NOVARTIS

Chief Medical Office & Patient Safety

Eltrombopag

ETB115

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Eltrombopag
Product(s) concerned (brand name(s)):	REVOLADE®
Document status:	Final
Version number:	54.1
Data lock point for this RMP	PSUR reporting period (01-Oct-2018 to 30-Sep-2021)
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Template version 6.3, Effective from 24-Feb-2021

Rationale for submitting an updated RMP: The current version (v54.1) of the RMP is updated based on recommendations made by PRAC Rapporteur Assessment Report (procedure number EMEA/H/C/001110/II/0068).

The PRAC has recommended to update cumulative clinical trial exposure data and to include a new table in which the cumulative clinical trial exposure data are broken down per indication. The exposure data is aligned as per the latest PSUR (reporting period 01-Oct-2018 to 30-Sep- 2021)

The module SVII.2 "new safety concerns and reclassification with a submission of an updated RMP" has been updated to indicate there are no new safety concerns and reclassification with this RMP submission.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 54.0
Part I	No change
Part II	SI: No change SII: No change SIII: Clinical trial exposure section and tables was updated with latest PSUR SIV: No change SV: No change SVI: No change SVII: The section was updated with "there are no new safety concerns and reclassification with this RMP submission". SVIII: No change
Part III	No change
Part IV	No change
Part V	No change
Part VI	No change
Part VII	Annex 1: No change Annex 2: No change Annex 3: No change Annex 4: No change Annex 5: No change Annex 6: No change Annex 7: No change Annex 8: Updated to reflect the changes made to the current RMP

Other RMP versions under evaluation:

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 53.1

Approved with procedure: EMEA/H/C/001110/II/0063

Date of approval (opinion date): 14-Jan-2021

QPPV name: Dr David Lewis

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization. The electronic signature is available on file.

Table of contents

List of tables

List of abbreviations

AA	Aplastic anemia
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ASH	American Society of Hematology
AST	Aspartate aminotransferase (SGOT)
ATG	Anti-thymocyte globulin
AUC	Area under the curve
Bili	Bilirubin
CI	Confidence Interval
cITP	chronic Idiopathic Thrombocytopenic Purpura
CsA	Cyclosporine A
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DAIDS	Division of AIDS
DB	Double blind
DDD	Defined Daily Dose
DIBD	Development International Birth Date
DILI	Drug Induced liver injury
DVT	Deep vein thrombosis
EEA	European Economic Area
EMA	European Medicines Agency
ENABLE 1	(Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C Related Liver DiseasE) Antiviral = peginterferon alfa-2a plus ribavirin
ENABLE 2	(Eltrombopag to INitiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C Related Liver DiseasE) Antiviral = peginterferon alfa-2b plus ribavirin
EU	European Union
EXTEND	TRA105325: EXTEND (Eltrombopag eXTENded Dosing Study)
FDA	Food and Drug Administration
Gi/L	10^9 (giga) units per liter
GPRD	General Practice Research Database
GSK	GlaxoSmithKline
HBLA	Hepatobiliary Laboratory Abnormalities
HCC	Hepatocellular carcinoma
HCV	Chronic Hepatitis C virus
HSCT	Hematopoietic stem cell transplantation
IDMC	Independent data monitoring committee
IFN	Interferon
IRR	Incidence Rate Ratio

IST	Immunosuppressive therapy
ITP	Primary immune thrombocytopenia
IVIg	Intravenous immunoglobulin
IWG	International Working Group
LENS	TRA108132: LENS – Long-term Eltrombopag ObservatioNal Study
LFT	Liver function tests
MAH	Marketing Authorization Holder
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MF	Myelofibrosis
NCPRR	Nordic Country Patient Registry for romiplostim
NIH	National Institute of Health
OL	Open-label
OXMIS	Oxford Medical Information System
PETIT	Eltrombopag PETIT: Eltrombopag in PEdiatric patients with Thrombocytopenia from ITP
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal haemoglobinuria
PRAC	Pharmacovigilance Risk Assessment committee
PSUR	Periodic Safety Update Report
PY	Patient Years
QD	Every day
QTc	Corrected QT interval
RAISE	TRA102537: RAISE - RAndomised placebo-controlled ITP Study with Eltrombopag
REPEAT	TRA108057: REPEAT - Repeated Exposure To Eltrombopag in Adults with Idiopathic Thrombocytopenic Purpura
RMP	Risk Management Plan
SAA	Severe aplastic anaemia
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SD	Standard deviation
SDAP	Summary Document Analysis Plan
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA query
TEE	Thromboembolic events
TPO	Thrombopoietin
TPO-R	Thrombopoietin receptor
TPO-RA	Thrombopoietin receptor agonists
ULN	Upper limit of normal

