12.5

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; SLPC: slope for the linear effect of IFN concentrations on platelet production; KDC: hypothetical elimination rate constant for IFN; KAI: hypothetical absorption rate constant for IFN; ω^2_{SLPC} = covariance of random effect of SLPC; SD=standard deviation of additive error (=$[\sigma^2 add]^{0.5}$); σ^2_{prop} = proportional component of the residual error model; $\sigma^2 add$ = additive component of the residual error model.

Source: kpd402g8.res

The stimulatory effect of eltrombopag on platelet production was not shown to vary between different subpopulations. This is in contrast to the results obtained from a similar analysis in subjects with CLD (72 and 11% were identified as having HCVB and C aetiology, respectively), in which East Asian subjects were found to be less sensitive to the stimulatory effect of eltrombopag. In the analysis for CLD population, the majority of East Asian subjects were from one Japanese study. It is possible that the estimated racial effect on the platelet response was confounded by the difference or variability between different studies involved in that analysis.

Simulations

A number of simulations were performed in order to assess the impact of alternate eltrombopag dosing regimens prior to the initiation of antiviral therapy and during the course of antiviral therapy.

Simulation indicated that steady-state platelet response was achieved between Week 5 and Week 6 following once daily dosing of eltrombopag (see Figure 2). Approximately 30% of the steady-state platelet response was achieved after 2 weeks dosing, and approximately 60% of steady-state platelet response was achieved after 3 weeks dosing.

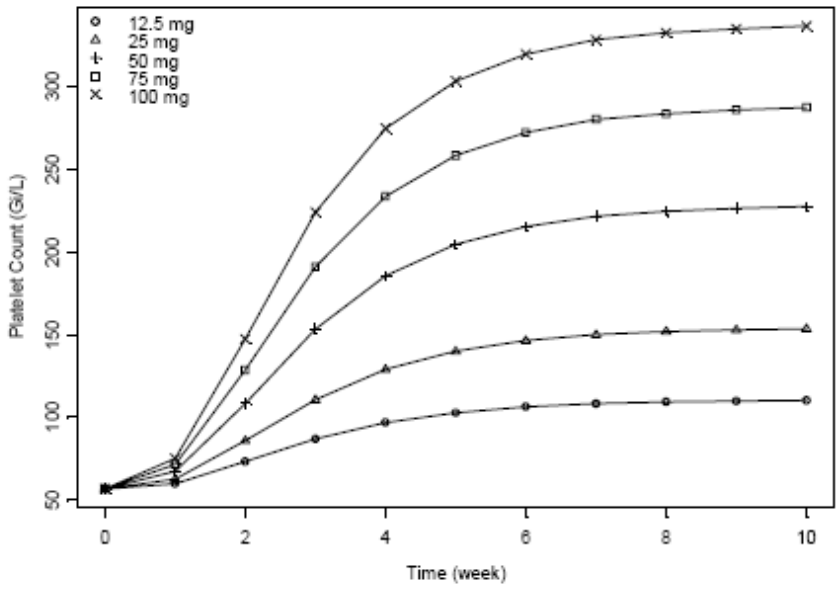


Figure 2. Median platelet count vs. time in thrombocytopenic HCV subjects following QD eltrombopag treatment for 10 weeks

Simulated platelet response following eltrombopag regimens of 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg once daily is proposed to support eltrombopag 25 mg once daily as an appropriate initial dose. The simulation predicted that approximately 45% (35%) of patients would achieve platelet counts >90 Gi/L (>100 Gi/L) following once daily dose of 25 mg eltrombopag for 2 weeks, enabling initiation of antiviral therapy (90 Gi/L for IFN alfa-2a and 100 Gi/L for IFN alfa-2b). Of these patients, approximately 97% would maintain platelet counts <200Gi/L.

Similar results were predicted across different subpopulations, with slightly higher proportion of East/Southeast Asian patients, 57% (47%), than non-East/Southeast Asian patients, 43% (32%), achieving platelet counts >90 Gi/L (>100 Gi/L) following 2 weeks of once daily dose at 25 mg eltrombopag, however the proportion of patients with platelet counts <200 Gi/L was comparable (94 to 98%) across subpopulations.

Simulation with a starting dose of 25 mg eltrombopag once daily followed by biweekly dose escalation up to 100 mg once daily were performed. In these simulations, the dose of eltrombopag was allowed to increase, in 25 mg increments up to a maximum of 100 mg, if the platelet count was predicted to be <60 Gi/L and to decrease in increments of 25 mg if the platelet count was predicted to be >200 Gi/L. Three different scenarios were simulated: platelet counts were evaluated once weekly, once every two weeks or once every three weeks. The dose of the pegylated IFN remained unchanged (180 µg/week for IFN alfa-2a or 1.5 µg/kg/week for IFN alfa-2b) during the course of the simulation.

Simulations indicated that approximately 50% of subjects required at least one eltrombopag dose adjustment during antiviral therapy to maintain sufficient platelet counts. Subjects who initiated antiviral therapy at the lowest eltrombopag dose of 25 mg were more likely to stay on the same dose through the antiviral therapy, whereas subjects who initiated antiviral therapy at 75 mg were more likely to require further eltrombopag dose escalation to 100 mg during antiviral

therapy. More frequent dose modification appeared to cause more subjects to be escalated to the higher eltrombopag doses. Finally, the results of simulations at the steady state which occurs 6 weeks post the last eltrombopag dose adjustment are shown in Table 9.

Table 9. Proportion of HCV subjects achieving target platelet thresholds 6 weeks after last eltrombopag dose adjustment following IFN initiation

		Platelet Threshold (Gi/L)			
Dose Modification Frequency/Duration	Eltrombopag Dose at End of Dose Modification	> 25	> 50	< 150	< 200
QW/15 weeks	Overall	95 (94, 95)	86 (84, 87)	74 (73, 76)	88 (87, 89)
	25 mg	100 (100, 100)	100 (99, 100)	45 (42, 49)	68 (64, 71)
	50 mg	100 (100, 100)	100 (99, 100)	79 (74, 83)	99 (97, 100)
	75 mg	100 (99, 100)	99 (98, 100)	83 (78, 87)	99 (97, 100)
	100 mg	86 (84, 89)	64 (61, 68)	97 (96, 98)	100 (100, 100)
E2W/14 weeks	Overall	94 (94, 95)	86 (84, 87)	75 (74, 77)	88 (87, 89)
	25 mg	100 (100, 100)	100 (100, 100)	46 (42, 50)	69 (65, 72)
	50 mg	100 (100, 100)	100 (99, 100)	82 (78, 85)	99 (98, 100)
	75 mg	100 (99, 100)	99 (97, 100)	89 (85, 92)	99 (98, 100)
	100 mg	83 (81, 86)	58 (54, 61)	99 (98, 99)	100 (100, 100)
E3W/15 weeks	Overall	94 (94, 95)	86 (84, 87)	75 (73, 77)	88 (87, 90)
	25 mg	100 (100, 100)	100 (100, 100)	46 (42, 49)	68 (65, 72)
	50 mg	100 (100, 100)	100 (99, 100)	82 (78, 85)	99 (98, 100)
	75 mg	100 (99, 100)	98 (97, 100)	91 (88, 94)	100 (99, 100)
	100 mg	82 (79, 84)	54 (51, 58)	99 (98, 99)	100 (100, 100)

Summarized as median (5^{th} percentile, 95^{th} percentile).

Drug-drug interaction study (TPL116010)

A drug-drug interaction (DDI) between eltrombopag and boceprevir or telaprevir has been initiated. The study evaluated the interaction between a single dose of eltrombopag 200 mg and repeat doses of boceprevir 800 mg Q8h (Cohort 1) and telaprevir 750 mg Q8h (Cohort 2) in healthy adult subjects. Preliminary results suggested no interaction between eltrombopag and boceprevir or telaprevir (Tables 10 and 11). Results of the impact of eltrombopag on plasma boceprevir PK are not yet available.

Table 10. Summary of Preliminary Results of Impact of Boceprevir and Telaprevir co-administration on Plasma Eltrombopag PK

Plasma eltrombopag PK parameter	**eltrombopag + boceprevir vs eltrombopag (N=26)**	**eltrombopag + telaprevir vs eltrombopag (N=27a)**
AUC(0-¥)	0.962 (0.853, 1.085)	0.939 (0.853, 1.035)
Cmax	0.923 (0.804, 1.060)	0.787 (0.610, 1.016)

N=26 for AUC(0-¥) Eltrombopag 200 mg single dose Boceprevir 800 mg Q8h x 10 days Telaprevir 750 mg Q8h x 10 days Treatment comparison presented as geometric least squares mean ratio (90% CI); ratio of 1.0=no drug interaction

Table 11. Summary of Preliminary Results of Impact of Eltrombopag co-administration on Plasma Telaprevir PK

Plasma telaprevir PK parameter	eltrombopag + telaprevir vs telaprevir (N=27)
AUC(0-t)	0.981 (0.939, 1.025)
Cmax	0.969 (0.913, 1.029)
Ct	0.948 (0.898, 0.999)
Eltrombopag 200 mg single dose Telaprevir 750 mg Q8h x 10 days Treatment comparison presented as geometric least squares mean ratio (90% CI); ratio of 1.0=no drug interaction	

2.4.4. Discussion on clinical pharmacology

Overall, the mean estimated PK parameters were similar to those published in literature. Certain subpopulations (females, elderly, East/Southeast Asian subjects) and HCV subjects with a Child-Pugh Score > 5 showed a lower CL/F, which translates into higher eltrombopag exposure. The PK parameters of pegylated IFN alfa-2a and alfa-2b were similar to what was already reported in the literature. The co-administration with eltrombopag did not show an impact on the PK of either IFN.

The influence of East Asian ethnicity (such as Chinese, Japanese, Taiwanese, Korean, and Thai) on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East Asians and 69 Southeast Asians). Based on estimates from the population pharmacokinetic analysis, East Asian patients had approximately 55 % higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimate, female HCV patient had approximately 41 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients (see SmPC section 5.2).

The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥ 75 years. Based on model estimate, elderly (≥ 65 years) patients had approximately 41 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients.

Data from the ELEVATE study were included in the model in order to have more subjects with a greater degree of hepatic impairment. The combined model confirmed both, age and hepatic impairment, as significant covariates. In addition, the MAH has also provided additional data on eltrombopag plasma exposure from HCV patients with and without hypoalbumemia (albumin<35 g/L). Based on the provided PK estimates and the observed safety profile, the CHMP agreed that the use of eltrombopag in patients with moderate-severe liver impairment (Child-Pugh score >5) should not be recommended. The SmPC has been updated to reflect the recommendations for eltrombopag use in subjects with hepatic impairment, including those with hypoalbuminemia. Moreover data available on patients with moderate-severe renal impairment is scarce and this fact has been appropriately reflected in the SmPC (see section 5.2).

The impact of age on eltrombopag CL/F was also re-evaluated on the combined model. Age remained a relevant covariate. The number of subjects ≥75 years old was small (n=4) and no PK data is available for subjects ≥85 years old. This has been adequately reflected in the SmPC (see section 5.2).

Results of a drug-drug PK interaction study show that co-administration of repeat doses of boceprevir 800 mg Q8h or telaprevir 750 mg Q8h with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg Q8h did not alter plasma telaprevir exposure. No information on the effect on boceprevir exposure is yet available (see SmPC section 4.5 and Benefit-risk balance). This data was considered important to address the safety and efficacy of eltrombopag in combination with new direct acting agents and has been included in the RMP as missing information. The applicant will provide post-authorisation the final results of the drug-drug interaction study of eltrombopag with boceprevir and telaprevir (TPL110610), and it has been reflected in the PhV plan of the RMP as category 3 (required additional pharmacovigilance activity).

2.4.5. Conclusions on clinical pharmacology

The effect of the co-administration of eltrombopag and IFN alfa-2a plus ribavirin or IFN alfa-2b plus ribavirin was studied by performing population PK analyses. 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.

The simulations provided by the MAH are comprehensive for the current recommended posology prior to and after initiation of antiviral therapy with IFN.

2.5. Clinical efficacy

The primary evidence for the efficacy and safety of eltrombopag in the treatment of adult patients with HCV-associated thrombocytopenia is provided by two Phase III double-blind, placebo-controlled studies, TPL103922 (ENABLE 1) and TPL108390 (ENABLE 2). The design of both studies followed the advice received from the EMA prior to initiating the Phase III studies. An additional phase II supportive dose-finding study was submitted.

2.5.1. Dose response study

TPL102357 Study

Methods

Study TPL102357 was a double-blind, randomized, placebo-controlled, multi-centre, dose-ranging, parallel group, Phase II pilot study in male and female subjects with HCV infection and platelet counts of 20 to <70Gi/L who were otherwise eligible to begin treatment with peginterferon and ribavirin.

Approximately 160 subjects were planned to be randomized equally (1:1:1:1) into one of four treatment groups of 40 subjects. Stratification was according to baseline platelet count (20 to <50 Gi/L and ≥50 to <70 Gi/L). Male and female subjects ≥ 18 years of age with chronic HCV (defined as the presence of HCV antibodies and detectable HCV RNA) who had compensated liver disease and pre-existing thrombocytopenia (platelet count of 20 to <70 Gi/L) were recruited. Subjects were required to have a liver biopsy indicative of chronic hepatitis, or radiographic evidence of cirrhosis or endoscopic evidence of portal hypertension.

The study was conducted in two phases, Parts 1 and 2. In Part 1, study subjects were randomized 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.

The primary objective of the study was to evaluate the effect of eltrombopag on platelet counts when administered once daily for 4 weeks (Part 1, Pre-antiviral Therapy Phase) to subjects with chronic HCV-related thrombocytopenia, prior to receiving antiviral therapy. Secondary objectives included evaluation of the following: effects of eltrombopag on platelet counts when administered once daily for 12 weeks during antiviral therapy (Part 2), effects of eltrombopag on markers of thrombopoiesis when administered once daily for 16 weeks, effects of eltrombopag on antiviral treatment outcome measures during and after antiviral therapy, safety and tolerability of eltrombopag when administered once daily for 16 weeks, and population pharmacokinetic (PK) profile of eltrombopag when administered once daily for 16 weeks to subjects with chronic HCV.

The primary endpoint was the proportion of subjects with a shift from baseline platelet count (between 20 and <70Gi/L) to ≥100Gi/L after 4 weeks (Part 1, pre-antiviral phase) of administration of eltrombopag prior to receiving antiviral therapy. For the purpose of the primary analysis, missing platelet count data from Weeks 2 to 4 in Part 1 was replaced with the previous observation, i.e. the last observation was carried forward (LOCF).

The study was initiated on 5 April 2005 in Europe and the USA. The study was originally planned with no interim analysis, except for a blinded review of safety and tolerability by an IDMC when 40 subjects completed Part 1. After the study began, Protocol Amendment 02 was implemented on 25 August 2005 which stipulated performing a formal interim analysis on the Part 1 data. The

interim analysis was conducted to assess treatment effect with the purpose of supporting a possible extension of the treatment period to 48 weeks. The interim analysis, conducted on 8 November 2005, included subjects who had completed 4 weeks of treatment or were withdrawn as of October 2005. The number of subjects included in the interim analysis was 33.

As a result of this first interim analysis, plasma levels of eltrombopag were found at a higher level in HCV-infected subjects than previously documented in healthy volunteers. The eltrombopag exposures observed were between the NOAEL and the level where cataracts were observed in repeat dose toxicity studies in rodents. As a result of this unexpected finding, the sponsor decided to suspend further enrolment into this study as of 22 December 2005 while additional PK/pharmacodynamic analyses were undertaken to better understand the exposure-response relationship and to try to identify if there were any underlying factors (e.g. decreasing liver function) that might explain the high exposure findings.

Subsequent inconclusive PK data generated from the first interim analysis resulted in Protocol Amendment 03 being implemented on 9 March 2006 to conduct a full analysis of Part 1 and Part 2 data from all subjects enrolled as of 22 December 2005 (N=74). This full analysis of all data collected in-house as of 2 June 2006 was planned to determine whether the data from additional subjects would provide sufficient evidence to permanently stop the study for efficacy or safety. Results from this analysis showed a statistically significant treatment effect on platelet response after 28 days of eltrombopag alone ($p<0.0001$). As a result of reaching the pre-defined statistical stopping criteria for efficacy, the sponsor officially terminated enrolment to this study on 23 June 2006.

The 74 subjects contained in the second and final analysis continued to be followed-up until the all subjects' 6 month post-treatment ocular assessment had been performed. The database for this study was frozen on 30 November 2006. The final results presented are based on the 30 November 2006 database.

Results

Subjects in the ITT Population had a median age of 51 years and 52 (70%) subjects were male. Most subjects (64 subjects, 86%) were White/Caucasian/European heritage. The four treatment groups were generally balanced with regard to demographic characteristics (see Table 12).

Table 12. Subject Disposition: ITT Population

Disposition Category	Number of Subjects, n (%)				
	PBO	30mg	50mg	75mg	Total
Number entering Part 1[a]	**18 (100)**	**14 (100)**	**19 (100)**	**23 (100)**	**74 (100)**
Number entering Part 2[b]	**4[c] (22)**	**10[d] (71)**	**14 (74)**	**21 (91)**	**49 (66)**
Pegasys + ribavirin	3 (17)	6 (43)	7 (37)	13 (57)	29 (39)
Peg-Intron + ribavirin	1 (6)	4 (29)	7 (37)	8 (35)	20 (27)

a. Part 1 was 4 weeks treatment with eltrombopag or placebo prior to antiviral therapy.
b. Part 2 was 8-12 weeks treatment with eltrombopag or placebo during antiviral therapy.
c. Three placebo-treated subjects were erroneously entered into Part 2. Two subjects (755 and 759) entered into Part 2, although their platelet counts were not sufficiently elevated. Both were withdrawn from Part 2. Subject 251 entered Part 2, received 1 dose of antiviral medication, and was withdrawn on Day 28 because of lack of efficacy (platelet counts too low).
d. Subject 16 entered Part 2 according to Attachment 4, Listing 17.04, although Attachment 4, Listing 16.01 states this subject withdrew on Day 21 due to an adverse event. On Day 21, the subject withdrew from treatment with eltrombopag, but not from the study.

In Part 1, 25 subjects (34%) were withdrawn from the study. Most of the withdrawals were from the placebo group due to lack of efficacy and the fewest were from the 75mg treatment group. At all treatment visits, the highest response rate was observed in the eltrombopag 75mg group (see Table 13).

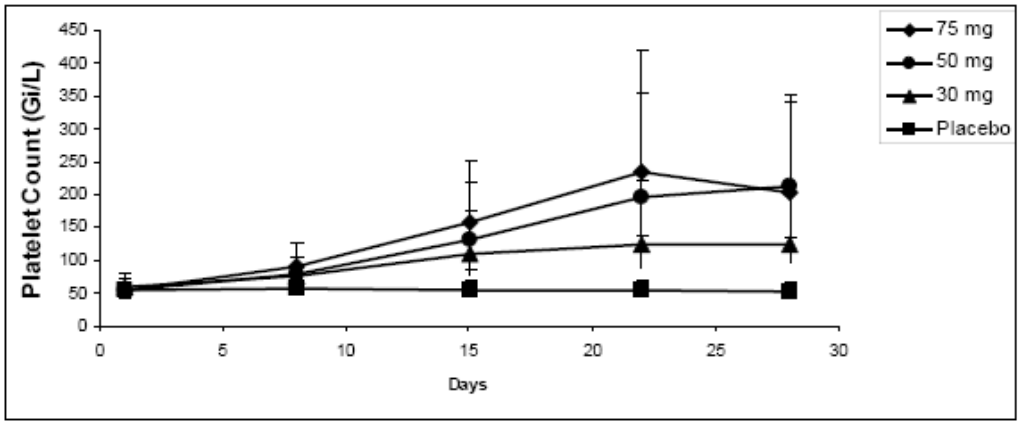
Table 13. Responders by Visit in Part 1: ITT Population (LOCF Data)

Assessment Visit	Treatment Group, Number of Responders[a] (%[b])			
	PBO N=18	30mg N=14	50mg N=19	75mg N=23
Day 8 Visit	0	2 (17)	4 (21)	6 (29)
Day 15 Visit	0	8 (67)	12 (63)	18 (86)
Day 22 Visit	0	8 (67)	15 (79)	20 (95)
Day 28 Visit (Week 4)	**0**	**9 (75)**	**15 (79)**	**20 (95)**

a. A responder was defined as a subject with a shift in baseline platelet count of 20Gi/L – <70Gi/L to ≥100 Gi/L at Day 28.
b. Percentage is calculated with the number evaluable as a denominator.

In Part 1 (prior to antiviral treatment), subjects with a baseline platelet count of 50 to <70Gi/L had higher response rates compared to subjects with a baseline platelet count of 20Gi/L to <50Gi/L. The number and percentage of responders to treatment in Part 1 in the per protocol and ITT populations using the Observed dataset (adjusting for baseline platelet count strata) was similar to that in the ITT Population using the LOCF dataset.

The mean change in platelet count from baseline was analysed using ANCOVA adjusting for baseline platelet count strata in the ITT Population (Observed Data). The mean change from baseline in platelet count with eltrombopag treatment increased in a dose-dependent manner at the Week 4 Visit (see Figure 3). There was a significant change from baseline in platelet counts compared to placebo at each dose of eltrombopag at the Week 4 Visit; results were -3.5, 119.9, 151.7 and 186.4 Gi/L for placebo, 30, 50 and 75 mg groups, respectively.



Bars represent inclusion of the 25th to 75th percentiles for each treatment group.

Figure 3. Median Platelet Counts in Part 1 Prior to Antiviral Therapy: ITT Population

The proportion of subjects who were responders with a platelet count >200Gi/L increased in a dose-dependent manner with eltrombopag treatment; results were 0, 25, 47, and 52% at the week 4 visit for placebo, 30, 50 and 75 mg groups, respectively. Once platelet values exceeded 200Gi/L, subjects were instructed to interrupt treatment until the platelet count dropped below approximately 100Gi/L.

In Part 2, subjects were to receive an additional 8 to 12 weeks of eltrombopag or placebo administered daily during antiviral therapy. The median platelet counts decreased during the antiviral treatment phase compared to the pre-antiviral phase, however they remained above the median baseline platelet counts in each eltrombopag treatment group (see Figure 4).