WBC	White blood cell
WHO	World Health Organization

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Eltrombopag
Pharmacotherapeutic group(s) (ATC Code)	Antihemorrhagics, other systemic hemostatics (B02BX05)
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	REVOLADE®
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class**: Eltrombopag olamine, the bis-monoethanolamine salt form of eltrombopag, is an orally bioavailable, small molecule thrombopoietin receptor (TPO-R) agonist.
	Summary of mode of action: Eltrombopag functions in a similar manner to endogenous thrombopoietin (TPO), inducing proliferation and differentiation of bone marrow progenitor cells.
	Important information about its composition: Daily oral administration of eltrombopag to healthy and thrombocytopenic humans results in a dose-dependent increase in platelet counts within 1-2 weeks for patients with immune thrombocytopenia (ITP) and chronic hepatitis C virus associated thrombocytopenia. For patients with refractory severe aplastic anaemia (SAA), hematologic responses were seen at 16 weeks.
Hyperlink to the Product Information	[Current approved SmPC] [Proposed SmPC]
Indication(s) in the EEA	**Current:** **Immune (primary) thrombocytopenia** Revolade is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade is indicated for the treatment of paediatric patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting

	6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).) **Chronic hepatitis C virus(HCV) -associated thrombocytopenia**: 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. **Severe aplastic anaemia**: Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation.
	Proposed (if applicable): None
Dosage in the EEA	**Current:** Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts. The powder for oral suspension may lead to higher eltrombopag exposure than the tablet formulation. When switching between the tablet and powder for oral suspension formulations, platelet counts should be monitored weekly for 2 weeks. **Immune (primary) thrombocytopenia:** Adults and paediatric population aged 6 to 17 years: The recommended starting dose of eltrombopag is 50 mg once daily For patients of East-/Southeast-Asian ancestry eltrombopag should be initiated at a reduced dose of 25 mg once daily Paediatric population aged 1 to 5 years: The recommended starting dose of eltrombopag is 25 mg once daily. **Chronic hepatitis C virus (HCV) -associated thrombocytopenia:** The recommended starting dose of eltrombopag is 25 mg once daily. No dosage adjustment is necessary for HCV patients of East/ Southeast--Asian ancestry or patients with mild hepatic impairment.

	Severe aplastic anaemia: Eltrombopag should be initiated at a dose of 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily. The treatment should not be initiated when the patient has existing cytogenetic abnormalities of chromosome 7.
	Proposed (if applicable): None
Pharmaceutical form(s) and strengths	**Current:** Film-coated tablets: 12.5 mg, 25 mg, 50 mg, 75 mg Powder for oral suspension: 25 mg
	Proposed: None
Is the product subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Immune (primary) thrombocytopenia

2.1.1 Epidemiology of the disease

Incidence

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to a chronically low peripheral blood platelet count of <150000/μL. The exact etiology of ITP is unknown

(BCSH 2003). Anti-platelet antibodies are thought to play a role in destruction of platelets, and may impede the production of platelets in the bone marrow.

In 2009, the International Working Group (IWG) released updated guidelines (Rodeghiero et al 2009), in which ITP was divided into newly diagnosed ITP (lasting up to 3 months from diagnosis), persistent ITP (lasting between 3 and 12 months from diagnosis) and chronic ITP (lasting more than 12 months from diagnosis). This classification was recently reaffirmed by the American Society of Hematology (ASH) (Neunert et al 2019) and a panel of international experts (Provan et al 2019).

Prospective European study of adult patients diagnosed with ITP (Neylon et al 2003), observed between 1993 and 1999 in an English community showed an annual incidence of 1.6 per 100,000 person-years. Incidence was similar for both genders, with greatest age-specific incidence in those patients aged >60 years. There was no gender difference observed except a female predominance in the subgroup aged 45 to 59 years. Another retrospective population-based study of Scandinavian adults (Frederiksen and Schmidt 1999), over two decades, found an adult ITP incidence rate of 2.68 per 100000 person-years. A slightly higher incidence among women (female: male ratio 1.7) and a doubling of the incidence with age were also identified in the study.

Data from the three European countries of UK, Germany and The Netherlands (Satia et al 2006) showed the average annual incidence rate (per 100,000 person-years) of 3.0, 2.7, and 1.9, respectively. Incidence rates were higher for women than men in the UK and The Netherlands but not in Germany. Rates did not increase during the period 1990 through 2003. Data from a nationwide population-based study in France showed a similar incidence rate of 2.9 per 100,000 PY (Moulis et al 2014).Based on 257 paediatric ITP patients diagnosed between 1990-2005 and recorded in the General Practice Research Database (GPRD), the overall incidence for childhood is ITP 4.2 cases per 100000 person-years (PY) (95% confidence interval (CI): 3.7–4.8). A prospective cohort study was conducted to describe the epidemiology of ITP from all paediatric clinics in five Nordic countries between 1998-2000 and incidence was calculated from cases registered in 1998–1999 (Zeller et al 2000, Zeller et al 2005). An ITP diagnosis was registered among 506 children for an estimated incidence in the Nordic population of 4.8 cases per 100,000 PY. More recent data estimates the incidence of childhood ITP between 1.9 and 6.4 per 100,000 PY with equal distribution between the sexes. (EMA guidelines 2014)

In summary, the incidence rate for adults ranges from 1.6 per 100,000 PY to 3.0 per 100,000 PY. In the pediatric population, incidence of ITP ranges between 1.9 and 6.4 per 100,000 PY.