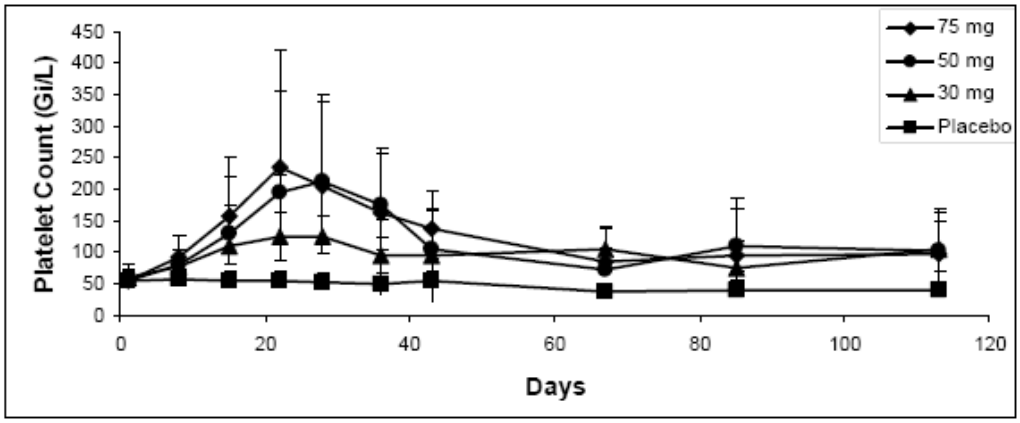


Figure 4. Median Platelet Counts in Parts 1 and 2: ITT Population

Results of other endpoints:

- The proportion of subjects with any peginterferon dose reductions decreased with increasing doses of eltrombopag.
- The viral load (average serum HCV RNA) was reduced following initiation of antiviral therapy in a dose-dependent manner.
- The number of subjects with a viral response (>2 $\log_{10}$ reduction from baseline assessment to endpoint assessment or undetectable HCV RNA at endpoint assessment) increased in a dose-dependent manner.

2.5.2. Main studies

Two pivotal Phase III studies investigating the safety and efficacy of eltrombopag in the treatment of thrombocytopenia in adults with HCV were conducted. ENABLE 1 and ENABLE 2 were both multi-centre, randomised, double-blind, placebo-controlled studies, with identical study designs, differing only in the pegylated interferon (peginterferon) used.

Title of Studies

ENABLE 1 (Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C Related Liver DiseasE): Randomised, placebo-controlled, multicentre study to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with

hepatitis C virus (HCV) infection who are otherwise eligible to initiate antiviral therapy (peginterferon alfa-2a plus ribavirin).

ENABLE 2 (Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C Related Liver DiseasE): Randomised, placebo-controlled, multicentre study to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with hepatitis C virus (HCV) infection who are otherwise eligible to initiate antiviral therapy (peginterferon alfa-2b plus ribavirin).

Methods

Study Participants

Main inclusion criteria

- Male or female subjects aged ≥ 18 years of age with chronic HCV infection who were appropriate candidates for peginterferon and ribavirin combination antiviral therapy
- Platelet count of <75 Gi/L (calculated as the average of the screening and baseline counts. Up to one additional platelet count assessment was allowed between screening and baseline.)
- Haemoglobin concentration ≥ 11.0 g/dL for men or ≥ 10.0 g/dL for women
- Creatinine clearance ≥ 50mL/minute
- Absolute neutrophil count ≥ 750/mm^3
- Enrolment of subjects with a baseline platelet count of <20 Gi/L, haemoglobin concentration <13.0 g/dL (men) or <12.0 g/dL (women), or ANC <1500/mm^3 required approval from the GSK Medical Monitor to ensure subject suitability for the study (ie, to exclude underlying medical conditions, other than the disease being studied, and in consideration of the safety of the subject with regard to the possibility of randomising to placebo during Part 2).

Main exclusion criteria

- Prior treatment with interferon within the 30 days of the screening visit
- Non-responders to previous treatment with peginterferon and ribavirin who failed to achieve a SVR for reasons other than thrombocytopenia, despite an optimal course of combination therapy
- Subjects with a known hypersensitivity, intolerance or allergy to peginterferon, ribavirin, eltrombopag or any of their ingredients
- Decompensated liver disease, e.g. Child-Turcotte-Pugh score >6 or history of ascites or hepatic encephalopathy or current evidence of ascites
- Evidence of portal vein thrombosis on abdominal imaging within 3 months of baseline visit
- History of arterial or venous thrombosis, **and** ≥ 2 of the following risk factors (except in Canada)
- hereditary thrombophilic disorders (e.g. Factor V Leiden, ATIII deficiency, etc.); hormone replacement therapy; systemic contraception therapy (containing oestrogen); smoking; diabetes; hypercholesterolaemia; medication for hypertension or cancer

- Any disease condition associated with active bleeding or requiring anticoagulation with heparin or warfarin
- Subjects with a history of platelet clumping that would prevent reliable measurement of platelet counts

Treatments

Treatment 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) (see Figure 5).

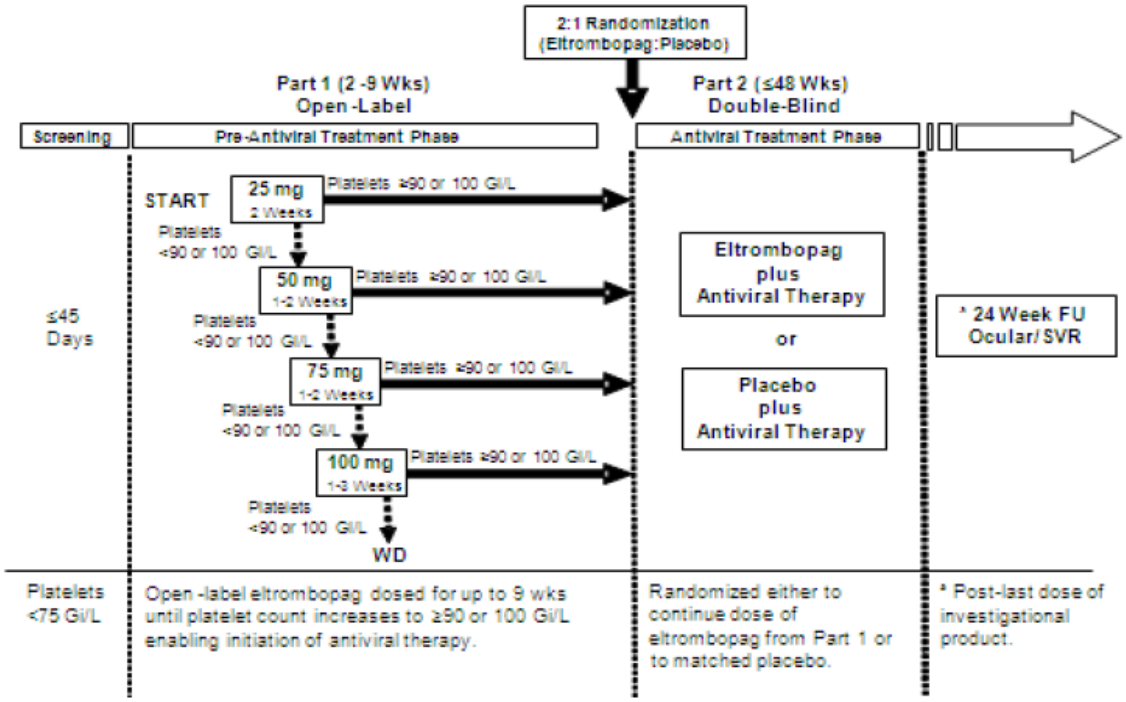


Figure 5. Study Schematic of Pivotal Studies ENABLE 1 and ENABLE 2

- Part 1 Pre-Antiviral Treatment Phase (OL Phase): All subjects received OL eltrombopag dosed once daily with the objective of increasing platelet counts to ≥90 Gi/L (ENABLE 1) or ≥100 Gi/L (ENABLE 2). 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 (ENABLE 1) or <100 Gi/L (ENABLE 2), 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 (ENABLE 1) or ≥100 Gi/L (ENABLE 2). Once subjects achieved platelet counts ≥90 Gi/L (ENABLE 1) or ≥100 Gi/L (ENABLE 2), they were eligible to enter the randomised part of the study (Part 2) and initiate antiviral therapy (peginterferon alfa-2a (ENABLE 1) or alfa-2b (ENABLE 2) plus ribavirin). Subjects with platelet counts <90 Gi/L (ENABLE 1) or <100 Gi/L (ENABLE 2) after the 9 week Pre-Antiviral Treatment Phase were discontinued from eltrombopag and switched to post-treatment follow-up visits.

- Part 2 DB Antiviral Treatment Phase (DB Phase): The overall aim of Part 2 was to avoid dose reductions of antiviral therapy due to thrombocytopenia by optimising the dose of eltrombopag/matched placebo. 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. In combination with ribavirin, the recommended dose of peginterferon alfa-2a is 180 µg per week, and that for peginterferon alfa-2b is 1.5 µg/kg per week; for genotype 2/3, 24 weeks treatment was to be given, for genotype non-2/3, 48 weeks of antiviral therapy. Subjects eligible to enter Part 2 of the study were instructed by study personnel on how to self administer the first dose of peginterferon at the Antiviral Treatment Phase baseline visit. Administration was by subcutaneous injection. 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/alfa-2b or ribavirin were performed as directed within the product labels.

Objectives

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

The secondary objectives were

- to evaluate the ability of eltrombopag to enable initiation of antiviral therapy in thrombocytopenic subjects with HCV infection
- to evaluate the effect of eltrombopag on platelet counts in thrombocytopenic subjects with HCV infection, before and during antiviral therapy
- to evaluate the 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
- to evaluate the ability of eltrombopag to enable maintenance of antiviral therapy in thrombocytopenic subjects with HCV infection
- to evaluate the safety and tolerability of eltrombopag when administered once daily in thrombocytopenic subjects with HCV infection
- to evaluate the impact of eltrombopag on subject 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)
- to describe the pharmacokinetics of eltrombopag and explore the relationship between the PK of eltrombopag and relevant safety and efficacy endpoints
- to describe the PK of peginterferon alfa-2a/b during concomitant dosing with eltrombopag.

Data published after the initiation of the ENABLE studies reported that genetic variants, rs12979860 and rs8099917, which map near IL28B are associated with IFN-induced SVR in patients with chronic hepatitis C. Therefore, a genetic analysis was conducted to evaluate if there

were any differences in the distribution of IL28B favourable response genotypes between subjects receiving placebo versus subjects receiving eltrombopag and to evaluate the association of the published IL28B favourable response genotypes with virologic response.

Outcomes/endpoints

Primary endpoint

SVR rate defined as percentage of subjects with undetectable HCV-RNA at end of treatment and all subsequent planned visits up to 24 weeks after completing treatment (generally Weeks 48 or 72 for genotype 2/3, or Week 72 for genotype non-2/3). If a subject had a positive HCV RNA ("blip") between two visits with undetectable HCV RNA, then the subject was considered a sustained virological responder provided that the detectable HCV RNA was of the same order of magnitude as the limit of detection.

Secondary endpoints

- Initiation of antiviral therapy: platelet shift from baseline count to ≥ 90/100 Gi/L with OL eltrombopag; proportion of subjects initiating antiviral therapy; time to initiation of antiviral therapy
- Antiviral therapy dose reductions: proportions of subjects requiring dose reductions and/or dose cessation of peginterferon and/or ribavirin therapy; time to the first antiviral therapy dose reduction
- Adherence to Antiviral Therapy: proportion of subjects showing adherence (defined as receiving at least 80% of the prescribed dose of peginterferon and of ribavirin, for at least 80% of the planned duration)
- Platelet counts with antiviral therapy: assessment of platelet counts throughout the study
- Other Antiviral Endpoints: proportions of subjects achieving the following antiviral outcome measures
- undetectable HCV RNA after 12 weeks of antiviral treatment (cEVR)
- clinically significant reduction in HCV RNA (≥ 2 log10 drop or undetectable) after 12 weeks of antiviral treatment (EVR)
- undetectable HCV RNA after 4 weeks of antiviral treatment (RVR)
- undetectable HCV RNA at the end of antiviral treatment (ETR).
- Pharmacogenetic investigation: to determine that the IL28B genotype frequencies do not differ between the study treatment populations and if IL28B variants (rs12979860 and rs8099917) affect PEG-IFN alfa/RBV-induced virological response (SVR and RVR) in subjects treated with eltrombopag to enable the use of PEGIFN/RBV for the treatment of chronic hepatitis C.

Platelet count eligibility (<75 Gi/L), confirmed at the baseline visit (Day 1) prior to administration of eltrombopag, was defined as the average of the screening and baseline counts. Up to 1 additional platelet count assessment was allowed between screening and baseline and in those cases the average of the 3 counts had to be <75 Gi/L for the subject to be eligible.

For subjects who prematurely withdrew, HCV RNA Viral Load was assessed at the 24 week follow up visit. The Hepatitis C Viral RNA quantitative transcription-mediated amplification was used to quantitate the level of HCV RNA in serum or plasma (down to the level of 5 IU/mL).

Sample size

Determination of the sample size was based on the following assumptions: the proportion with SVR with placebo will be 10%; the study would have 92.5% power to detect a statistically significant treatment effect of 10% at two-sided alpha=5%; there would be three interim analyses and one final analysis; Haybittle-Peto criteria would be used to protect against increasing the type I error rate with repeated interim analyses; treatments would be allocated on a 2:1 ratio of eltrombopag to placebo.

A total of 675 subjects (450 on eltrombopag and 225 on placebo) were required to be randomised. It was estimated that approximately 10% of subjects would not complete the pre-antiviral treatment phase. Therefore, 750 subjects would be enrolled in order to randomise 675 subjects.

Randomisation

All subjects received OL eltrombopag during Part 1 of the study. Prior to initiating antiviral therapy in Part 2, eligible subjects were randomised to either continue the eltrombopag dose from Part 1, or, matched placebo in a 2:1 ratio of eltrombopag: placebo in accordance with the randomisation schedule. Study centres registered and randomised subjects by telephone using an Interactive Voice Response System (IVRS). The IVRS was available 24 hours a day, 7 days a week. The OL eltrombopag and the DB eltrombopag/placebo supplies were managed through the IVRS.

Randomised treatment was given to the investigator or his/her designee through a mechanism which maintained the blind. Once allocated, a randomisation number was not reassigned to another subject.

Blinding (masking)

During Part 1 of the study, eltrombopag treatment was open label. During Part 2, eltrombopag/matched placebo treatment (but not dose) was blinded to the research subjects and all study and sponsor personnel. Treatment blind was maintained by the use of matching eltrombopag placebo tablets. The antiviral therapy was open label. Only in the case of an emergency, when knowledge of the study treatment was essential for the appropriate clinical management or welfare of the subject, was the investigator or treating physician permitted to unblind a subject's treatment assignment via IVRS (preferably after discussion and agreement with the Medical Monitor or appropriate GSK study personnel). Where the blind was broken for any reason, the investigator was required to notify the MAH immediately of the unblinding incident without revealing the subject's study treatment assignment, unless considered relevant to the safety of subjects in the study.

GSK's Global Clinical Safety and Pharmacovigilance staff could unblind the treatment assignment for any subject with a serious adverse event (SAE). If the SAE required that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying

the subject's treatment assignment, was sent to clinical investigators in accordance with local regulations and/or GSK policy.

Statistical methods

The ENABLE studies were monitored by an Independent Drug Monitoring Committee (IDMC). Three formal interim analyses of the primary efficacy endpoint were planned: after 25%, 50%, and 75% of the subjects in each study had completed all their follow-up visits. The p-values and confidence intervals (CI) reported for the primary analyses were adjusted for the interim analyses.

Except where otherwise noted, the statistical model on which inference was based included terms for the strata: HCV genotype (genotype 2/3, non-genotype 2/3), baseline platelet count (<50 Gi/L and ≥50 Gi/L), baseline HCV RNA (<800,000 IU/mL and ≥800,000 IU/mL). The primary endpoint was analysed separately for subgroups of geographic region, and various demographic and baseline disease characteristics.

Analysis populations

- Enrolled Population: subjects who had passed screening and entered the study.
- Safety population: subjects who had received OL study drug. The Safety population is a subset of the Enrolled population. The Safety population was used for the following objectives:
    - to evaluate the ability of eltrombopag to enable initiation of antiviral therapy;
    - to evaluate the safety and tolerability of eltrombopag.
- ITT population: all randomised subjects. Subjects were analysed according to the stratum and treatment they were assigned at randomisation, regardless of whether it was assigned correctly. The ITT population was a subset of the Safety Population and was the primary population for the analysis of efficacy during the DB Phase.
- Safety Double-Blind (DB) population: all randomised subjects who received DB study drug. Subjects were analysed as treated, i.e. according to the treatment received. The Safety DB population was a subset of the ITT population. The Safety DB population was used to compare the safety of eltrombopag (plus antiviral therapy) with placebo (plus antiviral therapy).
- Per-Protocol (PP) population: all randomised subjects who did not violate any important inclusion and exclusion criteria that pertained to the assessment of treatment efficacy, and who incurred no protocol deviations that pertained to the assessment of treatment efficacy. The PP population, identified prior to unblinding of the study, was used to analyse the primary endpoint and the key secondary endpoint.

Missing data

For the primary analysis, if a subject had a missing value between visits, then the previous non-missing HCV RNA assessment and associated classification was carried forward to fill in the missing value. If a subject's HCV RNA at 24 week follow-up assessment was missing for any reason, the subject was considered a non-responder. A subject with missing data due to premature discontinuation of treatment, or from the study for any reason was considered a non-responder for all subsequent visits.

Primary efficacy analysis

The proportion of subjects with SVR was summarised by treatment group, and were compared between eltrombopag and placebo using stratified Cochran-Mantel-Haenszel chi-square test statistics adjusting for HCV RNA genotype, baseline platelet count stratum, and baseline HCV RNA stratum (randomisation strata). The Breslow-Day test for homogeneity of treatment effect was used to evaluate the relevant interactions. The model-adjusted absolute difference in proportions and associated 95% CI were estimated. The estimate was derived using general linear modelling with the SAS GENMOD procedure. The dependent variable was SVR (yes/no) and the independent variables were actual stratification factors as well as treatment. The binomial distribution with identity link function was specified.

Secondary efficacy analyses

- Initiation of antiviral therapy: Platelet counts with OL eltrombopag were summarised using descriptive statistics for different levels of platelet cut off points. The proportion of subjects initiating antiviral therapy as well as the time to initiation of antiviral therapy was summarised. Endpoints related to initiation of antiviral therapy were analysed for the Safety Population.
- Antiviral therapy dose reductions: Subjects were assigned a score equal to the number of times their dose of antiviral therapy, either peginterferon or ribavirin was reduced. The proportions of subjects in each category were summarised by treatment group. The treatment groups were compared using the Wilcoxon rank sum test, adjusting for HCV genotype, baseline platelet count stratum, and baseline HCV RNA stratum (randomisation strata). Time to the first antiviral therapy dose reduction (peginterferon) was analysed using the stratified log-rank test adjusting for HCV genotype, baseline platelet count stratum, and baseline HCV RNA stratum (randomisation strata). Kaplan-Meier plot of time to first peginterferon dose reduction was produced.
- Adherence to Antiviral Therapy: Adherence has been defined as receiving at least 80% of the prescribed dose of peginterferon and at least 80% of the prescribed dose of ribavirin, for at least 80% of the planned duration (38 weeks for subjects with 48 weeks of planned treatment and at least 19 weeks for subjects with 24 weeks of planned treatment). The proportion of subjects showing adherence was analysed using stratified CMH chi-square test statistics adjusting for HCV genotype, baseline platelet count stratum, and baseline HCV RNA stratum (randomisation strata). Descriptive statistics for the association of adherence to antiviral therapy with SVR was computed. The strength of association was assessed using the chi-square tests for association.
- Permanent discontinuation of antiviral therapy: The proportion of subjects who discontinued from antiviral therapy (peginterferon) for any reason was analysed using stratified CMH chi-square test statistics adjusting for HCV genotype, baseline platelet count stratum, and baseline HCV RNA stratum (randomisation strata). Time to permanent discontinuation of antiviral therapy was analysed using stratified log-rank test adjusting for HCV genotype, baseline platelet count stratum, and baseline HCV RNA stratum. Kaplan-Meier plot of time to permanent discontinuation of peginterferon was produced. Reasons for permanent discontinuation were summarized by randomised treatment group.
- Platelet counts with antiviral therapy: Descriptive statistics were provided for platelet counts over time, change from baseline over time (i.e., at each scheduled visit), and

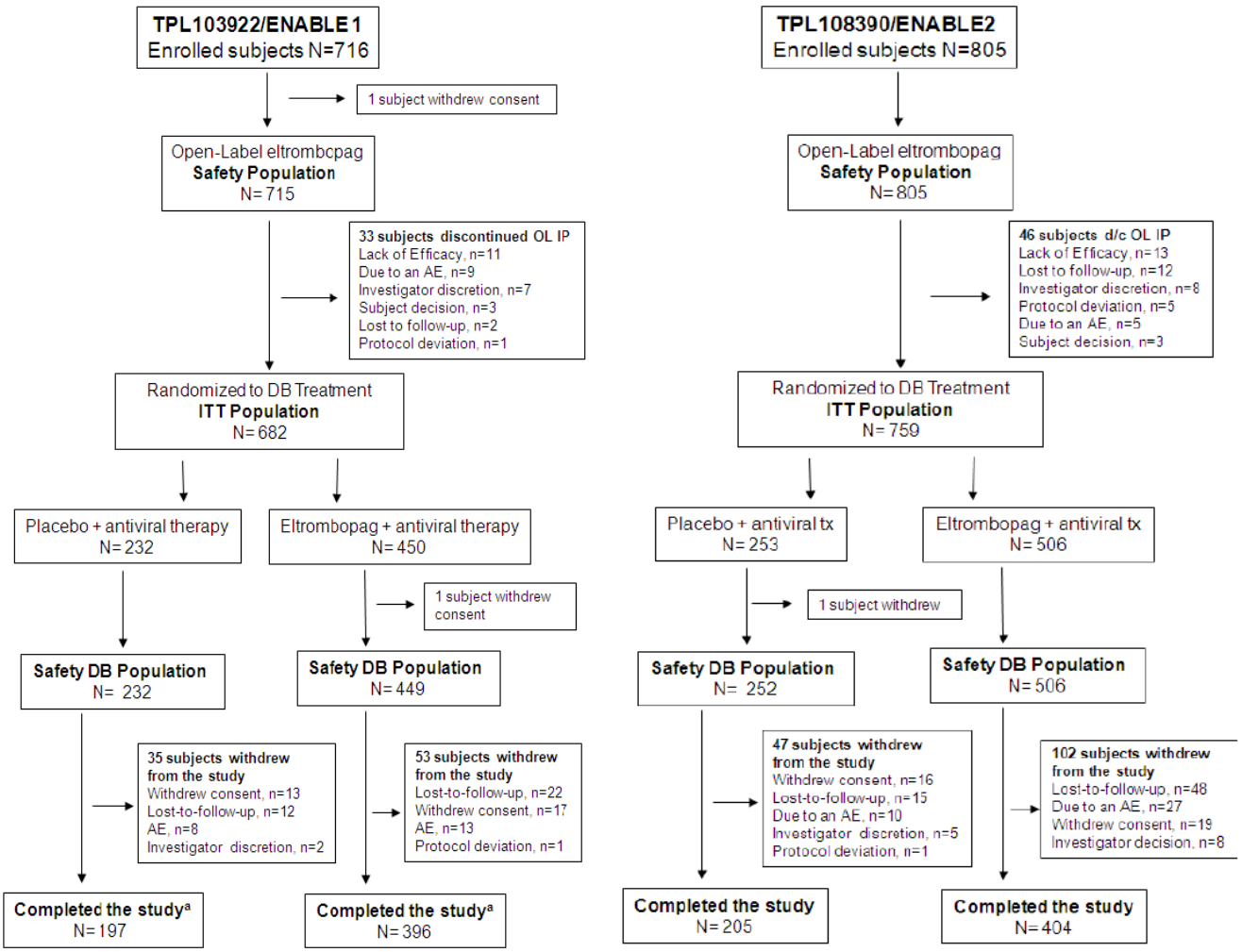
changes from antiviral baseline over time. Durability or duration of platelet response (count achieved to allow initiation of antiviral treatment) was defined as the time in weeks from antiviral baseline to the first time platelets became <50 Gi/L.

- Platelet counts with antiviral therapy after stopping DB study drug: Analysis of platelet counts after stopping double blind study drug were summarised using descriptive statistics or frequency counts as appropriate.

Other Antiviral Endpoints: The other antiviral endpoints were rapid virologic response (RVR), extended rapid virologic response (eRVR), early virologic response (EVR), end of treatment response (ETR), and virologic response at end of treatment as well as 12 week follow-up assessment. These were analysed for the ITT population using stratified CMH chi-square test statistics, adjusting for HCV genotype, baseline platelet count stratum, and baseline HCV RNA stratum wherever applicable.

Results

Participant flow



Recruitment

ENABLE 1 ran from 30 Oct 2007- 31-Mar 2011, and ENABLE 2 from 30 October 2007 – 23 August 2011.

Conduct of the study

The ENABLE protocols were amended 3 times.

- 24-Aug-2007 Amendment 01: Addition of enhanced renal safety monitoring. Revised Liver Chemistry stopping criteria. Modification of eligibility criteria. Addition of secondary endpoint Reclassification of exploratory endpoint to secondary endpoint. Minor changes to add clarity to protocol wording.
- 20-Nov-2007 Amendment 02: A Companion Protocol was written to encompass the pharmacogenetic research for Study TPL103922 in accordance with Brazilian Regulations. This amendment was required by Brazilian law and requested by the Comissao Nacional de Etica em Pesquisa (CONEP; National Comission for Ethics in Research). The Companion Protocol will apply only in Brazil to comply with Brazilian regulations and laws regarding genetic research (Rule 347, 2005).
- 19-Dec-2007 Amendment 03: A country specific Amendment to Exclusion Criteria No. 9. This amendment was requested by Health Canada to exclude subjects with any prior history of arterial or venous thrombosis, irrespective of associated risk factors.

Protocol deviations

In ENABLE 1, 6% of subjects were excluded from the PP Population; the exclusions were mainly due to evidence of decompensated liver disease (defined as a CP score >6) at baseline and this was similar between treatment groups (see Table 14).

Table 14. Summary of Reasons for Exclusion from the PP Population (ENABLE 1)

	Number of Subjects (%)		
	Placebo (N=232)	Eltrombopag (N=450)	Total (N=682)
Number of subjects excluded from the PP population[a]	16 (7)	26 (6)	42 (6)
Reason for exclusion			
Subjects with evidence of decompensated liver disease	15 (6)	22[b] (5)	37 (5)
Subjects who did not receive the treatment to which they were randomised	0	2 (<1)	2 (<1)
Subjects who did receive the treatment to which they were randomised, but subsequently switched treatments	0	2[c] (<1)	2 (<1)
Subjects without evidence of chronic HCV infection	1 (<1)	1 (<1)	2 (<1)

a. Protocol deviations and any action taken regarding exclusion of subjects or affected data are specified in the RAP Section 9.3.
b. Subject 348 had 2 reasons for exclusion from the PP Population
c. Both subjects were reandomized to eltrombopag and received eltrombopag. However, they did not receive the container number to which they were assigned

In ENABLE 2, 5% of subjects were excluded from the PP Population; again the exclusions were mainly due to evidence of decompensated liver disease at baseline and this was similar between treatment groups (see Table 15).

Table 15. Summary of Reasons for Exclusion from the PP Population (ENABLE 2)

	Number of Subjects (%)		
	Placebo (N=253)	Eltrombopag (N=506)	Total (N=759)
Number of subjects excluded from the PP population[a]	17 (7)	24 (5)	41 (5)
Reason for exclusion			
Subjects with evidence of decompensated liver disease	11 (4)[b]	15 (3)	26 (3)
Subjects who did not receive the treatment to which they were randomised	5 (2)[b]	4 (<1)	9 (1)
Subjects who did receive the treatment to which they were randomised, but subsequently switched treatments	2 (<1)	2 (<1)	4 (<1)
Subjects without evidence of chronic HCV infection	1 (<1)[b]	2 (<1)	3 (<1)
Subjects randomised with platelet count <100 Gi/L	0	1 (<1)	1 (<1)

a. Protocol deviations and any action taken regarding exclusion of subjects or affected data are specified in the RAP Section 9.3.

b. Two Subjects had 2 reasons for exclusion from the PP Population; decompensated liver disease plus Subject 1480 did not receive correct treatment and Subject 4164 had no evidence of chronic HCV (see Listing 26.0005)

Baseline data

ENABLE 1

The baseline demographic and disease characteristics are shown in Table 16.

Table 16. Baseline demographic and disease characteristics (ENABLE 1, safety population)

Demographics		
OL Phase (Part 1)	**Eltrombopag**	
N (Safety Population)	**715**	
Females: Males	269:446	
Mean Age, years (SD)	51.8 (8.45)	
White, n (%)	516 (72)	
HCV Genotype		
1	458 (64)	
2	54 (8)	
3	178 (25)	
4	17 (2)	
6	6 (<1)	
Child-Pugh Classification		
A (score 5 - 6)	670 (94)	
B (score 7 - 9)	44 (6)	
Mean Alanine Aminotransferase (SD); IU/L	87.55 (52.27)	
Mean HCV RNA (SD); IU/mL	1,897,064.5 (3,251,053.17)	
Mean Platelet Count (SD); Gi/L	56.51 (13.817)	
DB Phase (Part 2)	**Placebo**	**Eltrombopag**
N (ITT Population)	**232**	**450**
Females: Males	73:159	186:264
Mean Age; years (SD)	51.4 (8.52)	52.1 (8.35)
White; n (%)	166 (72)	326 (72)
HCV Genotype; n (%)		
1	149 (64)	292 (65)
2	22 (9)	27 (6)
3	54 (23)	115 (26)
4	5 (2)	11 (2)
6	2 (<1)	4 (<1)
Child-Pugh Classification; n (%)		
A (score 5 – 6)	217 (94)	424 (94)
B (score 7 – 9)	15 (6)	25 (6)
Previous Interferon Use; n (%)		
Naïve	152 (66)	307 (68)
Experienced	80 (34)	143 (32)
FibroSURE Score; n (%)		
0/1/2	23 (10)	37 (8)
3/4	185 (80)	354 (79)
ALT; n (%)		
Normal	54 (23)	103 (23)
Elevated	178 (77)	347 (77)
Mean HCV RNA (SD); IU/mL	1,880,278.4 (3,395,777.02)	1,870,562.1 (3,080,918.03)
Mean Platelet Count (SD); Gi/L	57.40 (12.890)	56.87 (13.603)

HCV FibroSURE is a noninvasive blood test that combines the quanitative results of 6 serum biochemical markers (α2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, γ-glutamyl transpeptidase (GGT), and ALT), with a subject's age and gender to generate a measure of fibrosis/cirrhosis and necroinflammatory activity in the liver. It provides a numerical quantitative estimate of liver fibrosis ranging from 0.00 to 1.00 corresponding the the Metavir scoring system of stages F0 to F4 (F0=no fibrosis, F1=portal fibrosis, F2=bridging fibrosis with few septa, F3=bridging fibrosis with many septa, F4=cirrhosis). A high proportion of subjects had FibroSURE score equivalent to Metavir F3 or F4, indicative of bridging fibrosis and cirrhosis.

Subjects were stratified at baseline by platelet count, HCV RNA and genotype (see Table 17). The proportion of subjects in each stratum was evenly distributed across the treatment groups.

Table 17. Summary of Actual Baseline Stratification Variables (ENABLE 1, ITT Population)

	Placebo (N=232)	Eltrombopag (N=450)	Total (N=682)
HCV RNA Genotype; n (%)			
Genotype 2/3	76 (33)	142 (32)	218 (32)
Non-genotype 2/3	156 (67)	307 (68)	463 (68)
Platelet Count; n (%)			
<50 Gi/L	62 (27)	124 (28)	186 (27)
≥50 Gi/L	170 (73)	326 (72)	496 (73)
HCV RNA, n (%)			
<800,000 IU/mL	112 (48)	236 (52)	348 (51)
≥800,000 IU/mL	119 (51)	214 (48)	333 (49)

Patients who have been previously treated with interferon are associated with poorer antiviral response. A similar proportion of subjects in both treatment groups had received prior HCV medications and the majority of these had received combination antiviral therapy (i.e. IFN+Ribavirin) (see Table 18).

Table 18. Summary of Prior Hepatitis C Therapies (ENABLE 1, ITT Population)

	Number of Subjects (%)	
	Placebo (N=232)	Eltrombopag (N=450)
Number of Subjects with Prior HCV Therapies[a]	81 (35)	146 (32)
Pegylated IFN	20 (9)	37 (8)
Pegylated IFN+Ribavirin	37 (16)	72 (16)
Regular IFN	25 (11)	26 (6)
Regular IFN+Ribavirin	9 (4)	30 (7)
>1 Previous IFN Based Therapy	11 (5)	24 (5)
Other Non-Approved Medications	3 (1)	12 (3)

ENABLE 2

The baseline demographic and disease characteristics are shown in Table 19.

Table 19. Baseline demographic and disease characteristics (ENABLE 2, safety population)

OL Phase (Part 1)	**Eltrombopag**	
N (Safety Population)	**805**	
Females: Males; n	295:510	
Mean Age, years (SD)	52.2 (8.95)	
White, n (%)	600 (75)	
HCV Genotype; n (%)		
1	499 (62)	
2	72 (9)	
3	179 (22)	
4	49 (6)	
6	1 (<1)	
Child-Pugh Classification; n (%)		
A (score 5 - 6)	769 (96)	
B (score 7 - 9)	34 (4)	
Mean Alanine Aminotransferase (SD); IU/L	92.44 (58.223)	
Mean HCV RNA (SD); IU/mL	1,672,687.3 (2,853,673.76)	
Mean Platelet Count (SD); Gi/L	56.30 (13.932)	
DB Phase (Part 2)	**Placebo**	**Eltrombopag**
N (ITT Population)	**253**	**506**
Females: Males; n	93:160	185:321
Mean Age; years (SD)	52.0 (9.15)	52.4 (8.61)
White; n (%)	188 (74)	388 (77)
HCV Genotype; n (%)		
1	160 (63)	320 (63)
2	28 (11)	40 (8)
3	47 (19)	113 (22)
4	17 (7)	30 (6)
6	0	1 (<1)
Child-Pugh Classification; n (%)		
A (score 5 – 6)	242 (96)	487 (97)
B (score 7 – 9)	11 (4)	17 (3)
Previous Interferon Use; n (%)		
Naïve	182 (72)	347 (69)
Experienced	71 (28)	159 (31)
FibroSURE Score (Metavir stage); n (%)		
0/1/2	19 (8)	46 (9)
3/4	199 (79)	405 (80)
Missing	35 (14)	55 (11)
ALT; n (%)		
Normal	49 (19)	113 (22)
Elevated	204 (81)	393 (78)
Mean HCV RNA (SD); IU/mL	1,656,788.0 (2,564,763.45)	1,702,729.6 (3,066,411.11)
Mean Platelet Count (SD); Gi/L	56.56 (13.571)	56.85 (13.311)

In addition a summary of baseline stratification variables and prior hepatitis C therapies are shown in Tables 20 and 21.

Table 20. Summary of Baseline Stratification Variables (ENABLE 2, ITT Population)

	Placebo (N=253)	Eltrombopag (N=506)	Total (N=759)
HCV RNA Genotype; n (%)			
Genotype 2/3	75 (30)	153 (30)	228 (30)
Genotype non-2/3	177 (70)	351 (69)	528 (70)
Missing	1 (<1)	2 (<1)	3 (<1)
Platelet Count; n (%)			
<50 Gi/L	77 (30)	140 (28)	217 (29)
≥50 Gi/L	176 (70)	366 (72)	542 (71)
HCV RNA; n (%)			
<800,000 IU/mL	132 (52)	266 (53)	398 (52)
≥800,000 IU/mL	120 (47)	238 (47)	358 (47)
Missing	1 (<1)	2 (<1)	3 (<1)

Table 21. Summary of Prior Hepatitis C Therapies (ENABLE 2, ITT Population)

	Number of Subjects (%)	
	Placebo (N=253)	Eltrombopag (N=506)
Number of Subjects with Prior HCV Therapies[a]	74 (29)	161 (32)
Pegylated IFN	11 (4)	43 (8)
Pegylated IFN+Ribavirin	37 (15)	89 (18)
Regular IFN	20 (8)	35 (7)
Regular IFN+Ribavirin	17 (7)	35 (7)
>1 Previous IFN Based Therapy	16 (6)	43 (8)
Other Non-Approved Medications[b]	9 (4)	11 (2)

Numbers analysed

The numbers analysed are summarised in Tables 22 and 23.

Table 22. Summary of Subject Accountability (ENABLE 1, Enrolled Population)

	Number of Subjects		
	Placebo	Eltrombopag	Total
Open-Label			
Enrolled population			716
Safety population			715[a]
Double-Blind			
Intent-to-treat population	232	450	682
Safety double-blind population	232	449	681[b]
Per protocol population	216	424	640

a. Subject 2819 did not receive open label treatment
b. Subject 4562 did not receive double blind treatment

Table 23. Summary of Subject Accountability (ENABLE 2, Enrolled Population)

	Placebo	Eltrombopag	Total
Open-Label			
Enrolled population			805
Safety population			805
Double-Blind			
Intent-to-treat population	253	506	759[a]
Safety double-blind population	252	506	758
Per protocol population	236	482	718

a. Subject 2106 was randomised to the DB Phase but was withdrawn due to a protocol deviation (CP Score >6) and did not receive DB treatment.

Outcomes and estimation

Primary endpoint

The main results for ENABLE 1 and ENABLE 2 are summarised in Tables 24 and 25.

Table 24. Sustained Virologic Response- Primary Analysis (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	

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 25. Univariate Analysis of Sustained Virologic Response for Actual Strata for Subjects with Successful Response (ITT Population)

ENABLE 1				
	Placebo (N=232)	Eltrombopag (N=450)	Percentage Difference (95% CI)[a] [%]	P-value for Interaction[b]
Actual HCV RNA Genotype, n/N (%)				
Genotype 2/3	18/76 (24)	50/142 (35)	9.2 (-3.0, 21.5)	0.6393
Genotype non 2/3	15/156 (10)	54/307 (18)	7.6 (1.4, 13.7)	
Actual Platelet Count, n/N (%)				
<50 Gi/L	10/62 (16)	28/124 (23)	6.1 (-5.4, 17.7)	0.5634
≥50 Gi/L	23/170 (14)	76/326 (23)	8.4 (2.1, 14.7)	
Actual HCV RNA, n/N (%)				
<800,000 IU/mL	22/112 (20)	65/236 (28)	7.8 (-1.0, 16.6)	0.4579
≥800,000 IU/mL	11/119 (9)	39/214 (18)	8.0 (0.9, 15.0)	
ENABLE 2				
	Placebo (N=253)	Eltrombopag (N=506)	Percentage Difference (95% CI)[a] [%]	P-value for Interaction[b]
Actual HCV RNA Genotype, n/N(%)				
Genotype 2/3	19/75 (25)	52/153 (34)	10.4 (-2.4, 23.3)	0.5900
Genotype non 2/3	13/177 (7)	45/351 (13)	5.3 (0.1, 10.6)	
Actual Platelet Count, n/N (%)				
<50 Gi/L	5/77 (6)	25/140 (18)	8.1 (-0.1, 16.3)	0.0741
≥50 Gi/L	27/176 (15)	72/366 (20)	4.9 (-1.1, 11.0)	
Actual HCV RNA, n/N (%)				
<800,000 IU/mL	23/132 (17)	54/266 (20)	3.7 (-3.4, 10.8)	0.0613
≥800,000 IU/mL	9/120 (8)	43/238 (18)	8.4 (1.6, 15.1)	

a. Adjusted for other actual strata
b. P-value is a test of the null hypothesis of homogeneity (i.e., no treatment-by-subgroup interaction)

Sensitivity analyses were performed on the primary endpoint using the PP population, and assessing the impact of using all assessments, of late treatment discontinuations and missing for other reasons, of LOCF, of using 24 week follow-up visit only, of using actual visits, of not using LOCF, and of using 12 week follow-up visit or later as LOCF for 24 week follow-up visit. Only the analysis using HCV RNA assessments at the actual end of treatment visit, 12 Week follow-up visit and 24 Week follow-up visit, regardless of the duration of treatment or the actual time relative to randomisation in ENABLE 2 showed a non-significant treatment difference in SVR rate (of 5%) between eltrombopag and placebo.

Secondary endpoints

- Initiation of antiviral therapy

Results on initiation of antiviral therapy and increase in platelet counts to required level with are shown in Tables 26 and 27.

Table 26. 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)

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 27. Increase in Platelet Counts to Required Level with Open-label Eltrombopag (Safety Population)

	ENABLE 1	ENABLE 2
	Eltrombopag (N=715)	Eltrombopag (N=805)
Target Platelet Count[a]	**90 Gi/L**	**100 Gi/L**
Platelet Count Increased to Required Level[a], n (%)		
Yes	691 (97)	773 (96)
(95% CI) [%][b]	(95, 98)	(94, 97)
Time (Weeks) to Achieve Required Platelet Count, n (%)		
Within 2 weeks	281 (39)	204 (25)
2 to <4 weeks	324 (45)	421 (52)
4 to <6 weeks	60 (8)	101 (13)
6 to <8 weeks	18 (3)	32 (4)
8 to 9 weeks	5 (<1)	7 (<1)
>9 weeks	3 (<1)	8 (<1)
Mean number of weeks (SD)	2.41 (1.419)	2.84 (1.671)
Median number of weeks (Min-Max)	2.14 (0.1-9.6)	2.14 (0.1-14.9)

a. Differing requirements due to use of peginterferon alfa-2a in ENABLE 1 and peginterferon alfa-2b in ENABLE 2
b. Exact 95% CI based on binomial distribution

The majority of subjects achieved a platelet count >90/100 Gi/L within 4 weeks; the mean number of weeks required was 2.4 in ENABLE 1 and 2.8 in ENABLE 2.

A total of 2% of subjects in each study achieved the required platelet counts to initiate antiviral therapy but did not randomize to Part 2 (DB). There was no pattern in the reasons for this failure to initiate therapy within or across the studies.

- Antiviral therapy dose reductions

Results on antiviral dose reductions are shown in Tables 28 and 29 and Figure 6.

Table 28. 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	
Time (Weeks) to First Peginterferon Dose Reduction	**n=163**	**n=193**	**n=171**	**n=208**
Mean (SD)	5.81 (5.304)	9.04 (9.371)	6.58 (7.336)	10.64 (9.305)
Median (Min-Max)	4.30 (1.1-36.7)	5.10 (1.1-44.1)	4.10 (0.9-45.0)	7.30 (1.0-43.1)
Time (Weeks) to First Ribavirin Dose Reduction	**n=63**	**n=162**	**n=79**	**n=189**
Mean (SD)	11.16 (9.219)	12.58 (9.830)	12.43 (9.681)	10.99 (8.984)
Median (Min-Max)	8.10 (1.1-40.3)	8.65 (1.3-44.0)	8.10 (2.0-40.1)	8.10 (1.0-45.0)

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 6. Median Time to First Peginterferon Dose Reduction (Pooled Data, ITT Population)

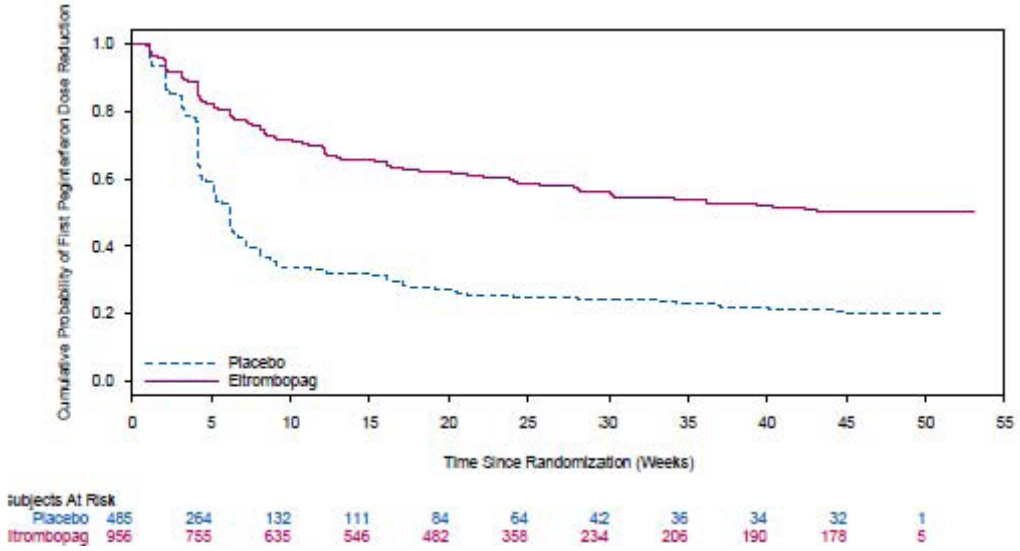


Table 29. Premature Discontinuation from Antiviral Therapy (ITT Population)

	ENABLE 1		ENABLE 2	
	Placebo (N=232)	Eltrombopag (N=450)	Placebo (N=253)	Eltrombopag (N=506)
Prematurely Discontinued Antiviral Therapy[a], n (%)				
Yes	129 (56)	184 (41)	164 (65)	242 (48)
Percentage difference (95% CI)[b] [%]	-16.0 (-23.3, -8.6)		-16.2 (-23.1, -9.3)	
P-value[c]	0.0001		<0.0001	

a. Discontinuation of peginterferon and/or ribavirin
b. Adjusted for the actual strata: HCV genotype, baseline platelet count, and HCV RNA
c. P-value for permanent discontinuation (yes/no) based on CMH chi-square test adjusted for the randomization strata

The commonest reasons for premature discontinuation of antiviral therapy were adverse events (27% placebo, 19% eltrombopag; the difference being mainly due to an increase in events of thrombocytopenia in placebo-treated subjects), and lack of antiviral efficacy.