Prevalence

Data from several publications indicate that the prevalence of primary ITP in adults is estimated as 9.5 per 100,000 PY. There is a predilection for female patients in younger adults, but the prevalence of ITP in men and women is fairly even in the elderly (>65 years). There is no evidence that ITP prevalence varies substantially across countries. (Fogarty 2009), (Schoonen et al 2009), (Moulis et al 2014)

The Nordic Country Patient Registry for romiplostim (NCPRR), established in 2009, keeps record of all adult patients in Denmark, Sweden and Norway with chronic ITP, including data from national health registries and medical records. Based on data from the NCPRR, as of

01-Apr-2009, the prevalence of registered adult patients with chronic ITP was 10.0 per 100,000 PY in Denmark (95% CI: 9.1–11.0) and 10.7 per 100,000 PY in Sweden (95% CI: 9.9–11.4) (Christiansen et al 2019).Paediatric ITP typically resolves spontaneously within several weeks or months following diagnosis (Neunert et al 2013). However, in 20 to 30% of pediatric patients, ITP remains a chronic disease (lasting more than 6 or 12 months, depending on the definition used in published studies) (Ahmed et al 2004; Akbayram et al 2011; Deel et al 2013; Glanz et al 2008; Imbach et al 2006; Kubota et al 2010; Kuhne et al 2003; Lowe and Buchanan 2002; Neunert et al 2013; Watts 2004; Zeller et al 2005). Further, ITP may recur after initial remission in 4-6% of patients (Jayabose et al 2006; Khalifa et al 1993; Vranou et al 2008).

Several studies investigated the ITP prevalence among pediatric populations. A recent study identified ITP patients using administrative codes from diagnoses made in Oklahoma hematologists' offices for a 2-year period, 2003-2004; the average annual prevalence was 8.1 per 100,000 children (Terrell et al 2012). Utilizing administrative data from the Maryland Health Care Commission, another study reported the prevalence of ITP per 100,000 children by age group, as follows:

a. ages 1-5 (9.3);
b. 6-11 (7.3);
c. 11-14 (4.1);
d. 15-18 (5.6); (Segal and Powe 2006)

In an earlier study conducted in Sweden focused exclusively on chronic ITP, as defined by platelet count <150 x 10^9/L for more than 6 months post-diagnosis, the prevalence of chronic ITP was estimated at 4.6 per 100,000 children (0-15 years old) (Hedman et al 1997).

In the paediatric population, the one-year prevalence of ITP ranges from 9.3 per 100,000 children for ages 1-5 years, to 5.6 per 100,000 children for ages 15-18 years, with a prevalence of 8.1 per 100,000 overall. Chronic ITP prevalence is 4.6 per 100,000 children.

Demographics of the population in the ITP population – age, gender, racial and/or ethnic origin

Immune thrombocytopenia is usually chronic in adults, the onset is often insidious, and approximately twice as many women as men are affected (Cines and Blanchette 2002). The male: female ratio in the adult group is 1:1.2–1.7 and the median age of adults at the diagnosis is 56 (Cines and McMillan 2005).

Overall, the incidence and prevalence of ITP is somewhat higher in adults compared to children (Terrell et al 2010; Terrell et al 2012). Additionally, important differences have been documented comparing the characteristics of paediatric and adult patients with ITP. While a male predominance has been observed in early childhood ITP, higher ITP incidence rates are generally reported for female adults (Schulze and Gaedicke 2011, Yong et al 2010).

The increased ITP incidence and prevalence observed among younger children is further supported by cross-sectional observational studies of paediatric ITP patients. One study of 2314 children with newly diagnosed ITP in children's hospitals across the US during 2008 to 2010 observed a median age of 6.5 years (Kime et al 2013). Among those children, 36% of cases were between the ages 1-3 years, 42% were 4-12 years old, and adolescents (1318 years)

comprised 22% of the patient population (Kime et al 2013). A similar age distribution was found in 2540 pediatric patients included in an international ITP registry; 69% of newly diagnosed patients were between 1-9 years old at the time of diagnosis (Kuhne et al 2003).

Risk factors for the disease

The incidence of fatal hemorrhage is reported between 5%-6.4% (George et al 1996, Fogarty and Segal 2007). In a pooled analysis of 17 clinical series including over 1800 adult patients with severe chronic ITP (Cohen et al 2000), the annual incidence of fatal hemorrhage was 1.6-3.9 cases per 100 patient-years, with an increasing rate of hemorrhage proportional to age, 0.4% and 13% per year in patients under 40 and over 60 years of age, respectively.

The main existing treatment options

The current standard-of-care, first-line therapy for ITP patients who need treatment consists of corticosteroids, unless there is a contraindication or need for more rapid platelet increase (Neunert et al 2019, Provan et al 2019). If a faster response is required, especially in case of severe bleeding, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin may be used (Kochhar et al 2021, Witkowski et al 2019). Other treatments that have been used include azathioprine, cyclosporine, cyclophosphamide, danazol, dapsone, rituximab, and romiplostim. Approximately 70-80% of patients initially respond to corticosteroids, but relapses are frequent and long-term remission rates are low (Cuker 2015). Moreover, the majority of patients treated with corticosteroids suffer from significant corticosteroid-related adverse events (AEs) such as mood swings, difficulty sleeping, weight gain, hypertension, and diabetes. Consequently, many patients need to stop corticosteroid treatment or to reduce the dose, which leads to suboptimal outcomes (Brown et al 2012).For children who are unresponsive to initial ITP treatment and/or who have persistent or chronic ITP, several small single-arm clinical studies have demonstrated the efficacy of rituximab in raising platelet counts, although it is not licensed for use in paediatric patients with ITP (Bennett et al 2006; Mueller et al 2009; Parodi et al 2008; Rao et al 2008; Taube et al 2005; Wang et al 2005). Alternatively, high-dose dexamethasone is recommended for treatment of children who have persistent or chronic ITP, also based on limited number of small single-arm studies. While splenectomy is considered a treatment option for some adults with ITP, it is generally avoided when treating children due to the lifelong risk of post-splenectomy infection (Schulze and Gaedicke 2011).

Recently, a panel of international experts and the American Society of Hematology (ASH) updated the guidelines on the diagnosis and management of ITP in adults and children (Neunert et al 2019, Provan et al 2019). Both guidelines recommend the use of thrombopoietin receptor agonists (TPO-RAs) for persistent ITP, i.e., within 3 to 12 months from ITP diagnosis. Moreover, in light of the serious side effects of prolonged steroid therapy, the guidelines do not recommend a prolonged course of corticosteroids, together with rapid tapering of steroids if there is no response within 2 weeks (Provan et al 2019). This international recommendation is consistent with the ASH guidelines, which do not recommend more than 6 weeks of steroid therapy, including tapering (Neunert et al 2019).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Literature on the epidemiology of ITP is currently sparse and the disease remains poorly described. Morbidity and mortality in adult patients with ITP have seldom been studied systematically. Mortality and morbidity of patients with the disease are highlighted in this module.

Mortality and morbidity (natural history)

It is estimated that mortality associated with ITP is about 4% but can be as high as 8%-16% in patients with refractory ITP (McMillan 1997, Cines and McMillan 2005a).

There are several potential or identified health risks associated with this disease. Epidemiological evidence suggests that patients with chronic ITP have a modest increase in risk of developing cataracts compared to people in the population without ITP and they are also at increased risk of developing acute or chronic renal failure (Enger et al 2008, Bennett et al 2008c). Both GlaxoSmithKline (GSK) epidemiology studies and published data in the literature provide evidence that patients with ITP are at increased risk of developing thromboembolic events, acute or chronic renal failure, and blood cancers including lymphoma and leukemia. Published data show the rate of thromboembolic events in ITP patients between 5% and 6.9% (Aledort et al 2004, Bennett et al 2008b). Acute or chronic renal failure occurs in about 6.1% of ITP patients and lymphoma and leukaemia occurs in 0.5% and 0.6% of patients, respectively (Bennett et al 2008a). Epidemiology of potential or identified risks is described in this module.

Epidemiology of liver function tests abnormalities in chronic patients with ITP was investigated in a retrospective database analysis using eligibility and medical claims data from a large U.S. health plan affiliated with i3 Drug Safety LLC (GlaxoSmithKline WEUKBRE3015 study 2008). Chronic adult ITP patients were defined between 01-Jan-2000 and 30-Sep-2006 with follow-up through 30-Sep-2007. Incidence and prevalence of hepatobiliary laboratory abnormalities (HBLA) are described in this module.

UK Adult ITP Registry results

The thromboembolic event (TEE) sub-study was conducted under the auspices of the UK Adult ITP Registry, an active, linked-anonymized repository of hospital-based data (e.g., patient demographics, bleeding events, ITP-specific treatments, laboratory results, and co-morbid conditions) on adults (i.e., >16 years) with primary ITP.

In total, 327 adults (The Royal London Hospital, UK =223; collaborating centers =104) with primary ITP were retrospectively followed for a median time of 5.6 years (inter-quartile range: 2.4-9.2 years). The mean age of patients was 42.9 ± 19.2 years, and a female-to-male ratio of 1.7:1.0 was observed. Of patients for whom data were available, 41.9% had been referred to their center by a hematologist, and 81.5% were Caucasian (self-reported). The median baseline platelet count was 31 x 10^9/L (inter-quartile range: 9-80 x 10^9/L).