- Adherence to Antiviral Therapy

Adherence to antiviral therapy are summarised in Table 30.

Table 30. Adherence to Antiviral Therapy (Pooled Data, ITT Population)

	Placebo (N=485)	Eltrombopag (N=956)
Adherence to Antiviral Therapy, n (%)		
Yes	186 (38)	507 (53)
Percentage difference[a] (95% CI) [%]	14.7 (9.6, 19.8)	
P-value[b]	<0.0001	

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

Adherence to antiviral therapy (defined as receiving at least 80% of the investigator-prescribed dose of peginterferon alfa-2b and at least 80% of the investigator-prescribed dose of ribavirin, for at least 80% of the planned duration) was associated with at least a doubling of the proportion achieving SVR, both for placebo and eltrombopag.

- Platelet counts with antiviral therapy

The results on platelet counts with antiviral therapy are shown in Figure 7 and Tables 31 and 32.

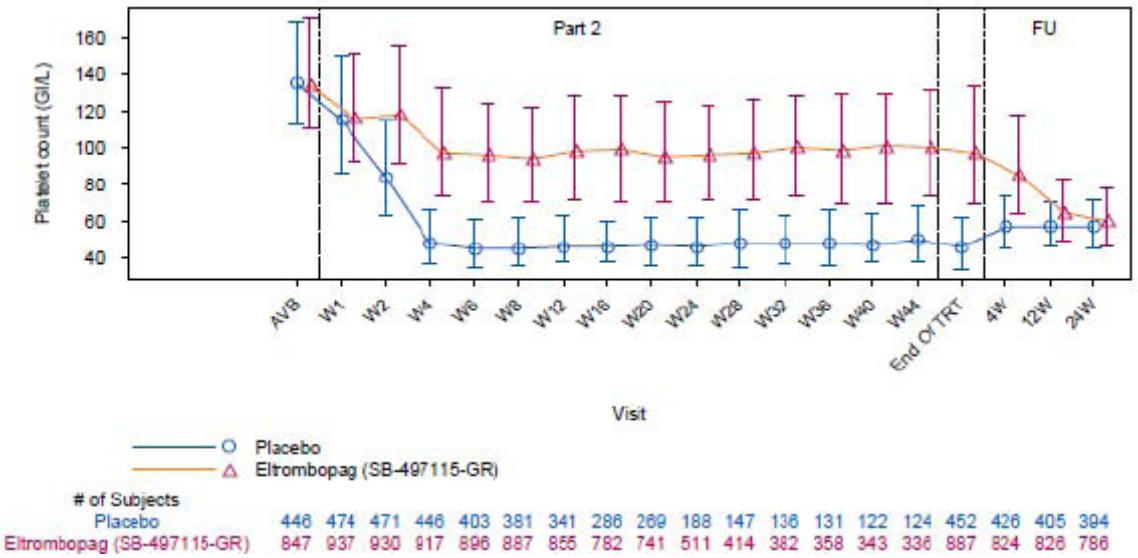


Figure 7. Median Platelet Counts (Gi/L) (Pooled Data, ITT Population)

Table 31. Summary of Minimum Platelet Count with Antiviral Therapy (Pooled Data, ITT Population)

	Placebo (N=485)	Eltrombopag (N=956)
Minimum Platelet Count on Antiviral Therapy, n (%)		
<25 Gi/L	97 (20)	32 (3)
≥25 to <50 Gi/L	294 (61)	201 (21)
≥50 to <90 Gi/L	68 (14)	508 (53)
≥90 to <150 Gi/L	21 (4)	193 (20)
≥150 to <200 Gi/L	2 (<1)	14 (1)
≥200 to <400 Gi/L	2 (<1)	5 (<1)
Missing	1 (<1)	3 (<1)

Table 32. Maximum Duration of Platelet Counts ≥50 Gi/L (Pooled Data, ITT Population)

	Placebo (N=485)	Eltrombopag (N=956)
All HCV Genotypes (Weeks)	**n=484**	**n=951**
Mean (SD)	8.67 (12.170)	25.97 (15.296)
Median (Min-Max)	3.14 (0.14-50.00)	24.14 (0.14-52.14)
HCV Genotype Non 2/3 (Weeks)	**n=333**	**n=657**
Mean (SD)	9.43 (13.280)	28.10 (16.488)
Median (range)	3.29 (0.14-50.00)	27.14 (0.14-52.14)
HCV Genotype 2/3 (Weeks)	**n=151**	**n=294**
Mean (SD)	6.97 (9.075)	21.19 (10.806)
Median (range)	3.14 (0.14-48.57)	23.21 (1.00-50.00)

Note: Maximum duration is the maximum of the durations between consecutive visits meeting criteria; the duration is counted as 1 for a non-consecutive visit

During the open label phase, 14% of subjects achieved a platelet count >200 Gi/L, the majority within 2 weeks, but only 6 subjects (of 1520, <1%) achieved a platelet count of >400 Gi/L. During the double-blind phase of ENABLE 1, 26% of eltrombopag-treated subjects achieved a

platelet count >200 Gi/L (compared with 14% of those on placebo). Comparative figures for ENABLE 2 have not been provided.

- Other Antiviral Endpoints

Other antiviral endpoints are shown in Table 33.

Table 33. 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	
Complete EVR (cEVR), n (%)	60 (26)	187 (42)	57 (23)	174 (34)
Percentage difference (95% CI)[a] [%]	14.8 (8.6, 21.1)		9.1 (3.5, 14.7)	
P-value[b]	<0.0001		0.0003	
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	
SVR at 12 week FU (SVR12), n (%)	36 (16)	103 (23)	29 (11)	106 (21)
Percentage difference (95% CI)[a] [%]	8.3 (2.7, 13.9)		8.6 (3.7, 13.5)	
P-value[b]	0.0256		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 randomization strata

In both studies, the results at the early antiviral milestones of RVR and eRVR were similar between the eltrombopag and placebo treatment groups and did not show any statistically significant difference in response.

- Pharmacogenetic investigation

A total of 906/1441 subjects, who were White and Asian subjects identified as non- Hispanic or Latino, were included in the combined PGx analysis population. No difference was detected in carriage frequencies for IL28B response genotypes between subjects randomized to the placebo and eltrombopag treatment groups in the DB portions of these studies (see Table 34).

Table 34. Distribution of Subjects with IL28B Genotypes in the Placebo and Eltrombopag Treatment Groups (Pooled Data, Combined PGx Analysis Population)

Genetic Variant	Genotype, n	Placebo, n (%)	Eltrombopag, n (%)
rs12979860[a]	N=904	N=307	N=597
CC[b]	350	114 (37)	236 (40)
CT	434	153 (50)	281 (47)
TT	120	40 (13)	80 (13)
rs8099917[a]	N=902	N=307	N=595
TT[b]	500	175 (57)	325 (55)
GT	346	118 (38)	228 (38)
GG	56	14 (5)	42 (7)

a. Six subjects in the combined PGx analysis population (N=906) had genotype information for only one of the two polymorphisms tested: 2 subjects lacked genotype results on rs12979860 and 4 subjects lacked genotype results on rs8099917

b. Denotes *Il28b* favorable response genotype

A higher proportion of subjects achieved SVR in the eltrombopag treatment group than in the placebo treatment group. This result occurred for subjects carrying all IL28B genotypes. However, subjects who carried the IL28B favourable response genotype were more likely to achieve virologic responses than were subjects who did not carry the favourable IL28B genotype in both the placebo and eltrombopag treatment groups. This trend was observed in subjects infected with any HCV genotype (see Table 35).

Subjects homozygous for the favourable response allele, 'C', of the IL28B polymorphism rs12979860 (i.e., subjects that carry 2 copies of the 'C' allele, 'CC') are more likely to achieve SVR compared to patients who carried one or no copy of this allele. Although both IL28B variants showed strong evidence for statistical association with virologic response, evaluating the effect of each marker conditioned upon the effect of the other indicated that rs12979860 represents the primary association with treatment response and the association with rs8099917 is secondary.

Analysis by viral genotype was performed in the Combined and in the White PGx Analysis sub-populations. Subjects infected with either HCV non 2/3 or 2/3 genotypes who carried the IL28B favourable response genotype were more likely to achieve virologic responses than were subjects who did not carry the favourable IL28B genotype. The strength of association between the IL28B response genotype was strongest in patients with baseline HCV non-2/3 genotypes (predominantly genotype 1; viral genotypes known to be less responsive to IFN/RBV treatment) compared with patients with either genotypes 2 or 3 (viral genotypes typically more responsive to IFN/RBV treatment).

Table 35. Distribution of IL28B rs12979860 Genotype Carriage by SVR in All Subjects and by HCV Genotype (Pooled Data, Combined PGx Analysis Population)

HCV Genotype	*IL28B* Genotype	Subject Number, N			
		Placebo		Eltrombopag	
		Responder n (%)	Non-responder n (%)	Responder n (%)	Non-responder n (%)
All HCV Genotypes[a]		N=307		N=597	
	CC	31 (27)	83 (73)	83 (35)	153 (65)
	CT or TT	13 (7)	180 (93)	48 (13)	313 (87)
HCV Genotype Non 2/3		N=214		N=423	
	CC	14 (23)	48 (77)	40 (28)	101 (72)
	CT or TT	5 (3)	147 (97)	27 (10)	255 (90)
HCV Genotype 2/3		N=92		N=173	
	CC	17 (33)	35 (67)	43 (45)	52 (55)
	CT or TT	8 (20)	32 (80)	21 (27)	57 (73)

a. Two subjects included in this group did not have HCV genotype information available at Baseline.

Ancillary analyses

In addition difference in SVR Rates by subgroup are shown in Figure 8.

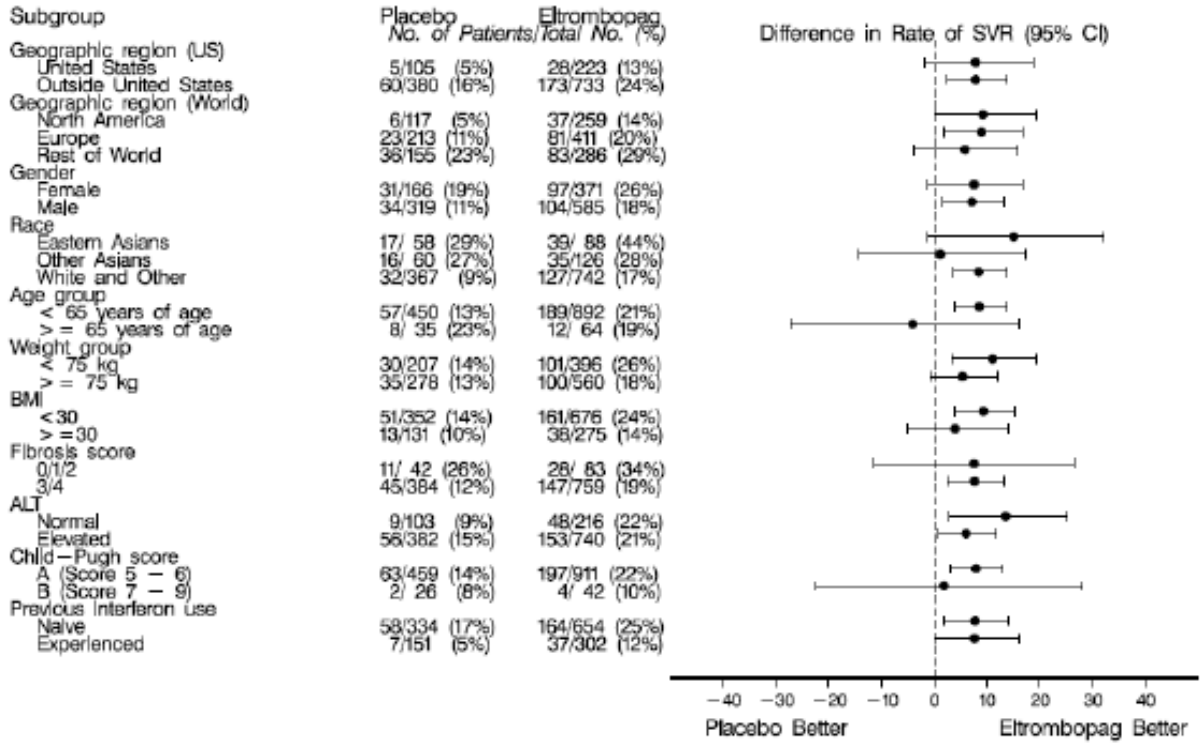


Figure 8. Forest Plot of Difference in SVR Rates (95% CI) by Subgroup (Pooled Data, ITT Population)

In thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤ 35 g/L or MELD score ≥ 10, the benefits of the treatment of eltrombopag in terms of the proportion achieving SVR compared with placebo compared with the group overall are shown in Table 36.

Table 36. Overall SVR by albumin levels ≤ 35 g/L and MELD score.

	% patients achieving virologic response	
	Eltrombopag	Placebo
Overall SVR [d]	21	13
Albumin levels[f]		
≤ 35g/L	11	8
> 35g/L	25	16
MELD score[f]		
> 10	18	10
≤ 10	23	17

Summary of main studies

The following table summarises the efficacy results from the main studies supporting the present application.

Summary of Efficacy for trials ENABLE 1 and ENABLE 2

Title: Eltrombopag: Investigation of efficacy in the treatment of thrombocytopenia in adults with HCV		
Study identifier	ENABLE 1, ENABLE 2	
Design	Multi-centre, randomised, double-blind, placebo-controlled.	
	Duration of open label phase: Duration of double-blind, main phase: Duration of follow-up phase:	2-9 weeks ≤48 weeks 24 weeks
Hypothesis	Superiority	
Treatments groups	Open label eltrombopag	Eltrombopag once daily, starting at 25 mg, titrated upwards, until platelet threshold reached (or week 9). 1520 randomised.
	Double-blind placebo	Placebo + peginterferon alfa-2a/b + ribavirin. 24 weeks (genotype 2/3) or 48 weeks (genotype non-2/3), 485 randomised.
	Double-blind eltrombopag	Eltrombopag (dose continued from OL phase) + peginterferon alfa-2a/b + ribavirin. 24 weeks (genotype 2/3) or 48 weeks (genotype non-2/3), 955 randomised.

Endpoints and definitions	Primary endpoint	SVR rate	Percentage of subjects with undetectable HCV-RNA at end of treatment and all subsequent planned visits up to 24 weeks after completing treatment
	Secondary endpoint	Initiation of antiviral therapy	Platelet shift from baseline count to ≥90/100 Gi/L with OL eltrombopag; proportion of subjects initiating antiviral therapy; time to initiation of antiviral therapy

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat, 24 weeks after treatment completion				
Descriptive statistics and estimate variability	Study	ENABLE 1		ENABLE 2	
	Treatment group	Placebo	Eltrombopag	Placebo	Eltrombopag
	Number of subjects	232	450	253	506
	SVR	14%	23%	13%	19%
	Difference (95% CI) (Difference is eltrombopag minus placebo)	7.9 (2.4, 13.4)		6.0 (1.2, 10.9)	

Analysis description	**Secondary analysis**		
Analysis population and time point description	Safety population, open label phase		
Descriptive statistics and estimate variability	Study	ENABLE 1	ENABLE 2
	Number of subjects	715	805
	Initiation of antiviral therapy % (CI)	95 (93, 97)	94 (92, 96)

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

The Applicant conducted an integrated analysis of pooled data from the pivotal studies. The studies were similar in design, the main difference being the type of peginterferon used, and the lower platelet threshold for dose adjustments. The results of the integrated analysis reflect the findings of the individual studies.

Clinical studies in special populations

No specific studies have been provided.

2.5.3. Discussion on clinical efficacy

Thrombocytopenia associated to the HCV infection is a limiting factor for the access to a potentially curative therapy. The reason is that thrombocytopenia is a common AE of the currently available regimens and treatment related thrombocytopenia is one of the critical factors that may compromise the completion of an optimal HCV treatment regimen, which is a pre-requisite for achieving a successful outcome. Therefore, any therapy able to allow patients to initiate and complete an optimal antiviral treatment are expected to increase the rates of sustained viral responses (SVR), which is a surrogate marker of the ultimate goal of treatment, i.e. to reduce the morbidity and mortality related to the chronic C hepatitis infection.

Results from the dose finding study TPL102357 support a 25 mg starting dose of eltrombopag. In this study 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 75mg.

Platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level which prevents the risk of bleeding or the need for interferon dose reductions (50,000/µl). Platelet counts > 100,000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Based on the data provided by the MAH the following posology was agreed and reflected in the SmPC:

Initiate eltrombopag at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian ancestry or patients with mild hepatic impairment.

Adjust the dose of eltrombopag in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate anti-viral therapy. Monitor platelet counts every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

During antiviral therapy, adjust the dose of eltrombopag as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding (see Table 2). Monitor platelet counts weekly during antiviral therapy until a stable platelet count is achieved, normally around 50,000-75,000/µl. CBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.

Do not exceed a dose of 100 mg eltrombopag once daily.

Dose adjustments of eltrombopag in HCV patients during antiviral therapy:

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥ 50,000/µl to ≤ 100,000/µl	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon
> 100,000/µl to ≤ 150,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments◆.
> 150,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg*.

* - For patients taking 25 mg eltrombopag once daily, consideration should be given to reinitiating dosing at 25 mg every other day.
◆ - On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued.

Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Two pivotal Phase III studies were submitted to support the efficacy of eltrombopag in the treatment of thrombocytopenia in adults with chronic, compensated HCV and advanced fibrosis or cirrhosis. ENABLE 1 and 2 used a different peginterferon, but otherwise had a similar design. The design of the studies was appropriate, with an open-label, dose titration phase to establish efficacy in initiation of antiviral therapy, followed by a randomised, double-blind, placebo controlled antiviral phase (peginterferon alfa-2a/b plus ribavirin). The duration of the double-blind phase was dependent on the HCV genotype. The primary endpoint was the proportion achieving sustained virologic response (percentage of subjects with undetectable HCV-RNA at end of treatment and all subsequent planned visits up to 24 weeks after completing treatment). Secondary endpoints included the proportion of subjects initiating antiviral therapy, requiring an antiviral dose reduction, adhering to antiviral therapy, and the platelet count during antiviral therapy.

Regarding the primary endpoint, treatment with eltrombopag produced a statistically significant absolute increase in the SVR rate of 8% in ENABLE 1 and 6% in ENABLE 2 over placebo. The other secondary endpoints were generally supportive of the efficacy of eltrombopag. In the double-blind treatment phase the rate of antiviral dose reductions in those on eltrombopag was

40% that of placebo-treated subjects. Correspondingly, the average time to requirement for a dose reduction was slightly prolonged in those on eltrombopag, and fewer patients required premature discontinuation of antiviral therapy. Adherence to antiviral therapy was higher in eltrombopag-treated subjects, and was shown to be related to a higher probability of achieving SVR.

For all the important subgroups evaluated, the ENABLE studies demonstrated that eltrombopag use in combination with interferon-based HCV antiviral therapy results in an improvement in SVR compared to interferon-based therapy alone (see SmPC section 5.1).

Protease inhibitors were not licensed in the EU until late 2011, and could not therefore have been incorporated into the ENABLE studies. In addition, they are only licensed for subjects with HCV genotype 1, and were not investigated in those with platelet counts of less than 90 Gi/L. The protease inhibitors also exacerbate the thrombocytopenic effects of interferon-based therapy, suggesting that their use would be limited in patients with significant thrombocytopenia at baseline. To date only preliminary PK results from a drug-drug interaction study to investigate the potential for interaction between eltrombopag and the protease inhibitors boceprevir and telaprevir have been presented to support its use in association with HCV triple therapy including direct acting antiviral agents. Full results are not yet available and are awaited but preliminary results show no significant effect of telaprevir or boceprevir on eltrombopag. However these results are unable to rule out potential safety concerns when combining these treatments. Therefore, at this stage the use of eltrombopag in patients receiving triple therapy including protease cannot be recommended and this has been clearly reflected in section 4.4 of the SmPC. Additional efficacy and safety data in these patients will be investigated by the MAH post-authorisation as reflected in the PhV plan of the RMP which includes 3 Post-Authorisation Safety Studies (PASS) (category 3, required additional pharmacovigilance activity).

Additional expert consultation

The Scientific Advisory Group on HIV/Viral Diseases (SAG-HIV/Viral Diseases) was convened on 2 July 2013 to discuss the benefits of afatinib from a clinical perspective.

The SAG-HIV/Viral Diseases provided advice on the following questions raised by the CHMP:

1. *Is there a place in therapeutics for eltrombopag in the treatment of thrombocytopenia in patients with advanced HCV-liver disease otherwise candidates to antiviral therapy to allow initiation and maintenance of a full IFN-based regimen?*
2. *In the light of the safety findings, do you consider that a positive benefit/risk balance could be concluded for the whole studied population, in particular in those patients with the poorest prognostic i.e. thrombocytopenic patients with advanced chronic liver disease, as defined by low albumin levels (<35g/L) or MELD score ≥10.*
3. *Subject to a positive answer to the previous one, could you discuss on the conditions for use under which a positive benefit/risk balance could be concluded.*

The SAG addressed the points raised by the CHMP in the joint response below:

The SAG agreed by consensus that there is public health need and a place for eltrombopag in the treatment of thrombocytopenia in patients with advanced HCV-liver disease, although very restricted. Indeed, a small number of patients where the degree of thrombocytopenia is the main reason for which an interferon (IFN)-based regimen is not feasible, could benefit from eltrombopag as its efficacy in treating thrombocytopenia would allow initiation and maintenance of a full interferon (IFN)-based regimen. Currently there aren't any treatment options available for this very advanced patient population since antiviral regimen cannot be initiated due to thrombocytopenia.