Table 2-1 Incident TEEs in the primary ITP cohort

Outcome	Person-Time	First events	Incidence Rate (95% CI)

	patient-years		per 10000 patient-years
Arterial TEEs	2203.1	10	45.39 (24.42-84.36)
Myocardial infarction (MI)	2266.8	5	22.06 (9.18-52.99)
Unstable angina (UA)	2270.4	3	13.21 (4.26-40.97)
Ischemic stroke (IS)	2263.9	5	22.09 (9.19-53.06)
Transient ischemic attack (TIA)	2270.7	2	8.81 (2.20-35.22)
Venous TEEs	2246.0	4	17.81 (6.68-47.45)
Deep vein thrombosis (DVT)	2252.8	3	13.32 (4.30-41.29)
Pulmonary embolism (PE)	2278.5	2	8.78 (2.20-35.10)

Important co-morbidities:

To examine important co-morbidities in ITP patients, GSK conducted two retrospective database analyses in UK and US. In the European study (GlaxoSmithKline WEUKSTV2498 Study) that included records from the United Kingdom GPRD study, ITP patients diagnosed between 01-Jan-1992 and 30-Sep-2005 were identified using Read or Oxford Medical Information System (OXMIS) codes. In the US, eligibility and medical claims data from a large U.S. health plan affiliated with i3 Drug Safety was investigated [GlaxoSmithKline WEUKSTV1116 Study]. Chronic adult ITP patients were defined between 01-Jan-2000 and 30-Sep-2006 with follow-up through 31-Dec-2006. In both studies, the incidence rates (per 10000 person years) of cataract, diabetes, acute or chronic renal failure, thromboembolic events, and blood cancers were calculated. Epidemiology of important co-morbidities in ITP patients is described in this module.

The incidence and prevalence of cataract, diabetes, renal failure, thromboembolic disease, and blood cancers are presented in the tables below for adult ITP patients from the United Kingdom (GPRD study [GlaxoSmithKline WEUKSTV2498 Study] and the US-based i3 Drug Safety claims study [GlaxoSmithKline WEUKSTV1116 Study] (Table 2-2).

Comorbidities among paediatric ITP patients are rare. In a study of 1784 children with newly diagnosed ITP from an international cohort, the prevalence of comorbidities was as follows: cancer (0.2%), cardiovascular diseases (0.5%), diabetes (0.2%), gastrointestinal disease (0.7%), and thyroid disease (0.3%). Splenomegaly was reported in 1% of the children, challenging the diagnosis of primary ITP (Kuhne et al 2011). Observational studies or analyses of cases series have reported 0-6% of paediatric ITP patients experience morbidity or mortality related to severe bleeding or intracranial hemorrhage (Bansal et al 2010; Cooper 2014; Neunert et al 2013).

The following table in this section provides the incidence and prevalence of co-morbidities among adult ITP patients:

Table 2-2 ITP - Important co-morbidities found in the target population

Co-morbidity	Incidence Rate [1, 2] (95% CI)	Prevalence [3] (%)	Development of comorbidity[3] (%)

Cataract	559.3 (491.9-633.5)	11.1	8.6
Diabetes	231.7 (190-279.0)	8.5; 11.6	3.8
Acute or chronic renal failure	373.9 (322.3-431.6)	1.8; 6.4	6.1
Venous thromboembolic events	70.83 (46.67,103.05) 40.5 (25.8-60.7)	6.8; 0.8	3.45; 0.7
Arterial thromboembolic events	82.02 (55.73,116.42) 278.0 (233.8-328.1)	10.4; 4.7	4.12; 4.5
Any Thromboembolic events	134.74 (99-179.18) 430.2 (373.2-493.4)	16.1; 8.2	6.67; 6.9
Deep vein thrombosis	19.76 (8.53-38.94) 21.0 (11.2-36.4)	0.3	0.97; 0.4
Pulmonary embolism	14.62 (5.36-31.81) 11.5 (4.8-23.6)	0.3	0.72; 0.2
Myocardial infarction	43.03 (25.06-68.89) 54.3 (36.8-77.3)	1.0	2.15; 0.9
Unstable angina	22.07 (10.09-41.89) 120.4 (92.9-153.5)	2.0	1.09; 2.0
Ischemic stroke	12.06 (3.92-28.15) 50.2 (33.6-72.40	0.6	0.6; 0.8
Transient ischemic attack	32.36 (17.23-55.33) 120.3 (92.9-153.5)	1.8	1.61; 2.0
Portal vein thrombosis	11.5 (4.8-23.7)	0.2	0.2
Other thromboembolic events	40.64 (23.23-65.99) 177.3 (143.1-217.4)	3.8	2; 2.9
Lymphoma	31.3 (18.6-49.6)	2.3	0.5
Non-Hodgkin's lymphoma	35.1 (21.5-54.3)	2.1	0.6
Leukemia	35.2 (21.6-54.4)	2.7	0.6
Chronic Lymphoid Leukemia	11.6 (4.8-23.9)	1.5	0.2
1. Per 10000 person years 2. If two rates provided, they are based on UK (1st rate) and US (2nd rate) studies. If one rate is provided, it is a US study 3. If two percentages provided, they are based on UK (1st percentage) and US (2nd percentage) studies. If one percentage is provided, it is a US study			