Indeed, while the SAG recognised that the use of eltrombopag was accompanied by a worrisome safety profile and that the rapid progress of HCV therapies might allow for IFN free regimens in the near future, the experts supported the use of this compound in a very limited population in which with the current practice an IFN-based regimen is not possible. The SAG defined this population as patients with advanced HCV-liver disease, in need of IFN-based therapy, and for whom the degree of thrombocytopenia is the main factor that limits the initiation or the ability to maintain the IFN-based treatment.

The experts acknowledged that in patients with the poorest prognostic i.e. thrombocytopenic patients with advanced chronic liver disease, as defined by low albumin levels (<35g/L) or MELD score ≥10, the benefits were less pronounced and the risks more significant. Nevertheless they considered the risk/benefit balance positive. However, they stressed the fact that adequate information should be provided to the prescribers to warn them of the increased risks and/or decreased efficacy which has been observed during the eltrombopag trials. In this regard the increased risk in portal vein thrombosis in these patients should be highlighted.

Moreover, due to the complexity in the treatment of such advanced patient population, the SAG was of the opinion that eltrombopag should be prescribed only by very experienced physicians in the treatment of HCV.

Finally, the SAG recommended the conduct of further studies on the use of eltrombopag, in particular the group agreed that there was a need to understand the safety and efficacy of eltrombopag as part of a triple therapy (IFN + ribavirin + direct-acting anti-viral agent). In addition, the long term benefits of achieving SVR, although described in the current literature, haven't been demonstrated in the data provided and should be confirmed post-authorisation.

2.5.4. Conclusions on the clinical efficacy

In summary, the results of the ENABLE studies provide evidence for the efficacy of eltrombopag in allowing initiation of antiviral therapy in thrombocytopenic HCV patients with compensated advanced fibrosis or cirrhosis, and demonstrate a modest benefit for the outcome of sustained viral response rate due to antiviral therapy. The patient group studied represents a cohort of HCV sufferers with severe disease and no treatment options since antiviral regimen cannot be initiated due to thrombocytopenia. Therefore, the treatment effect, though modest, represents an appreciable benefit.

2.6. Clinical safety

The safety of eltrombopag in combination with interferon-based antiviral therapy is supported by data from the 2 randomised, placebo-controlled, Phase III studies (ENABLE 1 and 2), and supportive data from the randomised, placebo-controlled, Phase II study TPL102357.

Patient exposure

A summary of the populations used for the safety analyses is shown in Table 37.

Table 37. Safety populations

	TPL103922 (ENABLE 1)		TPL108390 (ENABLE 2)		TPL102357		
Study Population	**Part 1**	**Part 2**	**Part 1**	**Part 2**	**Part 1**	**Part 2**	**Total**
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

Exposure to eltrombopag/placebo, peginterferon, and ribavirin in the double-blind phase of the ENABLE studies is detailed in Table 38.

Table 38. Exposure to Double-Blind Study Drug (Safety DB Population)

	Placebo (N=484)	**Eltrombopag (N=955)**
Mean daily dose, mg	n=482	n=948
Mean (SD)	76.37 (22.034)	64.16 (27.142)
Median (min-max)	83.05 (0.0-143.4)	68.34 (0.0-213.6)
Cumulative duration (days)	n=483	n=953
Mean SD)	169.3 (112.07)	213.3 (101.77)
Median (min-max)	167.0 (1-357)	182.0 (1-365)
Cumulative dose,mg	n=483	n=949
Mean (SD)	13,950.4 (10,796.33)	14,131.7 (9441.74)
Median (min-max)	11,375.0 (0-41,000)	12,600.0 (0-34,400)
Modal dose, mg	n=484	n=955
Mean (SD)	86.47 (26.044)	69.73 (31.481)
Median (min-max)	100.00 (25.0-100.0)	75.00 (12.5-100.0)

Adverse events

The adverse events identified during the double blind phase, including on treatment plus 30 day follow-up period are shown in Tables 39-41:

Table 39. Overall Summary of AEs During Double-Blind Phase (Safety DB Population)

	Placebo (N=484)		Eltrombopag (N=955)	
	n (%)	Events	n (%)	Events
Number of subjects with an AE	461 (95)	4384	905 (95)	10176
Number of subjects with an SAE	72 (15)	114	189 (20)	334
Number of subjects with a fatal AE	7 (1)	11	23 (2)	34
Number of subjects with a drug-related AE	442 (91)	3281	873 (91)	7098
Number of subjects with an AE leading to withdrawal from study	16 (3)	21	34 (4)	61
Number of subjects with an AE leading to IP discontinuation	138 (29)	190	200 (21)	306
Number of subjects with an SAE leading to withdrawal from study	9 (2)	13	28 (3)	45
Number of subjects with an ongoing AE at the end of study/withdrawal	238 (49)	560	505 (53)	1405

Table 40. AEs Occurring in ≥5% Subjects in Double-Blind Phase (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)
Neutropenia	179 (37)	311 (33)
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)
Thrombocytopenia	170 (35)	131 (14)
Chills	44 (9)	130 (14)
Leukopenia	71 (15)	128 (13)
Myalgia	48 (10)	116 (12)
Alopecia	27 (6)	100 (10)
Oedema peripheral	23 (5)	92 (10)
Arthralgia	37 (8)	88 (9)
Rash	34 (7)	87 (9)
Depression	31 (6)	86 (9)
Muscle spasms	29 (6)	82 (9)
Blood bilirubin increased	15 (3)	80 (8)
Hyperbilirubinaemia	16 (3)	80 (8)
Irritability	28 (6)	80 (8)
Dyspnoea	25 (5)	76 (8)
Vomiting	36 (7)	74 (8)
Weight decreased	26 (5)	74 (8)
White blood cell count decreased	27 (6)	74 (8)
Urinary tract infection	23 (5)	71 (7)
Ascites	16 (3)	68 (7)
Dizziness	37 (8)	66 (7)
Abdominal pain	23 (5)	65 (7)
Haemoglobin decreased	25 (5)	65 (7)
Abdominal pain upper	24 (5)	59 (6)
Epistaxis	51 (11)	57 (6)
Dry skin	18 (4)	52 (5)
Dyspepsia	19 (4)	50 (5)
Back pain	16 (3)	48 (5)
Oropharyngeal pain	17 (4)	46 (5)
Dyspnoea exertional	19 (4)	44 (5)
Dry mouth	9 (2)	43 (5)
Platelet count decreased	24 (5)	35 (4)

There were 8 AEs which, when compared with placebo, had a relative risk greater than 1 (and confidence intervals excluding 1): blood bilirubin increased, hyperbilirubinaemia, ascites, peripheral oedema, alopecia, diarrhoea, chills, and pyrexia.

Table 41. Grade 3 or Grade 4 Severity AEs During Double-Blind Phase Occurring in ≥1% Subjects (Safety DB Population)

Preferred term	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	**260 (54)**	**472 (49)**
Neutropenia	89 (18)	141 (15)
Anaemia	32 (7)	79 (8)
Hyperbilirubinaemia	6 (1)	51 (5)
Thrombocytopenia	131 (27)	50 (5)
Leukopenia	20 (4)	45 (5)
Blood bilirubin increased	6 (1)	33 (3)
Pyrexia	8 (2)	22 (2)
White blood cell count decreased	7 (1)	19 (2)
Hepatic neoplasm malignant	7 (1)	17 (2)
Lymphopenia	7 (1)	17 (2)
Asthenia	3 (<1)	16 (2)
Haemoglobin decreased	4 (<1)	15 (2)
Weight decreased	4 (<1)	14 (1)
Ascites	3 (<1)	13 (1)
Diarrhoea	0	11 (1)
Hepatic encephalopathy	0	11 (1)
Neutrophil count decreased	12 (2)	10 (1)
Pneumonia	5 (1)	8 (<1)
Fatigue	6 (1)	7 (<1)
Platelet count decreased	10 (2)	7 (<1)
Aspartate aminotransferase increased	6 (1)	2 (<1)

The MAH presented upon CHMP request during the D120 List of question revised tables for adverse events identified during the double blind phase, including on treatment plus 6 months follow-up period (data not shown). The results of the new analyses supported the conclusion of the on-treatment plus 30 days follow-up analyses previously presented.

In addition, a summary of adverse drug reactions observed for eltrombopag during treatment where causality was based on comparative incidence in clinical trials, 1 % higher incidence in the eltrombopag arm compared to placebo arm, is shown in Table 42.

Table 42. Summary of on Treatment Plus 30 Days Post Treatment Adverse Events Occurring in ≥1% Subjects (Safety Double-Blind Phase III Population)

	Eltrombopag	
	(N=955)	
System Organ Class		
Preferred Term		
ANY EVENT	905	(95%)
Infections and infestations		

Any event	323	(34%)
Urinary tract infection	71	(7%)
Upper respiratory tract infection	36	(4%)
Bronchitis	30	(3%)
Nasopharyngitis	30	(3%)
Influenza	28	(3%)
Oral herpes	23	(2%)
Gastroenteritis	12	(1%)
Pharyngitis	11	(1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Any event	44	(5%)
Hepatic neoplasm malignant	26	(3%)
Blood and lymphatic system disorders		
Any event	613	(64%)
Anaemia	384	(40%)
Lymphopenia	32	(3%)
Haemolytic anaemia	13	(1%)
Metabolism and nutrition disorders		
Any event	248	(26%)
Decreased appetite	172	(18%)
Hyperglycaemia	20	(2%)
Abnormal loss of weight	10	(1%)
Psychiatric disorders		
Any event	293	(31%)
Insomnia	151	(16%)
Depression	86	(9%)
Anxiety	37	(4%)
Sleep disorder	33	(3%)
Confusional state	13	(1%)
Agitation	11	(1%)
Nervous system disorders		
Any event	326	(34%)
Headache	202	(21%)
Dizziness	66	(7%)
Disturbance in attention	27	(3%)
Dysgeusia	22	(2%)
Hepatic encephalopathy	18	(2%)
Lethargy	15	(2%)

Memory impairment	15	(2%)
Paraesthesia	11	(1%)
Eye disorders		
Any event	196	(21%)
Cataract	37	(4%)
Retinal exudates	32	(3%)
Retinal haemorrhage	15	(2%)
Dry eye	13	(1%)
Ocular icterus	13	(1%)
Ear and labyrinth disorders		
Any event	39	(4%)
Vertigo	13	(1%)
Cardiac disorders		
Any event	52	(5%)
Palpitations	18	(2%)
Respiratory, thoracic and mediastinal disorders		
Any event	311	(33%)
Cough	141	(14%)
Dyspnoea	76	(8%)
Oropharyngeal pain	46	(5%)
Dyspnoea exertional	44	(5%)
Productive cough	22	(2%)
Gastrointestinal disorders		
Any event	521	(55%)
Nausea	179	(19%)
Diarrhoea	178	(19%)
Vomiting	74	(8%)
Ascites	68	(7%)
Abdominal pain	65	(7%)
Abdominal pain upper	59	(6%)
Dyspepsia	50	(5%)
Dry mouth	43	(5%)
Constipation	40	(4%)
Abdominal distension	24	(3%)
Toothache	23	(2%)
Stomatitis	21	(2%)
Gastrooesophageal reflux disease	17	(2%)
Haemorrhoids	17	(2%)

Abdominal discomfort	16	(2%)
Gastritis	13	(1%)
Varices oesophageal	13	(1%)
Aphthous stomatitis	11	(1%)
Oesophageal varices haemorrhage	10	(1%)
Hepatobiliary disorders		
Any event	149	(16%)
Hyperbilirubinaemia	80	(8%)
Jaundice	20	(2%)
Hepatic failure	11	(1%)
Portal vein thrombosis	11	(1%)
Skin and subcutaneous tissue disorders		
Any event	375	(39%)
Pruritus	139	(15%)
Alopecia	100	(10%)
Rash	87	(9%)
Dry skin	52	(5%)
Eczema	20	(2%)
Rash pruritic	19	(2%)
Erythema	14	(1%)
Hyperhidrosis	13	(1%)
Pruritus generalised	13	(1%)
Night sweats	10	(1%)
Skin lesion	10	(1%)
Musculoskeletal and connective tissue disorders		
Any event	306	(32%)
Myalgia	116	(12%)
Arthralgia	88	(9%)
Muscle spasms	82	(9%)
Back pain	48	(5%)
Pain in extremity	35	(4%)
Musculoskeletal pain	16	(2%)
Bone pain	15	(2%)
Renal and urinary disorders		
Any event	77	(8%)
Dysuria	12	(1%)
General disorders and administration site conditions		
Any event	685	(72%)

Pyrexia	284	(30%)
Fatigue	263	(28%)
Influenza like illness	170	(18%)
Asthenia	153	(16%)
Chills	130	(14%)
Oedema peripheral	92	(10%)
Irritability	80	(8%)
Pain	42	(4%)
Malaise	37	(4%)
Injection site reaction	24	(3%)
Non-cardiac chest pain	21	(2%)
Oedema	17	(2%)
Injection site rash	12	(1%)
Chest discomfort	11	(1%)
Injection site pruritus	10	(1%)
Investigations		
Any event	298	(31%)
Blood bilirubin increased	80	(8%)
Weight decreased	74	(8%)
White blood cell count decreased	74	(8%)
Haemoglobin decreased	65	(7%)
Neutrophil count decreased	32	(3%)
International normalised ratio increased	22	(2%)
Activated partial thromboplastin time prolonged	17	(2%)
Blood glucose increased	17	(2%)
Blood albumin decreased	16	(2%)
Electrocardiogram QT prolonged	11	(1%)

Serious adverse event / deaths / other significant events

Serious Adverse Events (SAEs)

Serious adverse events identified during the double blind phase, including on treatment plus 30 day follow-up period, are shown in Table 43:

Table 43. SAEs During the Double-Blind Phase in ≥0.5% 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)

Deaths

In the open label phase there were 2 deaths.

- One subject experienced an SAE of hepatorenal syndrome on study Day 46, and died the same day. This subject had current medical history of cirrhosis, hypertension, and myocardial ischemia. The subject was interferon naive. Baseline platelet count was 20 Gi/L and baseline MELD score was 15. The subject received open-label eltrombopag 25 mg daily for 2 weeks. Eltrombopag was increased to 50 mg/day on Day 15 (platelet count 39 Gi/L), to 75 mg daily on Day 29 (platelet count, 35 Gi/L), and to 100 mg daily on Day 36 (platelet count, 36 Gi/L). On Day 46, the subject was hospitalized with general deterioration, vomiting, and diarrhoea. Laboratory tests showed elevated bilirubin, direct bilirubin, serum creatinine, INR, and sodium. The event was not considered related to eltrombopag.
- One subject had a fatal hepatic neoplasm malignant and died more than one year after they had completed study treatment. The subject received open-label eltrombopag 25 mg daily for 15 days. The eltrombopag dose was increased to 50 mg/day on Day 16 (platelets 29 Gi/L), 75 mg/day on Day 31 (platelets 46 Gi/L), and 100 mg/day on Day 42 (platelets 42 Gi/L). The subject was withdrawn from open-label study treatment on Day 65 due to insufficient platelet response, and died on Day 626 (18 months post-therapy) due to HCC.

  In the two Phase III studies, 39 subjects (3%) with 57 fatal AEs died during the on-treatment plus 6 months follow-up period: 29 (3%) in the eltrombopag group and 10 (2%) in the placebo group (see Table 44). Of these deaths, those that occurred within 30 days of treatment cessation numbered 19 in the eltrombopag group, and 4 in the placebo group.

Table 44. Fatal AEs On-Treatment Plus 6 Months Follow-Up During the DB Phase (Safety DB Population)

Preferred term	Number of Subjects (%)	
	Placebo (n=484)	Eltrombopag (n=955)
Any event	**10 (2)**	**29 (3)**
Hepatic failure	1 (<1)	3 (<1)
Ascites	0	2 (<1)
Death	1 (<1)	2 (<1)
Gastrointestinal haemorrhage	0	2 (<1)
Hepatic encephalopathy	0	2 (<1)
Hepatorenal syndrome	0	2 (<1)
Oesophageal varices haemorrhage	1 (<1)	2 (<1)
Pneumonia	0	2 (<1)
Renal failure	1 (<1)	2 (<1)
Respiratory failure	0	2 (<1)
Sepsis	1 (<1)	2 (<1)
Upper gastrointestinal haemorrhage	0	2 (<1)
Abdominal sepsis	0	1 (<1)
Cardiac arrest	0	1 (<1)
Cerebellar haemorrhage	0	1 (<1)
Cerebrovascular accident	0	1 (<1)
Encephalopathy	0	1 (<1)
Generalised oedema	0	1 (<1)
Haematemesis	0	1 (<1)
Hepatic cirrhosis	0	1 (<1)
Hepatic neoplasm malignant	3 (<1)	1 (<1)
Mechanical ileus	0	1 (<1)
Meningitis cryptococcal	0	1 (<1)
Myocardial infarction	0	1 (<1)
Multi-organ failure	1 (<1)	1 (<1)
Peritonitis bacterial	1 (<1)	1 (<1)
Sudden death	0	1 (<1)
Thrombocytopenia	0	1 (<1)
Acinetobacter bacteraemia	1 (<1)	0
Cardio-respiratory arrest	1 (<1)	0
Hypoglycaemic coma	1 (<1)	0
Lung neoplasm malignant	1 (<1)	0
Multi-organ disorder	1 (<1)	0
Portal vein thrombosis	1 (<1)	0

Most of the subjects who died had baseline MELD scores ≥10 (22/29 subjects [76%] in the eltrombopag group and 8/10 subjects [80%] in the placebo group). Eleven deaths were considered by the investigator to be related to one of the investigational products (ie, either eltrombopag/placebo, or peginterferon/ribavirin), and all of these occurred in eltrombopag-treated patients. Five of these deaths were attributed to antiviral therapy, five to all of the investigational products, and one to eltrombopag.

This death was classified as 'sudden death'. The subject had a baseline MELD score of 10, HCV RNA >2 million IU/mL, and platelet count of 52 Gi/L. Concurrent medical conditions included hepatitis B, cirrhosis, type 2 diabetes, and portal hypertension with oesophageal varices. The subject was found dead on Day 104 while on study treatment. In total, the patient received

eltrombopag 25-50 mg/day for more than 79 days, and peginterferon 150 µg/week and ribavirin 1200 mg/day for more than 57 days. The cause of death was unknown, though a diagnosis of lobar pneumonia was made on autopsy.

Adverse events of special interest

Based on non-clinical findings and clinical signals with eltrombopag and the mechanism of action of the drug, several categories of AEs of special interest were analysed further: thromboembolic, hepatobiliary, renal-related, malignancies, thrombocytopenia, bleeding and ocular.

Thromboembolic Events

Thromboembolic events reported during the study were identified using the "Embolic and Thrombotic Events" and "Myocardial Infarction" standard MedDRA query and preferred terms. No thromboembolic event occurred during the OL Phase of either of the Phase III studies. During the on-treatment plus 30 days follow-up period, 36 subjects experienced 39 confirmed or suspected events. There were 34 events in 31 eltrombopag subjects (3%) and 5 events in 5 placebo subjects (1%). Portal vein thrombosis (PVT) was the most common event in both the eltrombopag treated group (1%) and the placebo group (<1%). Table 45 summarises the thromboembolic events observed during eltrombopag treatment.

Table 45. Summary of Thromboembolic Events During On-Treatment Plus 30 Days Post-Treatment (Safety DB Population)

	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	**5 (1)**	**31 (3)**
Portal vein thrombosis	2 (<1)	11 (1)
Deep vein thrombosis	0	4 (<1)
Retinal infarction	0	2 (<1)
Retinal vein occlusion	1 (<1)	2 (<1)
Thrombosis	0	2 (<1)[a]
Angina unstable	1 (<1)	1 (<1)
Acute myocardial infarction	0	1 (<1)
Cerebrovascular accident	0	1 (<1)
Femoral artery occlusion	0	1 (<1)
Ischaemic stroke	0	1 (<1)
Mesenteric vein thrombosis	0	1 (<1)
Myocardial infarction	0	1 (<1)
Pulmonary embolism	0	1 (<1)
Retinal vascular occlusion	0	1 (<1)
Retinal vein thrombosis	0	1 (<1)
Venous thrombosis	0	1 (<1)
Venous thrombosis limb	0	1 (<1)
Retinal ischaemia	1 (<1)	0

a. Subject 4081/TPL108390 thromboembolic event was reported by the investigator as "minimal old thrombosis" which was captured under preferred term "thrombosis". GSK Medical Monitor considered this event of the portal venous system and is included in the subsequent section "Portal Venous System Events".

The subjects in the placebo group had a median platelet count of 44 Gi/L at the time of the event. In the eltrombopag group, the median platelet count was 108 Gi/L at the time of the event; no subject with a thromboembolic event had platelets above 200 Gi/L.

A further 11 thromboembolic events occurred >30 days post-treatment (10 in eltrombopag subjects). Seven events involved the portal venous system, including 2 subjects who had previously experienced an event of the portal venous system on treatment.

Upon CHMP request during the D120 List of Questions the MAH performed an additional assessment on the risk of TEE in ENABLE studies (separated and pooled). All cases were counted, avoiding the use of arbitrary limits (e.g. on-treatment plus 30 days). Cases of thromboembolic events were provided separately by trial, dose, duration, platelet counts, and risk factors. In addition, a comprehensive cumulative review of all cases of thromboembolisms including an analysis of time to onset, age, sex, dose, platelet counts, disease condition and severity (e.g HCV genotype, Child-Pugh classification, presence and/or stage of liver fibrosis and cirrhosis), prior antiviral medications, concomitant medications and outcome was also provided.

Results of these analyses showed a total of 50 TEE cases in 44 subjects, 38 (4%) eltrombopag patients vs 6 (1.2%) placebo treated patients. The time adjusted incidence was 3.9/100 PY in eltrombopag vs 1.38/100 PY in placebo (pool data), with around 30% and 50% being SAE in eltrombopag and placebo, respectively. Approximately half of subjects had a portal VT (20/44), while 13/44 VE and 10/44 arterial thrombosis. Recovery was only accounted in 66% of cases. The data indicated that eltrombopag was associated with an increased risk for TEE in this particularly advanced liver disease population. In this regard, age ≥60 years and albumin <35g/L were significant risk factors for TEE in the ENABLE studies (see Table 46). The frequency of TEE was also higher in subjects with higher MELD scores (≥10), but one third of cases occurred in patients with MELD score <10. No specific temporal relationship between start of treatment and TEE was observed. No discernible pattern was observed involving gender or dose of eltrombopag.

Table 46. TEE model: Adjusted OR and 95% CI and p-value for presented category compared to reference category among variables that were statistically significant in the stepwise regression.

Covariate	Odds Ratio (95% CI)	p-value (covariate)
Treatment		
Eltrombopag/ Placebo	3.14 (1.31, 7.53)	0.0103
Albumin (g/L)		
≤35 / >35	2.64 (1.43, - 4.89)	0.0020
Age (y)		
<50 / ≥60	0.33 (0.15, - 0.73)	0.0067
50-<60 / ≥60	0.39 (0.19, - 0.79)	

Table Source: SDAP Table 8.7307

The majority of TEEs resolved and did not interfere with antiviral treatment (66%) but in 1/3 of cases not complete recovery could be reached (with 2 fatal cases, one in each treatment group).

Hepatobiliary Events

The analyses of hepatobiliary safety for the Safety DB Population are shown in Table 47:

Table 47. Hepatobiliary AEs On-Treatment Plus 30 Days Follow-Up in ≥1% Subjects in Either Treatment Group (Safety DB Population)

Preferred term	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	**78 (16)**	**312 (33)**
Blood bilirubin increased	15 (3)	80 (8)
Hyperbilirubinaemia	16 (3)	80 (8)
Ascites	16 (3)	68 (7)
Hepatic neoplasm malignant	10 (2)	26 (3)
International normalised ratio increased	5 (1)	22 (2)
Jaundice	4 (<1)	20 (2)
Hepatic encephalopathy	1 (<1)	18 (2)
Blood albumin decreased	4 (<1)	16 (2)
Ocular icterus	2 (<1)	13 (1)
Varices oesophageal	5 (1)	13 (1)
Hepatic failure	1 (<1)	11 (1)
Oesophageal varices haemorrhage	4 (<1)	10 (1)
Aspartate aminotransferase increased	9 (2)	6 (<1)
Alanine aminotransferase increased	7 (1)	5 (<1)

With the exception of bilirubin abnormalities (largely due to increases in indirect bilirubin, which is generally considered benign) 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 interferon and ribavirin (see Table 48).

Table 48. Hepatobiliary Parameters On-Treatment Plus 30 Days Follow-Up During DB Phase (Safety DB Population)

	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)

To evaluate hepatotoxic potential, the MAH presented a series of eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) plots showing the peak total bilirubin/ULN (upper limit of normal) against the peak ALT/ULN on-treatment during the DB Phase for both ENABLE studies (data not shown). This is based on the notion that a concomitant elevation in serum ALT and total bilirubin (Hy's Law) is the most specific biomarker for potentially serious Drug-Induced Liver Injury.

When ALT and bilirubin values were normalized for baseline, there were 17 subjects (11 eltrombopag and 6 placebo) with substantial elevations in both ALT and bilirubin during the study. When subjects were analysed relative to their own baselines, 11 eltrombopag subjects and 6 placebo subjects were located in the right-hand quadrants, associated with liver injury. In this setting, definition of Hy's Law cases is complicated by the fact that other causes for the increase in ALT and bilirubin exist, namely HCV infection and concomitant use of ribavirin and peginterferon.

In addition the MAH provided upon CHMP request a review of all cases of liver injury including an analysis of time to onset, age, sex, dose, outcome, among others (data not shown). Events of liver injury (ALT or AST >3xULN) and severe liver injury (ALT or AST >3xULN and total Bilirubin >1.5x ULN with fractionated bilirubin ≥35%) were reported at a similar frequency in eltrombopag and placebo-treated patients. The age and gender distribution of those with liver injury was similar in the two treatment groups. A greater number of placebo-treated subjects with severe and non-severe liver injury discontinued treatment than those on eltrombopag with liver injury.

Moreover a detailed presentation of the changes in hepatobiliary parameters during the DB phases of ENABLE 1 and 2 studies (on treatment plus 6 months follow-up) was provided. These data show that transaminases increments are similar between the treatment groups with ALT or AST >3x ULN in 46% placebo vs 44% in eltrombopag.

Potentially serious DILI (defined as increments in transaminases plus fractionated bilirrubin >35%) were more common on placebo compared to eltrombopag, suggesting that eltrombopag doesn't cause hepatotoxicity in this patient population. However, hiperbilirrubinemia, associated with increments in transaminases, is a common AEs associated with the use of eltrombopog in this HCV population. 4(0.8%) cases of jaundice in placebo and 34(4%) in eltrombopag have been reported, of those experimented ALT or AST>3xULN 2 case in placebo and 16 in eltrombopag. Overall 2/484 (0.1%) in placebo and 16/955(1.6%) in eltrombopag had jaundice and transaminases increments. Changes in bilirubin (>2ULN) occurred in 55% of patients in eltrombopag vs 26% in placebo. In the majority of jaundice reported cases (23/38, 68%) patients recovered without sequelae.

Hepatic decompensation

AEs suggestive of hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis, HCC, death) were collected to identify patterns of events (see Table 49). A blinded independent review of these events was conducted by hepatology experts external to the MAH. The external adjudication panel assessment showed a 6% higher proportion of subjects experienced an event suggestive of hepatic decompensation in the eltrombopag treatment group compared with the placebo group.

Table 49. Events Suggestive of Hepatic Decompensation On-Treatment Plus 30 Days Follow-Up During the DB Phase (External-Adjudication)

	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any Event	**35 (7)**	**125 (13)**
Ascites	14 (3)	55 (6)
HCC	12 (2)	27 (3)
Hepatic encephalopathy	4 (<1)	24 (3)
Deaths	7 (1)	23 (2)
Variceal haemorrhage	4 (<1)	13 (1)
Spontaneous bacterial peritonitis	2 (<1)	8 (<1)
Other decompensation events[a]	1 (<1)	15 (2)
Time to event (days)		
Mean (SD)	166.51 (89.118)	166.91 (85.961)
Median (min-max)	148.0 (37-401)	161.0 (36-427)

a. Other decompensation events included hepatic failure (9 eltrombopag, 1 placebo), hepatorenal syndrome (1 eltrombopag), and other (5 eltrombogpag [1 hepatitis alcoholic, 2 hepatic cirrhosis, 1 hepatic function abnormal, 1 liver disorder], 1 placebo [hepatic cirrhosis]) (Data Source Table 8.9018)

Factors related to an increased probability of experiencing a hepatic decompensation event included baseline MELD score ≥10, non-Asian ancestry, and baseline albumin ≤35 g/L.

There was no clear correlation between eltrombopag dose and hepatic decompensation events. The mean daily dose of eltrombopag was 65.6 mg in those experiencing an event, and 63.6 mg in those not. The cumulative eltrombopag dose was 9276 mg in those experiencing an event, and 14454 mg in those not (though around a third of those experiencing events had treatment withdrawn due to the event). The proportion who received the maximum dose (100 mg) of eltrombopag prior to an event was comparable in those experiencing an event (54%) and those not (53%). The distribution of eltrombopag doses taken (ie, proportions taking 12.5, 25, 50, 75 and 100 mg doses) in those experiencing events and those not was also comparable. Similar results were observed for those randomised to placebo.

Six percent of placebo subjects had an increase of 2 or more points in the Child-Pugh score from baseline to the end of follow-up, compared with 8% of eltrombopag subjects.

Median MELD score increased during the open label phase, and in the double-blind phase for those treated with eltrombopag but not placebo (data not shown). Because MELD is dependent on serum bilirubin, which can be pharmacologically increased with concomitant eltrombopag and ribavirin, the MELD scores during the on-treatment period are difficult to interpret.

Median interquartile range (INR) values in the eltrombopag treatment group were stable in the DB Phase and were similar to the median INR values for placebo-treated subjects, including at end-of-treatment and during follow-up.

Renal-Related Adverse Events

Renal-related adverse events that occurred on-treatment plus 30 days follow up is shown in Table 50:

Table 50. Renal-Related AEs On-Treatment Plus 30 Days Follow- Up in ≥1% Subjects in Either Treatment Group (Safety DB Population)

Preferred term	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	**53 (11)**	**147 (15)**
Urinary tract infection	23 (5)	71 (7)
Haematuria	5 (1)	7 (<1)
Pollakiuria	5 (1)	7 (<1)

Two eltrombopag subjects who had a fatal AE of renal failure did so in the context of multi-organ failure.

- One subject died on Day 333, 17 days post-treatment, from generalized edema, spontaneous bacterial peritonitis, renal failure, hepatic failure, gastrointestinal bleeding, and multiple organ failure (all Grade 4 SAEs). The subject's baseline MELD score was 14. Medical conditions ongoing at study entry included hypertension, left atrial enlargement, left ventricular overload, esophageal varices, and depression.
- One subject died 3 weeks post –therapy (Day 186) due to sepsis with ensuing hepatic and renal failure. Subject's baseline MELD score was 14. Medical conditions ongoing at study entry were reported as "aplastic anaemia", glaucoma, and cirrhosis.

Subjects with increases in serum creatinine of 44.3 µmol/L (0.5 mg/dL) and 26.6 µmol/L (0.3 mg/dL) in ≥2 consecutive assessments were identified. More subjects treated with eltrombopag (16 subjects, 2%) had at least 2 consecutive assessments of creatinine ≥26.6 μ mol/L above baseline compared with placebo (4 subjects, <1%). All other assessments were similar between both treatment groups. Similar proportions of subjects in both treatment groups (eltrombopag, 8%; placebo, 6%) had decreases in creatinine clearance (to 60-89 mL/min) at ≥ 2 consecutive visits (data not shown).

The occurrences of hypokalemia, hyponatremia or hypomagnesemia were investigated and compared between the placebo and eltrombopag treatment groups. Two subjects in the eltrombopag group (<1%) and no subjects in the placebo group had a Grade3/Grade4 hypokalemia. Eight subjects in the eltrombopag group (<1%) had a Grade3/Grade4 hyponatremia compared with none in the placebo group. Similar proportions of subjects in both treatment groups experienced a shift from baseline to a toxicity Grade ≥ 2 for magnesium (eltrombopag: 4%; placebo: 4%).

Malignancies

Malignancies were reported by 66 subjects during the DB Phase (see Table 51).

Table 51. Malignancy adverse events during DB phase (safety DB population)

Preferred term	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	**20 (4)**	**46 (5)**
Hepatic neoplasm malignant	15 (3)	40 (4)
Hepatic neoplasm	2 (<1)	2 (<1)
Alpha 1 foetoprotein increased	2 (<1)	0
Basal cell carcinoma	0	1 (<1)
Bile duct cancer	1 (<1)	0
Gastric cancer	0	1 (<1)
Hepatic lesion	1 (<1)	0
Lung neoplasm malignant	1 (<1)	0
Lung squamous cell carcinoma stage unspecified	0	1 (<1)
Non-small cell lung cancer	0	1 (<1)[a]

a. Subject 311/TPL103922 was diagnosed post-study with "myelodysplastic/myeloproliferative neoplasm, unclassifiable"; 6 months after radiotherapy for NSCLC and 13 months after last dose of study medication. A narrative for this subject is provided in Section 16 of the study TPL103922 CSR

During double blind phase, 81 subjects, 55(6%) eltrombopag and 26 (5%) in placebo reported "hepatic lesions", most of them were "confirmed or suspected" hepatocelullar carcinoma HCC", 44 (5%) in eltrombopag and 19 (4%) in placebo. In addition four subjects had a report of hepatic neoplasm during open-label phase. Development of hepatocelullar carcinoma is not unexpected in patients with advance HCV disease. No relevant differences between treatment arms have been found.

The MAH also reported two patients with myelodysplastic/myeloproliferative neoplasm, none of them related with eltrombopag therapy.

Thrombocytopenia Adverse Events

During the DB Phase on-treatment plus 30 days follow-up period, the proportion of subjects reporting a thrombocytopenic event was lower in the eltrombopag group (17%) compared with the placebo group (40%).

Bleeding Adverse Events

The following section is focused on non-variceal bleeding events. Variceal (oesophageal and/or gastric) bleeding events are considered a consequence of hepatic decompensation and are discussed in more detail above.

During the DB Phase On-treatment plus 30 days follow-up, the proportion of subjects reporting a non-variceal bleeding event was lower in the eltrombopag treatment group (16%) compared with the placebo group (21%) (see Table 52).

Table 52. Adjudicated Non-Variceal Bleeding Events On-Treatment Plus 30 Days Follow-Up in ≥1% Subjects in Either Treatment Group (Safety DB Population)

Preferred term	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	**102 (21)**	**154 (16)**
Epistaxis	51 (11)	57 (6)
Gingival bleeding	21 (4)	23 (2)
Retinal haemorrhage	8 (2)	15 (2)
Haemoptysis	5 (1)	8 (<1)
Haematuria	5 (1)	7 (<1)
Contusion	5 (1)	3 (<1)

Seven subjects in the ENABLE studies (1 placebo, 6 eltrombopag) had a bleeding event that preceded a fatal event. The placebo event was due to a ruptured cerebral aneurysm. The eltrombopag events include a haemorrhagic stroke, and 5 cases of GI haemorrhage.

In addition upon CHMP request during the D120 List of Outstanding issues the MAH has provided details about the post-therapy platelet counts and bleeding episodes during the follow up phase. In general a lower proportion of subjects in the eltrombopag group (50%) had post-therapy platelet count less than baseline compared to the placebo group (73%). Moreover after withdrawal of eltrombopag, platelet counts gradually return to baseline values over a 24 week follow-up period, which is reassuring.

With regard to bleeding events, 48 (5%) patients in eltrombopag and 22(5%) in placebo experimented bleeding events, with higher numbers in the eltrombopag arm experiencing serious (27% vs 38% in placebo/eltrombopag, respectively), G3/4 bleedings (18% vs 35%, respectively) and fatal (4 subjects, 8% of cases in eltrombopag) bleedings. When the data are analysed by the type, either non-GI vs GI bleedings, it appears that these differences are mainly driven by the GI bleedings (19 subjects (2%) reported 22 events in eltrombopag arm vs 7 subjects (1%), 8 events in placebo arm) for which more cases/serious and fatal cases are reported in the eltrombopag treatment arm.

Ocular Events

Cataracts were first observed in toxicology studies of eltrombopag in mice and rats, but not in dogs. Subjects were actively monitored and detailed ocular assessments (including assessments for cataracts) were therefore added at screening or baseline, every 12 weeks, end-of-treatment, and at 3-month and 6-month follow-up visits. Cataract events were categorised as progression of existing cataracts and development of new cataracts. Results are shown in Table 53.

Table 53. CEC Adjudicated Cataract Events During DB Phase

Preferred term	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	**24 (5)**	**74 (8)**
Subjects with progression of pre-existing cataract at baseline	**12 (2)**	**38 (4)**
Bilateral incidence	8 (2)	21 (2)
Unilateral incidence	4 (<1)	17 (2)
Subjects with an incident cataract	**12 (2)**	**36 (4)**
Bilateral progression	5 (1)	23 (2)
Unilateral progression	7 (1)	13 (1)

Comparative incidences by exposure time were provided by the MAH upon CHMP request during the D120 List of Questions. The rates of development of new cataract and the progression of pre-existing cataract in subjects treated with eltrombopag were double those of placebo-treated subjects. Baseline risk factors for cataract were generally comparable in the groups. However, 33% of the placebo subjects with a cataract event had a history of diabetes, compared with 20% of the eltrombopag subjects. Diabetes is a significant risk factor for cataract, and the imbalance of this confounding factor may suggest a larger effect of eltrombopag on cataract risk than observed from the results observed in the ENABLE studies.

In addition four cases of cataract have been reported in the post-marketing data for eltrombopag in ITP. Assessment of causality was, however, confounded by the use of steroids in these patients.

Laboratory findings

Overall, abnormalities in the haematology parameters were balanced between treatment groups with the exception of Grade 4 lymphopenia, which occurred more frequently with eltrombopag (25%) than placebo (13%).

Clinical chemistry parameters examined during the study included calcium, glucose, potassium, and sodium. No systematic differences or patterns were observed between the treatment groups.

Each subject's vital signs (heart rate, systolic blood pressure and diastolic blood pressure) and weight were measured throughout the DB Phase. There were no consistent patterns of change in vital signs during the DB Phase. Subjects in both arms had a mean decrease in weight during the studies, with those in the eltrombopag arm consistently experiencing slightly greater weight loss (mean change from baseline at end of treatment -2.7 kg placebo, -4.4 eltrombopag). This weight difference between the arms became less evident during the post-treatment follow-up.

The proportions of ECG findings (normal, abnormal – not clinically significant, abnormal – clinically significant) at baseline, at the end of treatment, and at the 24 week follow-up were similar in the two treatment groups, with most ECGs listed as normal or abnormal, not clinically significant. However, a greater proportion of eltrombopag subjects were considered to have a clinically significant change from baseline compared with placebo subjects (12 vs. 2).

With regard to the worst ECG finding during the study, the proportions with a clinically significant change from baseline were 2% (8 subjects) for placebo, and 5% (43 subjects) for eltrombopag. Of the 8 placebo subjects, there were 2 corresponding AEs, both involving ST segment abnormalities. Of the 43 eltrombopag subjects, there were 26 corresponding AEs:

- 3 atrial fibrillation
- 1 right ventricular failure
- 9 QT prolonged (3 to >480 ms)
- 3 T-wave abnormalities
- 3 atrioventricular blocks
- 1 extra systoles
- 1 PR prolongation
- 1 ECG abnormal
- 1 bundle branch block left
- 1 bradycardia

- 1 bundle branch block right
- 1 acute myocardial infarction (ST elevated)

The proportions of subjects who had an increased QTcF from the screening assessment to the antiviral baseline assessment or end-of-treatment/withdrawal were similar between the eltrombopag group and the placebo group (see Table 54). A greater proportion of eltrombopag subjects had a worst case increase in QTcF of 31-60 msec compared with the placebo group.

Table 54. QTcF (msec) Increases During DB Phase (Safety DB Population)

	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Antiviral Baseline	**n=451**	**n=901**
Increase to ≥450 - <481	39 (9)	40 (4)
Increase to ≥481 - <501	2 (<1)	9 (<1)
Increase to ≥501	1 (<1)	3 (<1)
End of Treatment / Withdrawal	**n=409**	**n=800**
Increase to ≥450 to <481	31 (8)	49 (6)
Increase to ≥481 to <501	2 (<1)	12 (2)
Increase to ≥501	1 (<1)	2 (<1)
Worst Case	**n=479**	**n=952**
Increase to ≥450 to <481	72 (15)	119 (13)
Increase to ≥481 to <501	11 (2)	31 (3)
Increase to ≥501	2 (<1)	13 (1)

	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Antiviral Baseline	**n=451**	**n=901**
Increase of 31-60	26 (6)	52 (6)
Increase of >60	8 (2)	13 (1)
End of Treatment / Withdrawal	**n=409**	**n=800**
Increase of 31-60	21 (5)	91 (11)
Increase of >60	9 (2)	14 (2)
Worst Case	**n=479**	**n=952**
Increase of 31-60	49 (10)	150 (16)
Increase of >60	18 (4)	44 (5)

The MAH provided a mixed effects modelling analysis to study the relationship between eltrombopag concentration and cardiac repolarization in patients with HCV (data not shown). A total of 98 subjects with time-matched electrocardiogram (ECG) and serial pharmacokinetics (PK) data were included in the analysis (analysis population). The analysis concluded that eltrombopag is predicted to have no clinically significant effect on QTc intervals at either therapeutic or supratherapeutic doses in subjects with HCV infection.

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

- HCV Genotype (non-2/3 (69%), 2/3 (31%))

- baseline MELD Score (<10 (56%), ≥10 (43%))
- baseline albumin (≤35 g/L (29%), >35 g/L (71%))
- fibrosis score (F0/F1/F2 (9%), F3/F4 (79%))
- age (<65 years (93%), ≥65 years (7%))
- gender (Female (37%), Male (63%))
- race (Eastern Asian heritage (10%), other Asian heritage (13%), White and other (77%))
- BMI (<30 (71%), ≥30 (28%))

HCV Genotype

Subjects in the two HCV genotype subgroups were treated differently. The HCV genotype non-2/3 subgroup had a longer median cumulative duration of treatment for all 3 IPs than the genotype 2/3 subgroup. In the HCV genotype non-2/3 subgroup, the safety profile was similar to that for the overall safety. In the HCV genotype 2/3 subgroup, the safety profile was similar between the placebo and eltrombopag treatment groups.

Subjects with HCV genotype non-2/3 had a higher frequency of AEs, including death, than subjects with HCV genotype 2/3. There were 17 eltrombopag subjects (3%) with a fatal event in the HCV genotype non-2/3 group, compared with 6 subjects (2%) in the HCV genotype 2/3 group. Table 55 shows Grade 3 or Grade 4 AEs by HCV Genotype.

Table 55. Grade 3 or Grade 4 AEs by HCV Genotype

HCV Genotype non-2/3	Number of Subjects (%)	
	Placebo (N=333)	Eltrombopag (N=657)
Any event	**175 (53)**	**354 (54)**
Neutropenia	61 (18)	100 (15)
Anaemia	20 (6)	68 (10)
Hyperbilirubinaemia	5 (2)	42 (6)
Thrombocytopenia	91 (27)	36 (5)
Leukopenia	14 (4)	33 (5)
Blood bilirubin increased	2 (<1)	22 (3)
Pyrexia	6 (2)	19 (3)
Lymphopenia	6 (2)	17 (3)
Hepatic neoplasm malignant	3 (<1)	15 (2)
White blood cell count decreased	1 (<1)	13 (2)
Weight decreased	4 (1)	12 (2)
Asthenia	3 (<1)	11 (2)
Ascites	1 (<1)	10 (2)
Fatigue	5 (2)	5 (<1)
Neutrophil count decreased	9 (3)	5 (<1)
HCV Genotype 2/3	**Number of Subjects (%)**	
	Placebo (N=150)	Eltrombopag (N=295)
Any event	**85 (57)**	**118 (40)**
Neutropenia	28 (19)	41 (14)
Thrombocytopenia	40 (27)	14 (5)
Leukopenia	6 (4)	12 (4)
Anaemia	12 (8)	11 (4)
Blood bilirubin increased	4 (3)	11 (4)
Hyperbilirubinaemia	1 (<1)	9 (3)
Diarrhoea	0	7 (2)
Haemoglobin decreased	1 (<1)	6 (2)
White blood cell count decreased	6 (4)	6 (2)
Asthenia	0	5 (2)
Neutrophil count decreased	3 (2)	5 (2)
Hepatic neoplasm malignant	4 (3)	2 (<1)
Platelet count decreased	6 (4)	1 (<1)
Aspartate aminotransferase increased	3 (2)	0

MELD Score

The median cumulative duration of treatment for DB study drug, peginterferon and ribavirin were all longer for the eltrombopag treatment group compared with the placebo group for both MELD subgroups. However, this difference between the treatment groups was greater in the MELD ≥10 (~35% difference) subgroup for each of the 3 IPs compared to MELD <10 (~9% difference). This difference was primarily due to the shorter median cumulative duration of treatment for the MELD ≥10 placebo group compared to the MELD <10 placebo group.