2.2 Indication: Chronic Hepatitis C virus (HCV)-associated thrombocytopenia

2.2.1 Epidemiology of the disease

Incidence and prevalence

Chronic Hepatitis C virus (HCV) is the most common blood-borne infection with a global prevalence of 2.2 to 3%; representing 130 to 170 million people worldwide (Lauer and Walker 2001, Lavanchy 2009). Of these, more than three-quarters are at risk of developing chronic

infection and hence are at risk of severe liver-related morbidity (Shiffman 2003). The disease is spread mainly through intravenous drug use and prior to its discovery in 1989 transfusion of blood/blood products was a major route of transmission. Country-specific differences in the relative contributions of these transmission methods in the past have led to different patterns of infections across age-groups (Wasley and Alter 2000).

In Europe, the HCV prevalence estimates show high variability between countries ranging from $\leq 0.5\%$ in the northern European countries to $\geq 3\%$ in the Romania and rural areas in Greece, Italy and Russia (Cornberg et al 2011). Despite eradication of transmission by transfusion of blood products, there is still an increase in HCV incidence in some countries due to immigration and continuous increase in Increased Drug Use IDU across Europe, especially in Eastern Europe.

Direct determination of HCV incidence is difficult mainly due to the asymptomatic nature of the disease and disease surveillance systems will therefore underestimate true disease incidence. In addition, differences in surveillance systems and case definitions do not permit accurate comparability of estimates between countries. In many European countries, incidence of acute HCV is reported to World health organization (WHO) which estimates the annual incidence of acute HCV to be 6.19 per 100000 in the WHO European region (Muhlberger et al 2009).

Thrombocytopenia in HCV

Chronic HCV infection has been associated with the development of several extrahepatic manifestations including thrombocytopenia. Thrombocytopenia is a haematological condition defined as platelet count <150000/μL and is divided traditionally into mild, moderate, and severe based on the degree of thrombocytopenia and displays different clinical significance.

The prevalence of thrombocytopenia in HCV patients is not well established and the existing literature provides a wide range of estimates and definitions. (Louie et al 2010) Most of the published studies use a platelet cut-off of <140000 or <150000 /μL and no information was available about prevalence of very low platelet counts (<50-75000/μL). To estimate the proportion of HCV patients with lower levels of platelet count, the Company sponsored a large observational data collection of HCV-associated thrombocytopenia in five European countries (UK, Germany, France, Spain and Italy). The study was a retrospective chart review and consisted of two parts; 1) a cross-sectional data collection of demographic data and selected clinical information including platelet counts in 2006 for all chronic HCV patients at each of the sites (a total of almost 5000 patients) and 2) a longitudinal in-depth chart review of a random sample of HCV patients with a platelet count <150000/ μL in 2006. The second part of the study includes a total of 911 patients for which details about laboratory results, antiviral treatment, co-morbidities and concomitant medications was collected covering information for each patient for a period of 2.5 years (Jan-2005 to Jul-2007). This part of the study was done to collect information describing clinical characteristics and management of this patient group. In total about 60 sites across the five countries was included in the study (WEUKSTV1115 Study 2010). The prevalence results from the study are included in the table below.

Grade	Platelet Count range (per µL)	Clinical Significance	Prevalence in the HCV population* (%)
Mild	75001 – 150000	Typically minimal	23
Moderate	50000-75000	Some increased risk of bleeding during invasive procedures	4.1
Severe	<50000	Significant morbidity; complicates management of HCV and advanced liver disease. Significant bleeding risk during invasive procedures, such as liver biopsy	1.7
* Source: WEUKSTV1115 Study, Afdhal et al 2008.			

The pathophysiology of thrombocytopenia in patients with HCV infection is not completely understood but is believed to be multifactorial. Thrombocytopenia is however clearly linked to the progression of cirrhosis. In the European observational study sponsored by the Sponsor (described above) 82% of patients with a platelet count of <50000/µL were found to have severe fibrosis whereas among patients with normal platelet count (>150000/µL) only 29% had severe fibrosis (WEUKSTV1115 Study).

Prevalence of target population

In a large company sponsored data collection the prevalence of chronic HCV patients with a platelet count below 75000/µL was 5.8%.

This study was a retrospective chart review of close to 5000 patients with chronic HCV who were diagnosed and seen by a specialist in 2006. In total about 60 sites from five European countries (UK, Germany, France, Spain and Italy) were included. Demographic data, severity of disease and the first and lowest platelet count recorded in 2006 was collected for each patient. For the prevalence estimate here, the first platelet count was used. (WEUKSTV1115 Study, 2010).