Subjects with a baseline MELD score ≥10 had a higher frequency of AEs, including death, than subjects with a baseline MELD score <10. There were 6 eltrombopag subjects (1%) with a fatal event in the MELD <10 group, compared with 16 subjects (4%) in the MELD ≥ 10 group. For the

baseline MELD <10 subgroup, the safety profile was similar between the placebo and eltrombopag treatment groups. Results are shown in Tables 56 and 57.

Table 56. Adverse Events of Special Interest by Baseline MELD Score (Safety DB Population)

	Number of Subjects (%)			
	Grouping: Baseline MELD Score <10		Grouping: Baseline MELD Score ≥10	
	Placebo (N=264)	Eltrombopag (N=541)	Placebo (N=213)	Eltrombopag (N=400)
Any special interest event	**72 (27)**	**137 (25)**	**76 (36)**	**160 (40)**
Thromboembolic[a]	2 (<1)	13 (2)	3 (1)	17 (4)
Events suggestive of hepatic decompensation[a]	11 (4)	38 (7)	24 (11)	85 (21)
Malignancies[b]	4 (2)	12 (2)	9 (4)	17 (4)
Non-variceal bleeding[a]	53 (20)	78 (14)	47 (22)	73 (18)
CEC adjudicated cataract events[b]	11 (4)	37 (7)	13 (6)	33 (8)

Data Source: ISS Section 6.1.2

a. On-treatment plus 30 days follow-up

b. On-treatment plus 6 months follow-up

Table 57. Adverse Events Suggestive of Hepatic Decompensation by Baseline MELD Score (Safety DB Population)

	Number of Subjects (%)			
	Grouping: Baseline MELD Score <10		Grouping: Baseline MELD Score ≥10	
	Placebo (N=264)	Eltrombopag (N=541)	Placebo (N=264)	Eltrombopag (N=541)
Any event	**11 (4)**	**38 (7)**	**24 (11)**	**85 (21)**
Ascites	2 (<1)	13 (2)	12 (6)	41 (10)
HCC	3 (1)	12 (2)	9 (4)	15 (4)
Death	2 (<1)	6 (1)	5 (2)	16 (4)
Hepatic encephalopathy	1 (<1)	7 (1)	3 (1)	16 (4)
Variceal haemorrhage	3 (1)	4 (<1)	1 (<1)	9 (2)
Other decompensation events	0	3 (<1)	1 (<1)	12 (3)
Spontaneous bacterial peritonitis	0	0	2 (<1)	7 (2)

Data Source: ISS Section 6.1.2

Albumin

Subjects with baseline albumin ≤35 g/L had a higher frequency of AEs, including death, than subjects with baseline albumin >35 g/L. There were 15 eltrombopag subjects (5%) with a fatal event in the albumin ≤35 g/L, compared with 8 subjects (1%) in the albumin >35 g/L. For the baseline albumin >35 g/L subgroup, the safety profile was similar between the placebo and eltrombopag treatment groups

Subjects with baseline albumin ≤35 g/L treated with eltrombopag had a higher incidence of AEs suggestive of hepatic decompensation (25%) compared with subjects with baseline albumin >35 g/L treated with eltrombopag (8%), and higher than the corresponding placebo group (10%) (see Table 58 and 59).

Table 58. Adverse Events of Special Interest by Baseline Albumin (Safety DB Population)

	Number of Subjects (%)			
	Grouping: Baseline Albumin ≤35 g/L		Grouping: Baseline Albumin >35 g/L	
	Placebo (N=139)	Eltrombopag (N=275)	Placebo (N=345)	Eltrombopag (N=680)
Any special interest event	**44 (32)**	**123 (45)**	**106 (31)**	**180 (26)**
Thromboembolic[a]	2 (1)	15 (5)	3 (<1)	16 (2)
Events suggestive of hepatic decompensation[a]	14 (10)	69 (25)	21 (6)	56 (8)
Malignancies[b]	5 (4)	13 (5)	8 (2)	16 (2)
Non-variceal bleeding[a]	29 (21)	58 (21)	73 (21)	96 (14)
CEC adjudicated cataract events[b]	6 (4)	26 (9)	18 (5)	48 (7)

Data Source: ISS Section 6.1.3

a. On-treatment plus 30 days follow-up

b. On-treatment plus 6 months follow-up

Table 59. Adverse Events Suggestive of Hepatic Decompensation by Baseline Albumin (Safety DB Population)

	Number of Subjects (%)			
	Grouping: Baseline Albumin ≤35 g/L		Grouping: Baseline Albumin >35 g/L	
	Placebo (N=139)	Eltrombopag (N=275)	Placebo (N=345)	Eltrombopag (N=680)
Any event	**14 (10)**	**69 (25)**	**21 (6)**	**56 (8)**
Ascites	6 (4)	36 (13)	8 (2)	19 (3)
Death	3 (2)	15 (5)	4 (1)	8 (1)
Hepatic encephalopathy	1 (<1)	17 (6)	3 (<1)	7 (1)
HCC	5 (4)	11 (4)	7 (2)	16 (2)
Other decompensation events	0	11 (4)	1 (<1)	4 (<1)
Variceal hemorrhage	2 (1)	4 (1)	2 (<1)	9 (1)
Spontaneous bacterial peritonitis	1 (<1)	3 (1)	1 (<1)	5 (<1)

Data Source: ISS Section 6.1.3

Overall Summary of Adverse Events by Baseline MELD Score and Baseline Albumin

In the ENABLE studies baseline MELD ≥10 was associated with a 3-fold higher rate of progression to decompensated liver disease in comparison to baseline MELD <10. This was observed in both the placebo and the eltrombopag treatment groups. Subjects in both treatment groups with a baseline MELD score ≥10 had a higher frequency of adverse events, including death, than subjects with a baseline MELD score <10 (see Table 60). In contrast, the safety profile was similar between the placebo and eltrombopag treatment groups for the baseline MELD <10 subgroup. Subjects in both treatment groups with baseline albumin levels <35 g/L had a higher frequency of AEs suggestive of hepatic decompensation, including death. Similar to subjects with baseline MELD score <10, the safety profile was similar between the placebo and eltrombopag treatment groups for subjects with albumin levels >35 g/L.

Table 60. Overall Summary of Adverse Events by Baseline MELD Score and Baseline Albumin On-Treatment Plus 30 Days Follow-up (Pooled Data, Safety DB Population)

	Grouping: Baseline MELD Score <10				Grouping: Baseline MELD Score ≥10			
	Placebo (N=264)		Eltrombopag (N=541)		Placebo (N=213)		Eltrombopag (N=400)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Number of subjects with an SAE	31 (12)	43	76 (14)	123	41 (19)	71	110 (28)	205
Number of subjects with a fatal AE	2 (<1)	2	6 (1)	7	5 (2)	9	16 (4)	25
	Grouping: Baseline Albumin ≤35 g/L				Grouping: Baseline Albumin >35 g/L			
	Placebo (N=139)		Eltrombopag (N=275)		Placebo (N=345)		Eltrombopag (N=680)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Number of subjects with an SAE	27 (19)	39	88 (32)	172	45 (13)	75	101 (15)	162
Number of subjects with a fatal AE	3 (2)	5	15 (5)	21	4 (1)	6	8 (1)	13

Data Source: SDAP Table 8.1028

The safety profile was similar for patients treated with eltrombopag and placebo for subjects with genotype 2/3, MELD <10, or albumin levels >35 g/L, whilst the SVR rates were higher in the subjects in these subgroups.

Fibrosis Score

FibroSURE category F0/F1/F2 had a lower incidence and occurrence of AEs, SAEs, fatal AEs, drug related AEs and AEs leading to IP discontinuation when compared with category F3/F4 and the overall safety DB population, although this subgroup (F0/F1/F2) had a small number of subjects.

Age

Although the proportion of patients aged at least 65 years was small, they appeared to experience a disproportionate number of adverse events of special interest (other than those suggestive of hepatic decompensation) (see Table 61). In particular, non-variceal bleeding events and cataract events occurred at a higher frequency in older subjects.

Table 61. Adverse Events of Special Interest by Age

	Number of Subjects (%)			
	Grouping: <65 years of age		Grouping: ≥65 years of age	
	Placebo (N=449)	Eltrombopag (N=891)	Placebo (N=35)	Eltrombopag (N=64)
Any special interest event	141 (31)	273 (31)	9 (26)	30 (47)
Thromboembolic[a]	5 (1)	28 (3)	0	3 (5)
Events suggestive of hepatic decompensation[a]	32 (7)	119 (13)	3 (9)	6 (9)
Malignancies[b]	11 (2)	26 (3)	2 (6)	3 (5)
Non-variceal bleeding[a]	99 (22)	138 (15)	3 (9)	16 (25)
CEC adjudicated cataract events[b]	21 (5)	61 (7)	3 (9)	13 (20)

Gender

Overall, the AE profile was generally similar for the eltrombopag group compared with the placebo group for both genders.

Race

Population PK analysis have shown that Eastern Asians (such as Japanese, Chinese, Taiwanese and Korean) have a higher plasma eltrombopag AUC value than non East Asians. The small number of subjects in the Eastern Asian (10%) and Other Asian (13%) categories, however, make it difficult to draw any meaningful conclusions regarding differences between the subgroups.

Eastern Asians received slightly lower cumulative doses of eltrombopag and antivirals than Whites, but over a longer duration than other racial groups.

Adjudicated events of special interest were analysed by the three racial groups (see Table 62). The AE profile was similar with that observed for the overall Safety DB Population, though events in East Asians were more common than in other racial groups.

Table 62. Adverse Events of Special Interest by Race

	Number of Subjects (%)					
	Grouping: Eastern Asians		Grouping: Other Asians		Grouping: White and Other	
	Placebo (N=58)	Eltrombopag (N=87)	Placebo (N=60)	Eltrombopag (N=126)	Placebo (N=366)	Eltrombopag (N=742)
Any special interest event	27 (47)	30 (34)	16 (27)	30 (24)	107 (29)	243 (33)
Thromboembolic[a]	1 (2)	4 (5)	1 (2)	3 (2)	3 (<1)	24 (3)
Events suggestive of hepatic decompensation[a]	6 (10)	15 (17)	5 (8)	14 (11)	24 (7)	96 (13)
Malignancies[b]	5 (9)	7 (8)	3 (5)	1 (<1)	5 (1)	21 (3)
Non-variceal bleeding[a]	18 (31)	12 (14)	9 (15)	16 (13)	75 (20)	126 (17)
CEC adjudicated cataract events[b]	4 (7)	10 (11)	2 (3)	7 (6)	18 (5)	57 (8)

BMI

Overall, the adverse event profile was generally similar for the eltrombopag group compared with the placebo group for both BMI categories. The exception was the incidence of SAEs, which was higher in the eltrombopag group compared with the placebo group for the BMI <30 category (20% vs. 13%). There was a higher proportion of subjects in the placebo group compared with the eltrombopag group with AE leading to IP discontinuation for both BMI categories.

Safety related to drug-drug interactions and other interactions

The potential for interaction of eltrombopag with the organic anion transporter polypeptide, OATP1B1, the breast cancer resistance protein, polyvalent cations, and high-fat foods is already detailed in the SmPC. Post-marketing reports have not highlighted any additional concerns regarding interactions.

Upon CHMP request the MAH provided preliminary findings of a DDI study to investigate the potential for an interaction between eltrombopag and the protease inhibitors telaprevir and boceprevir. The study involved 56 healthy volunteers; high single doses of eltrombopag were used (200 mg), with maximum recommended single and multiple dose levels of the protease

inhibitors. The study design, with steady-state dosing of the protease inhibitors, was designed to document the effect of protease inhibitors on eltrombopag pharmacokinetics. Preliminary results show no significant effect of telaprevir or boceprevir on eltrombopag however the full study report is awaited before any conclusion can be made.

Discontinuation due to adverse events

A greater proportion of placebo subjects (29%) discontinued investigational product due to an AE compared with eltrombopag treated subjects (22%) as shown in Table 63. This difference was mainly attributed to events of thrombocytopenia. Hematological toxicities were the most common reasons for discontinuation in both treatment groups.

Table 63. AEs Leading to Permanent Discontinuation of Any Investigational Product or Withdrawal from the Study During DB Phase (Safety DB Population)

Preferred term	Number of Subjects (%)	
	Placebo (N=484)	Eltrombopag (N=955)
Any event	140 (29)	206 (22)
Anaemia	15 (3)	24 (3)
Thrombocytopenia	61 (13)	24 (3)
Ascites	3 (<1)	13 (1)
Hepatic failure	1 (<1)	10 (1)
Hepatic neoplasm malignant	6 (1)	10 (1)
Hyperbilirubinaemia	1 (<1)	10 (1)
Neutropenia	16 (3)	7 (<1)
Oesophageal varices haemorrhage	1 (<1)	7 (<1)
Asthenia	3 (<1)	6 (<1)
Blood bilirubin increased	0	6 (<1)
Cataract	1 (<1)	6 (<1)
Gastrointestinal haemorrhage	1 (<1)	6 (<1)
Haemoglobin decreased	3 (<1)	6 (<1)
Encephalopathy	1 (<1)	5 (<1)
Oedema peripheral	0	5 (<1)
Pneumonia	2 (<1)	5 (<1)
Retinal exudates	0	5 (<1)
Depression	1 (<1)	4 (<1)
Diarrhoea	1 (<1)	4 (<1)
Fatigue	2 (<1)	4 (<1)
Hepatic encephalopathy	0	4 (<1)
Pyrexia	0	4 (<1)
Abdominal pain	3 (<1)	3 (<1)
Hepatic cirrhosis	0	3 (<1)
Jaundice	0	3 (<1)
Leukopenia	1 (<1)	3 (<1)
Pancytopenia	0	3 (<1)
Portal vein thrombosis	1 (<1)	3 (<1)
Sepsis	0	3 (<1)

Post marketing 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). As of 31 March 2012, there were 2261 spontaneous and post marketing cases (5215 AEs) received for marketed use of eltrombopag, received from 41 countries (the majority from the US) (see Table 64).

Table 64. Ten Most Frequently Reported Adverse Events from Spontaneous and Post-Marketing 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.

There were 489 cases with a fatal outcome out of the 2261 cases reported from marketed usage of eltrombopag. These cases have been presented in detail in periodic safety update reports. Many reports with fatal outcome primarily described elderly patients with multiple underlying medical conditions and co-morbidities that likely contributed to the fatal outcome. The majority of the cases with a fatal outcome were from the post marketing studies (402/489). There was a wide age range reported (3-100 years), with the majority of reported cases describing patients greater than 65 years of age. The cause of death was unknown or unspecified in over 30% of the cases received by GSK. The remaining causes of death pertained to primarily elderly patients with underlying malignancies, infections including sepsis, cardiac disorders, renal disease, respiratory conditions, and nervous system disorders.

The most frequently reported hepatobiliary events were liver function test abnormal (47), liver disorder (37), aspartate aminotransferase increased (29), alanine aminotransferase increased (27), hepatic enzyme increased (27), hepatic function abnormal (18), and blood bilirubin increased (15). The outcomes of the 206 cases were improved/resolved (80), unresolved (22), fatal (40), and unknown (64). 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. 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.

2.6.1. Discussion on clinical safety

The safety database for eltrombopag in combination with interferon-based antiviral therapy in chronic HCV comprises placebo-controlled data for 955 patients from up to 6 months of dosing in two double-blind trials, preceded by an initial uncontrolled dosing period. Supportive data are also available from the small dose-ranging Phase II study. Eltrombopag has been licensed for use in chronic immune thrombocytopenic purpura for over 2 years. It is known to be associated with a risk of hepatotoxicity (increases in serum transaminases and bilirubin) and thrombotic/thromboembolic events. Eltrombopag has been also associated with cataract in rodent studies.

In the ENABLE studies there were significantly more AEs, including SAEs, fatal AEs, drug-related AEs, AEs leading to study withdrawal, and AEs leading to study medication discontinuation, in those treated with eltrombopag as compared to placebo. The commonest SAEs and causes of death were related to hepatic decompensation. The incidence of SAEs related to hepatic decompensation in eltrombopag subjects was double that in placebo subjects (8% vs. 4%). There were 30 fatal events related to hepatic decompensation: 7 in the placebo group (1.4%) and 23 in the eltrombopag group (2.4%). There were also 5 cases of fatal GI haemorrhage, all occurring in those on eltrombopag.

Thrombotic/thromboembolic events were more common in those on eltrombopag. Upon CHMP request the MAH provided a very detailed discussion on the TEE cases observed during the ENABLE 1 and 2 studies showing that 38 out of 955 subjects (4 %) treated with eltrombopag and 6 out of 484 subjects (1 %) in the placebo group experienced TEEs. Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2 % in patients treated with eltrombopag versus < 1 % for placebo). In addition significant risk factors for TEEs included age ≥ 60 and albumin < 3.5 g/L. This information has been included in the SmPC.

No cases of elevated platelet levels occurred in patients with maximum platelets counts < 100 Gi/L and the majority of cases occurred in patients >150 Gi/L (26/44) elevated platelet. Furthermore, median platelet levels near to the event tended to be higher in the eltrombopag treatment arms compared to placebo (93 Gi/L vs 50 Gi/L). Although low platelet levels do not prevent from TEE, there seems to be a higher risk in patients with higher platelet levels during the course of treatment. Therefore, the CHMP agreed that the recommended posology should keep platelets values <150 Gi/L and treatment with eltrombopag should be stopped when platelet values >150 Gi/L to minimise the risk for TEE. In addition, an additional statement has been included in section 4.2 of the SmpC highlighting the need to use the lowest dose of eltrombopag to achieve and maintain a platelet count ≥50 Gi/L.

Hepatobiliary events were also more common in those treated with eltrombopag. This was partly due to an increase in events of hyperbilirubinaemia; eltrombopag is known to inhibit a metabolising enzyme of bilirubin, resulting in elevation of unconjugated bilirubin. Although increases in serum transaminases were comparable to the placebo group, events suggestive of hepatic decompensation (such as ascites, hepatocellular carcinoma, and hepatic encephalopathy) occurred nearly twice as frequently in those on eltrombopag (OR 1.9, CI 1.3 to 2.9). This did not appear to be a dose-dependent finding, and is further complicated by the fact that those treated with eltrombopag were exposed to higher doses of peginterferon/ribavirin. However, the association between peginterferon/ribavirin therapy and hepatotoxicity is not strong. Therefore, the CHMP agreed that a statement regarding hepatic decompensation should be added to the eltrombopag SmPC to adequately address the risk. In addition the SmPC has been updated to provide appropriate information to warn physicians on the risk of transaminases increments and hyperbillirubinemia in relation to eltrombopag.

The numerical trend for more serious bleeding GI events after stopping therapy is a matter of concern and has been reflected adequately in the SmPC. Additional follow up of this risk at post-approval has also been included in the RMP.

The rates of development of new cataract and the progression of pre-existing cataract in subjects treated with eltrombopag were higher than those of placebo-treated subjects (8 % of the eltrombopag group and 5 % of the placebo group). Baseline risk factors for cataract were generally comparable in the groups. However, 33% of the placebo subjects with a cataract event had a history of diabetes, compared with 20% of the eltrombopag subjects. Diabetes is a significant risk factor for cataract, and the imbalance of this confounding factor may suggest a larger effect of eltrombopag on cataract risk than observed from the results observed in the ENABLE studies.

Nevertheless, cataract has been included as an 'important identified risk' in the RMP, since it has been demonstrated in non-clinical studies and confirmed by clinical data, and the magnitude of difference in occurrence between the eltrombopag and placebo groups is of sufficient magnitude, with no other convincing explanation, to suggest a causal relationship. Section 4.4 of the SmPC has been amended to add the rates of cataract events in the eltrombopag and placebo groups and the recommendation to monitor for cataract. The risk is adequately detailed in the SmPC and patient information leaflet.

A PK modelling analysis of subjects in the ENABLE studies to examine the relationship between plasma eltrombopag concentration and change in QTc interval from baseline revealed a low risk of QTc prolongation at maximum and supratherapeutic doses of eltrombopag. However, neither non-clinical studies nor the clinical thorough QT-Study conducted to assess the potential effect on eltrombopag on QT demonstrated any effect of concern. During the DB phase clinically significant changes from baseline in ECG were seen in 1% (12) patients in eltrombopag vs <1% (2 cases) in placebo. Further, differences in the incidence of ECG related AEs during this D-B phase were also found, with again small differences between treatments (a total 3% in placebo vs 4% in eltrombopag). In addition, when considering only those cases of AE related to QT/repolarisation abnormalities, there were no cases in placebo vs 13 in eltrombopag treated patients.

While the specific studies to detect QT/QTc interval prolongation and proarrhythmic effect concluded “no effect”, the results obtained from ENABLEs studies appears to contradict that conclusion and section 4.8 of the SmpC includes “electrocardiogram QT prolonged “ as a common adverse reaction”. Given this discrepancies and the fact that this is a particularly susceptible population, the CHMP was of the opinion that this risk had to be included in the RMP as a safety concern and will be followed up by routine pharmacovigilance activities. The SmPC has been also been updated to better reflect this risk.

Patients with MELD score ≥10 and those with baseline albumin levels ≤ 35 g/L are at an increased risk of a SAE and fatal events. This is not unexpected and it is supported by the data provided, which indicates that patients with a more advance disease are at particular risk for AEs. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE (see Benedfit-risk balance and SmPC sections 4.4 and 4.8).