Demographics of the target population – age, sex, race/ethnic origin

In a large company sponsored retrospective chart review of close to 5000 patients with chronic HCV, demographic data, severity of disease and platelet count was collected. Results are presented below. In total about 60 sites from five European countries (UK, Germany, France, Spain and Italy) were included. (WEUKSTV1115 Study, 2010)

The majority of the patients in this study with a platelet count of <75000/µL were Caucasian (86%), 65% were male and average age was 56 years.

Table 2-3 Demographics of the target population by age

Age (year)	Patient distribution (%)
<18	0
18-29	3
30-49	34
50-64	34
65+	29

Table 2-4 Demographics of the target population by ethnic origin

Ethnic origin	Patient distribution (%)
White/Caucasian	86
Afro/Caribbean	2
Asian – Indian subcontinent.	5
Hispanic	1
Asian – other	3
Other	3

Risk factors for the disease

Chronic Hepatitis C virus patients with a platelet count below 75000/µL are typically patients with a very advance liver disease and are at high risk of developing decompensation events, hepatocellular carcinoma and end-stage liver disease including death or liver transplantation.

Main treatment options

The primary option available for the treatment of thrombocytopenia in HCV patients receiving antiviral therapy is to reduce the dose of interferon (IFN). When eltrombopag is given in combination with antiviral therapies reference should be made to the full prescribing information of the respective co-administered medicinal products for comprehensive details of administration including dose reduction for thrombocytopenia. The directions regarding the posology, dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications for the respective antiviral medicinal products should be followed.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Mortality and morbidity (natural history)

It is well documented that chronic hepatitis C may progress to cirrhosis. The development of cirrhosis is a slow process that takes on average 21 years and the rate is highly variable. However, once cirrhosis has established approximately 15% of the patients decompensate and develop major life-threatening complications of cirrhosis, including variceal hemorrhage, refractory ascites, spontaneous bacterial peritonitis, refractory hepatic encephalopathy and/or liver cancer within five years (Shiffman 2003). The prognosis of decompensated HCV-related cirrhosis is poor, with a 5-year survival rate of only 40-50%. (Dienstag et al 2011)

The complication rate for cirrhotic patients with thrombocytopenia is substantially higher than those without thrombocytopenia. In a study by Dienstag et al 2011 more than 1000 HCV patents with advances fibrosis or cirrhosis were followed for 8 years. They found that the annualized incidence of hepatocellular carcinoma (HCC), decompensation (variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy) and death was 3.6%, 6.0% and 5.3%, respectively, among HCV patients with <100000/µL. The same rates were found to be 1.0%, 1.1% and 1.9% among patients with platelet count between 150000 and 200000/µL.

Untreated HCV patients with a platelet count <100000/µL has an annual rate of death or liver transplantation of about 7.3%. There are no estimates available for patients with platelet count below 75000/µL but the association between decrease in platelet count and severity in liver disease suggests an even higher rate of death or liver transplantation in the target population. (Dienstag et al 2011).

Important co-morbidities found in the target population

The following tables provide information regarding the most common co-morbidities among chronic HCV patients with low platelet counts. The information was provided by the company sponsored study of HCV-associated thrombocytopenia in five European countries. The data was restricted to patients who did not receive anti-viral treatment during the observational window and who had a platelet count of <50000/µL. (WEUKSTV1115 Study, 2010)

Table 2-5 Important co-morbidities found in the target population

Co-morbidity	Prevalence (%)
Diabetes	18.75
Hypertension	16.67
HCC (Hepatocellular Carcinoma)	14.58
Liver cirrhosis/ failure	12.50
Esophageal Varices II	8.33
Anemia (including renal anemia)	8.33
Portal Hypertension	8.33
Chronic alcoholism	6.25
Obesity	6.25
Depression	6.25
Other cardiovascular disorder	6.25
Steatosis	4.17
Essential mixed cryoglobulinaemia	4.17
Arthritis	4.17
Asthma	4.17
COPD	4.17
Chronic renal failure	4.17
Arthrosis/ Arthralgia	4.17
Sjogren's syndrome	4.17
Anxiety	2.08
Muscle weakness	2.08

Source: (WEUKSTV1115 Study, 2010)

2.3 Indication: Severe aplastic anemia (SAA)

2.3.1 Epidemiology of the disease

Incidence and prevalence

Aplastic anemia is extremely rare, with overall incidence rates worldwide reflecting approximately 2 to 3 cases per million. There is a trend consistently seen among several population based studies indicating two peaks in incidence in aplastic anemia: in late adolescence and early 20s and in adults greater than 60 years of age. Some country specific incidence data is available and is summarized below.