Other baseline factors, such as age, gender, BMI, and race, did not appear to have a significant effect on the safety findings.

Relevant risks to the HCV-associated thrombocytopenia, in particular thromboembolic events, hepatic decompensation and fatal adverse events, will be addressed in the already existing healthcare professional information pack containing educational materials to be provided prior to launch to all physicians who intend to prescribe eltrombopag.

The CHMP was of the opinion that it was necessary to further characterize known safety concerns (e.g. thromboembolisms, hepatic decompensation) including possible risks factors, and to generate efficacy/safety data on populations with important missing information (e.g. safety and efficacy of eltrombopag with new acting agents). The effects of eltrombopag on liver-related outcome (including mortality) should be studied. Until these data is available, the CHMP was of the opinion that the safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection. Section 4.4 of the SmPC includes an adequate warning informing of this fact.

The MAH agreed to further explore the safety and efficacy of using eltrombopag including combination with direct acting antiviral agents (triple therapy) in three post-authorisation safety studies (PASS). Two of the studies will be nested within existing multicentre, prospective observational cohort HCV Research UK and Hepatitis C Therapeutic Registry and Research Network (HCVTARGET), and the third one will be conducted by GSK.

Safety outcomes in all three post-authorization studies will include:

- Hepatic decompensation
- Myocardial infarction
- Ischemic Stroke
- Portal vein thrombosis
- Deep vein thrombosis
- Pulmonary embolism

• All cause mortality

• Cause-specific mortality from the death certificate

• Other long term outcomes, to be identified during protocol development

The studies will include the following effectiveness outcomes:

• Initiated interferon-based antiviral therapy

• Maintained interferon-based antiviral therapy

• Reached sustained virologic response or early virologic response

• Other long term outcomes, to be identified during protocol development

In addition, the CHMP was of the opinion that additional pharmacovigilance activities were necessary in order to characterise the off-label use of eltrombopag. To address this concern the MAH will perform a Drug Utilization Study (DUS) post-marketing.

Moreover, the CHMP agreed on the need to provide data on the effectiveness of the risk minimization measures, therefore the MAH was requested to conduct post-authorisation a study to measure the effectiveness of the educational material.

All requested studies have been included in the RMP and are listed in the approved pharmacovigilance plan as category 3 (required additional pharmacovigilance activity).

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

2.6.2. Conclusions on the clinical safety

The use of eltrombopag in thrombocytopenic HCV patients in the ENABLE studies was associated with a range of adverse events, but in particular an increase in fatal AEs, and an increased risk of thrombotic events and hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis). In subjects with poor prognostic factors (MELD score ≥10 or albumin <3.5 g/dL) the risks were particularly high.

In summary, treatment with eltrombopag offers patients with end-stage HCV, and an otherwise poor prognosis, an opportunity to undergo antiviral therapy, increasing their chances of achieving SVR by half. The risks are not insignificant, but several may be associated with concomitant antiviral therapy, and may be treatable. Patients with the poorest prognosis face the highest risk, but this group of patients represents those most at need of successful antiviral therapy.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The MAH submitted Risk Management Plan.

- **Safety concerns**

The MAH identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	ITP Hepatotoxicity Thromboembolic Events Post therapy Reoccurrence of Thrombocytopenia Cataract HCV-Associated Thrombocytopenia Hepatotoxicity Hepatic Decompensation Thromboembolic Events Portal Vein Thrombosis Cataract Retinal Haemorrhage Post therapy Reoccurrence of Thrombocytopenia
Important potential risks	ITP Potential for Increased Bone Marrow Reticulin Formation Haematological Malignancies Renal Tubular Toxicity Phototoxicity Potential for Haematological changes Potential for Endosteal Hyperostosis HCV-Associated Thrombocytopenia Potential for Increased Bone Marrow Reticulin Formation Haematological Malignancies QT/QTc interval prolongation Renal Tubular Toxicity Phototoxicity Potential for Haematological changes Potential for Endosteal Hyperostosis
Missing information	ITP and HCV-Associated Thrombocytopenia Paediatrics Pregnant or lactating females Asian population

	Black Race population Very elderly patients Patients with hepatic impairment Patients with renal impairment Off-label use HCV-Associated Thrombocytopenia Elderly patients HCV patients with FibroSURE score of F0, F1, F2 HCV patients infected with genotype other than 1, 2 or 3 HCV patients with Child Pugh score B (7-9) Safety and efficacy of eltrombopag in combination with new direct acting agents (telaprivir/boceprevir)

The CHMP agreed.

- **Pharmacovigilance plans**

The Applicant proposed the following pharmacovigilance activities in the proposed indication.

GSK PASS Study - Post Authorization Safety Study of HCV patients treated with Eltrombopag: Multicenter, Prospective Observational Cohort Study of Thrombocytopenic HCV Patients Receiving Eltrombopag	6 months interim analysis 12 months interim analysis 18 month interim analysis Final report	2016 2017 2018 2019
HCV-TARGET: Proposed Post Authorization Safety Study of HCV patients treated with Eltrombopag: Hepatitis C Therapeutic Registry and Research Network	First interim Final Report	2016 2019
HCV Research UK: Proposed Post Authorization Safety Study of HCV patients treated with Eltrombopag	First interim Final Report	2016 2019
Proposed Drug utilization study	Final report	2016
Effectiveness of Eltrombopag Educational Materials for Hepatitis C associated thrombocytopenia	Interim report Final report	2014 2016
TPL116010 Drug Drug Interaction Study: Eltrombopag Boceprevir and Eltrombopag Telaprevir	Final report	2013

The CHMP, having considered the data submitted, was of the opinion that the proposed post-authorisation Pharmacovigilance plan is sufficient to identify and characterise the risks of the product in the proposed indication.

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatotoxicity	ITP - Current text in SmPC Statement in Section 4.4. Warning and Precaution of the SmPC advising to monitor and manage patient with hepatotoxicity. Specify liver testing before initiation, every 2 weeks during the first 3 months, thereafter every 4-6 weeks Liver stopping criteria: Specific instructions for discontinuation of eltrombopag to avoid further elevations of hepatobiliary laboratory values Increased ALT, AST and indirect bilirubin have been added in Section 4.8 (Undesirable effects). HCV-Associated Thrombocytopenia - Proposed text in SmPC In the SmPC, a warning regarding the potential for Hepatobiliary laboratory abnormalities (ALT, AST, bilirubin, and alkaline phosphatase) will be proposed for addition to Section 4.4 (Special warnings and precautions for use). Also, preferred terms related to hepatotoxicity will be proposed for addition to Section 4.8 (Undesirable effects).	Educational materials
Hepatic Decompensation	HCV-Associated Thrombocytopenia - Proposed text in SmPC In the SmPC, a warning regarding the potential for hepatic decompensation will be proposed for addition to Section 4.4 (Special warnings and precautions for use). Also, preferred terms related to hepatic decompensation will be proposed for addition	Educational materials

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	to Section 4.8 (Undesirable effects). Also, preferred terms related to hepatic decompensation will be proposed for addition to Section 4.8 (Undesirable effects)	
Thromboembolic Events Portal Vein Thrombosis	- Current text in SmPC Section 4.2 (Posology and method of administration), section 4.4 (Special warnings and precautions for use), and section 5.2 (Pharmacokinetic properties) of the SmPC state that eltrombopag should not be used in patients with moderate to severe hepatic impairment unless the expected benefit outweighs the identified risk of portal venous thrombosis. Section 4.2 of the SmPC further states that if the use of eltrombopag is deemed necessary [in patients with moderate to severe hepatic impairment] the starting dose must be 25mg once daily. A statement in Section 4.4 (Special warnings and precautions) regarding the potential for thromboembolic events is included including caution for patient with known risk factors for TEE. The PIL also reflects this information Thromboembolic events are included in Section 4.8 (Undesirable effects). Information regarding patients with chronic liver disease and the risk of thromboembolic events is included in Sections 4.4 and 4.8 of the SmPC.Thromboembolic events HCV-Associated Thrombocytopenia - Proposed text in SmPC In the SmPC, a warning regarding the potential for thromboembolic events including portal vein thrombosis will be proposed for addition to Section 4.4 (Special warnings and precautions for use). Also, thromboembolic events will be proposed for addition to Section 4.8 (Undesirable effects).	Educational materials
Post therapy Reoccurrence of Thrombocytopenia	Current text in SmPC A statement in Section 4.4 (Special Warnings and precautions) regarding the potential for decrease in platelet counts post	Educational materials

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	discontinuation of therapy. The PIL also reflects this information. A warning has been added to Section 4.4 (Special warnings and precautions) of the SmPC stating that in HCV clinical trials, gastrointestinal bleeding was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding. The PIL also reflects this information. Thrombocytopenia following discontinuation of treatment is included in Section 4.8 (Undesirable effects).	
Cataracts	Current text in SmPC A statement in Section 4.4 (Special Warnings and precautions) regarding the routine monitoring for cataracts is included. The PIL also reflects this information.	None
Retinal haemorrhage	Proposed text in SmPC A warning in Section 4.4. (Special warnings and precautions) is proposed that states retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2 % of the eltrombopag group and 2 % of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended. The PIL also reflects this information.	None
Potential for increased bone marrow reticulin formation	Current text in SmPC A statement in Section 4.4 (Special Warnings and precautions) of the SmPC informing prescribers to monitor for immature or dysplastic cells and the potential for increase in bone marrow reticulin fibres is included, the PIL also reflects this information.	Educational materials
Haematological malignancies	Current text in SmPC Section 4.4 of the SmPC (Special Warnings and precautions) states that the diagnosis of ITP in adults and elderly patients	Educational materials

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	should have been confirmed by the exclusion of other clinical entities with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs. An update to Section 4.4 (Special warning and precautions) of the SmPC informing prescriber of a concern that thrombopoietin receptor (TPO-R) agonists may stimulate the progression of existing haematopoietic malignancies such as MDS	
QT/QTc interval prolongation	Current text in SmPC A statement in Section 4.4 (Special warning and precautions) of the SmPC stating a QTc study indicates that eltrombopag will not have a clinically significant effect on cardiac repolarisation at therapeutic or supra-therapeutic doses. QTc interval prolongation has been reported in clinical trials of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.	None
Renal tubular toxicity	Current text in SmPC A statement in Section 5.3 (Pre-clinical safety data) that the clinical relevance of the renal tubular toxicity finding in rodents is unknown.	None
Phototoxicity	Current text in SmPC A statement in Section 5.3 (Pre-clinical safety data) that there is a potential risk of photoallergy and that the clinical relevance of the in-vitro finding is unknown.	None
Potential for haematological changes	Current text in SmPC A warning is in Section 4.4. (Special warnings and precautions) of the SmPC informing prescribers to monitor for immature or dysplastic cells. A statement in Section 5.3 (Pre-clinical safety data) of the haematological changes findings in rats and dogs and that the clinical relevance of the finding is unknown.	None
Potential for Endosteal hyperostosis	Current text in SmPC A statement in Section 5.3 (Pre-clinical safety	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	data) of the endosteal hyperostosis findings in rodents and that the clinical relevance of the finding is unknown.	
Paediatric population	Current text in SmPC Section 4.2 (Posology and method of administration) of the SmPC, states that the safety and efficacy of eltrombopag in paediatric patients (< 18 years of age) has not been established.	None
Pregnant or lactating female	Current text in SmPC The SmPC (Section 4.6) and package leaflet states that the risk to pregnant or lactating women is unknown.	None
Asian Populations	Current text in SmPC A statement the SmPC (Section 4.2 Posology) states the following: *East Asian patients* Initiation of eltrombopag at a reduced dose of 25 mg once daily may be considered for ITP patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Thai or Korean) (see section 5.2). Initiate eltrombopag at a dose of 25 mg once daily in HCV patients of East Asian ancestry. Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed. For ITP or HCV patients of East Asian ancestry with hepatic impairment initiate eltrombopag at a dose of 25 mg once daily.	None
Black race Populations	None	None
Elderly and very elderly	Current text in SmPC The SmPC (Section 4.2 Posology) states that there are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. There are limited data on the use of eltrombopag in HCV patients aged over 75 years. Caution should be exercised in these patients.	
Patients with hepatic impairment	The SmPC (Section 4.2 Posology) states the following: *Hepatic impairment* Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment wait 3 weeks before increasing the dose. No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Thrombocytopenic patients with chronic HCV should initiate eltrombopag at a dose of 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment wait 2 weeks before increasing the dose. There is an increased risk for adverse events, including thromboembolic events, in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedures or in HCV patients undergoing antiviral therapy.	None
Patients with renal impairment	The SmPC (Section 4.2 Posology) states the following: *Renal impairment:* No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	creatinine and/or performing urine analysis.	
HCV patients with a FibroSURE score of F0/F1/F2	The SmPC (Section 5.1 Pharmacodynamic properties) states the following: The majority of patients were HCV genotype 1 (64 %), had mild hepatic impairment (Child-Pugh Score 5-6), and had a FibroSURE score equivalent to Metavir F3 or F4, indicative of bridging fibrosis and cirrhosis.	None
HCV patients infected with genotype other than 1, 2 or 3	The SmPC (Section 5.1 Pharmacodynamic properties) states the following: The majority of patients were HCV genotype 1 (64 %), had mild hepatic impairment (Child-Pugh Score 5-6), and had a FibroSURE score equivalent to Metavir F3 or F4, indicative of bridging fibrosis and cirrhosis.	None
HCV patients with Child Pugh score B (7-9)	The SmPC (Section 4.4) states the following: Eltrombopag should not be used in patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, exercise caution when administering eltrombopag to patients with hepatic impairment.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Off label use	The SmPC (Section 4.1) states the following: Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated. Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia prevents the initiation or limits the ability to maintain optimal interferon-based therapy (see section 5.1). *Paediatric population* Revolade is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.	None
Safety and efficacy of eltrombopag in combination with new direct acting agents (telaprevir/boceprevir)	Current text in SmPC A statement in Section 4.4 that Safety and efficacy have not been established for eltrombopag in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.	None

The CHMP, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

The applicant requested to have a combined package leaflet for the 25 mg, 50 mg and 75 mg strengths. This was considered acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The clinical program for eltrombopag was designed to investigate the proportion of thrombocytopenic patients with HCV who could reach a platelet count sufficient to enable initiation of interferon therapy, and then to randomise patients to receive either ongoing treatment with eltrombopag or placebo and to measure the proportion achieving SVR. This endpoint was relevant because the success of interferon/ribavirin therapy may be compromised by thrombocytopenia, in terms of treatment interruptions or dose reductions.

In the ENABLE studies approximately 95% of thrombocytopenic patients achieved the threshold platelet count and were able to start antiviral therapy, mostly within 4 weeks. In the subsequent placebo-controlled phase, the proportion of those treated with eltrombopag achieving SVR was 23% in ENABLE 1 and 19% in ENABLE 2, representing a difference to placebo of 8% and 6%, respectively. This represents a relative increase in response of around 50% in a group of patients who may otherwise be ineligible for antiviral therapy, or who, if treated, may respond poorly.

The other secondary endpoints were supportive of the efficacy of eltrombopag. In the double-blind treatment phase the rate of antiviral dose reductions in those on eltrombopag was 40% that of placebo-treated subjects. Correspondingly, the average time to requirement for a dose reduction was slightly prolonged in those on eltrombopag, and fewer patients required premature discontinuation of antiviral therapy. Adherence to antiviral therapy was higher in eltrombopag-treated subjects, and was shown to be related to a higher probability of achieving SVR.

During antiviral therapy, those on eltrombopag maintained consistently higher platelet counts than those on placebo, and remained at levels above 50 Gi/L for considerably longer periods.

Uncertainty in the knowledge about the beneficial effects.

The relevance of the study results was questioned given that current clinical practice involves the new treatment options available, including DAA+pegIFN +Ribavirin. The CHMP agreed that the results remain relevant as long as interferon is the backbone of HCV antiviral therapy and preliminary PK results from a drug-drug interaction study to investigate the potential for interaction between eltrombopag and the protease inhibitors boceprevir and telaprevir have been presented to support its use in association with HCV triple therapy including direct acting antiviral agents. Preliminary results show no significant effect of telaprevir or boceprevir on eltrombopag. Further data will be submitted to further address this issue (see benefit-risk balance).

Risks

Unfavourable effects

The use of eltrombopag in thrombocytopenic HCV patients in the ENABLE studies was associated with a range of adverse events, but in particular an increase in fatal AEs, and an increased risk of thrombotic events and hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis). In subjects with poor prognostic factors (MELD score ≥10 or albumin <3.5 g/dL) the risks were particularly high.

Uncertainty in the knowledge about the unfavourable effects

Nowadays the standard of care for HVC patients is triple therapy with new direct antivirals. There is no comprehensive data on the safety profile of eltrombopag added to a triple combination regimen of antivirals. To date only preliminary PK results from a drug-drug interaction study to investigate the potential for interaction between eltrombopag and the protease inhibitors boceprevir and telaprevir have been presented to support its use in association with HCV triple therapy including direct acting antiviral agents. Full results are not yet available and are awaited but preliminary results show no significant effect of telaprevir or boceprevir on eltrombopag. Further data will be submitted to further address this issue (see benefit-risk balance)

Benefit-risk balance

Importance of favourable and unfavourable effects

Treatment with eltrombopag offers patients with end-stage HCV, and an otherwise poor prognosis, an opportunity to undergo antiviral therapy, increasing their chances of achieving SVR by half. SVR not only represents cure from viral infection, but also provides the prospect of changing the natural history of the disease.

The use of eltrombopag in thrombocytopenic HCV patients in the ENABLE studies was associated with a range of adverse events, including an increased risk of thrombotic events and hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis).

Benefit-risk balance

In view of the benefits in terms of SVR that is likely to represent cure from infection, the toxicity was considered acceptable and the benefit-risk balance was considered positive in the following revised indication:

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.

The benefit in terms of SVR was slightly lower in patients with MELD score ≥10 and those with baseline albumin levels ≤ 35 g/L who are at an increased risk of a SAE and fatal events. This is not unexpected and it is supported by the data provided, which indicates that patients with a more advance disease are at particular risk for AEs. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE (see Benefit-risk balance and SmPC sections 4.4 and 4.8).

Although the safety and efficacy of eltrombopag have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection, based on the available pharmacokinetic drug-drug interaction data, a restriction of the indication to exclude use in combination with direct acting antiviral agents does not seem appropriate as important differences in terms of safety and efficacy are unlikely. The need for additional efficacy and safety data is reflected in the SmPC and will be addressed in a post-authorisation safety study.

Discussion on the benefit-risk balance

In the ENABLE studies approximately 95% of thrombocytopenic patients achieved the threshold platelet count and were able to start antiviral therapy, mostly within 4 weeks. In the subsequent placebo-controlled phase, the proportion of those treated with eltrombopag achieving SVR was 23% in ENABLE 1 and 19% in ENABLE 2, representing a difference to placebo of 8 and 6 percentage points, respectively. This represents a relative increase in response of around 50% in a group of patients who may otherwise be ineligible for antiviral therapy, or who, if treated, may respond poorly.

The risks are not insignificant, in particular an increased risk of thrombotic events and hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) and an increased risk of fatal AEs. In subjects with poor prognostic factors (MELD score ≥10 or albumin <3.5 g/dL) the risks were particularly high, however this group of patients represents those most at need of successful antiviral therapy.

Although several AEs may be associated with concomitant antiviral therapy, and may be treatable, the CHMP considered necessary to revise the wording of the indication initially proposed by the MAH to reflect that only patients who otherwise could not initiate or maintain an IFN-based HCV regimen should be candidates to this treatment.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers the following group of variations consisting of an Extension, a type II and a type IA variation acceptable and therefore recommends, by consensus, the variations to the terms of the marketing authorisation, concerning the following changes:

Extension of the Marketing Authorisation concerning:

a new strength: 75 mg film-coated tablet

and

Variation(s) accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
B.I.b.1.b	Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	IA

Extension of indication for Revolade in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy. Consequently, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. Moreover, the key elements to be included in the educational material in Annex II and the package leaflet have been updated accordingly. In addition, the product information has been revised in line with QRD template version 9.0 and the list of local representatives in the package leaflet has been amended.

Variation for Revolade to lower the threshold for drug related impurities.

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product

in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

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

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

Key elements to be included in the educational material

Hepatotoxicity

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

Thromboembolic events
ITP patients

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

HCV patients

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

Posology

- Educate patients on the appropriate administration of Revolade (e.g. titration of Revolade, food-drug interaction, dose recommendations for special populations [e.g. East Asians]).
- Awareness to prescribers of the labelled indication and warnings associated with non-indicated populations (e.g. not recommended for use in children, pregnant or breast-feeding women, other off label uses).

Food Interactions

- Educate patients about the potential food-drug interaction (i.e. chelation with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours apart from Revolade dosing to avoid significant reduction in Revolade absorption due to chelation.
- Assist patient in developing a plan to administer Revolade at a time each day that fits into the patient's own daily schedule.

Reoccurrence of Thrombocytopenia

- Educate patients about the potential risk of bleeding after treatment has stopped (include incidence in clinical trials and likelihood of reoccurrence of thrombocytopenia after cessation of treatment).

- Following discontinuation of Revolade, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding.
- Monitor platelet count weekly for 4 weeks following discontinuation of Revolade.

Increased Bone Marrow Reticulin Fibres

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

Haematological malignancies

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

Potential for Off-label Use

- The risk-benefit for the treatment of thrombocytopenia outside of the registered indication has not been established.
- The risk-benefit of Revolade in paediatric ITP and paediatric HCV-associated thrombocytopenia has not been established. The paediatric population is defined as those persons aged between 0 and 18 years.

Hepatic Decompensation (use with interferon)

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

Fatal Adverse Events in thrombocytopenic patients with HCV

- In thrombocytopenic patients with chronic HCV, patients who receive anti viral therapy in combination with eltrombopag may be at greater risk of fatal adverse events, particularly those with the poorest prognosis, i.e.:

    - MELD score ≥10,
    - Albumin ≤ 35 g/L
- Educate patients with the poorest prognosis about the increased risk of fatal adverse events, particularly hepatic decompensation (hepatic failure, ascites, encephalopathy and bleeding varices), infective and ischemic complications.
- Treatment with eltrombopag should be stopped if signs and symptoms suggestive of thrombotic events and hepatic decompensation occur (see TEE and hepatic decompensation above).

Additional Data/Market exclusivity

Furthermore, the CHMP reviewed the data submitted by the applicant, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, by consensus that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.