Spain

A recent study conducted in Spain among a population-based community near Barcelona identified the incidence of acquired aplastic anemia to be the following shown in Table 2-6 Incidence of acquired aplastic anemia from population-based study in Spain, stratified by age and by sex (Montane et al 2008). The authors did not note any difference in the incidence of aplastic anemia when stratified by sex.

Table 2-6 Incidence of acquired aplastic anemia from population-based study in Spain

	Age at diagnosis					No. of cases	Total Incidence*
	2-14	15-24	25-44	45-64	65+		
Male							
N case	17	25	22	28	31		
Incidence	1.92	2.83	1.52	2.56	5.89	123	2.54
Female							
N Case	12	11	15	31	43		
Incidence	1.43	1.41	1.00	2.58	4.89	112	2.16
Total							
N Case	29	36	37	59	74		
Incidence	1.68	2.16	1.26	2.57	5.33	235	2.34

*Incidence is number cases per 1 million persons per year

United Kingdom

The incidence of aplastic anemia in the United Kingdom was evaluated in a study in 1988 (Cartwright et al 1988). This study found a crude incidence of 2.3 cases per million in the year 1985, which is well-aligned with the Spanish study conducted in 2008. However, in the UK study, there were differences noted with respect to the sex distribution of incidence rates; the crude incidence among males and females was 1.4 and 3.2 cases per million, respectively.

France

A study conducted in 1990 in France found the crude incidence of aplastic anemia to be approximately 1.5 per million persons per year, slightly lower than the Spain and United Kingdom estimates (Mary et al 1990). This study noted no differences among sex, but was in alignment with the Spanish study finding a bimodal incidence with respect to age (ages 15-30 and > 60 years).

Scandinavia

In Scandinavia, including Denmark, Finland, Iceland, Norway and Sweden, a population-based study was conducted in children under the age of 15 years old in 1982-1993 (Clausen et al 1996). Results from this study yielded incidence rates of 2.4 and 1.5 per million for boys and girls respectively. These findings are contrary to the sex ratio identified in the United Kingdom study, although the total incidence (1.9 cases per million) is in alignment.

United States (Baltimore)

A study conducted in the United States in Baltimore, Maryland, calculated age and sex-adjusted incidence of aplastic anemia in 1985 (Table 2-7, Szklo et al 1985).

Table 2-7 Age- and sex-specific Incidence rates of aplastic anemia in Baltimore, USA (whites only)

	Age at diagnosis						
	0-9	10-19	20-39	40-59	60+	Total Incidence*	Age-adjusted Incidence*
Male	3.7	5.2	0.5	6.0	31.7	7.0	7.1
Female	2.0	1.5	1.5	6.3	22.5	6.1	5.4

*Incidence number of cases per million

Brazil

A study focused on a state of Brazil (Parana) to calculate the incidence of aplastic anemia in 2002 (Maluf et al 2002). This study identified an overall crude annual incidence rate of 2.3 per million inhabitants. This study also found a peak in incidence among those aged 15-29 at 4.2 per million people and those older than 60 years of age (3.6 per million). Among the paediatric population, aged 0-14 years old, male and female incidence rates were 2.1 per million and 1.8 per million, respectively.

Studies conducted in various countries show a consistent incidence of approximately two cases per million. In most studies, the incidence was higher in males as compared to females. There is a biphasic age distribution with peaks in adolescence years and older age groups were consistently reported.

Demographics of the target population – age, sex, race/ethnic origin

The incidence of SAA is similar in males and females. Some articles reported a higher proportion of males in their study population, ranging from 52.3% (Montane et al 2008) to 66.7% (Clausen et al 1996). However, two Swedish studies found a non-significant difference in the incidence between males and females: 51% females in one study (Bottiger and Bottiger 1981), and an exact same number of males and females in the other study (Bottiger and

Westerholm 1972). These findings are further corroborated by an additional study (Marsh et al 2009).

Three studies focused on SAA cases of all ages. Of these three studies, one found a median age of reported cases of 30 years (range 7-70 years) (Mikhailova et al 1996), one an age range of 1 to 73 years (Tichelli et al 1994), and the other a proportion of 48.9% of SAA cases aged 0 to20 years (Bacigalupo et al 1988). These studies reflect the biphasic age distribution of SAA, with peaks at 10 to 25 years and >60 years (Marsh et al 2009).

With regard to race and ethnicity, the incidence has been noted to be 2-3 times higher in East Asian patients (Marsh et al 2009) which is thought to be related to environmental factors.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Morbidity

Three studies reported on different morbidity aspects of aplastic anemia (AA) (Clausen et al 1996, Quarello et al 2012, Bacigalupo et al 1988). Quarello et al 2012 reported that 54% of AA cases developed an incident infectious episode. This proportion was related to the severity of AA. The frequency of infection increases as the severity of the aplastic anemia increases. Incidence rates of different infectious episodes in these AA patients can be found in the evidence table.

Clausen et al (1996) reported that 26.8% of surviving SAA cases had not obtained complete remission after a median of 72 months after diagnosis, 4.2% had a relapse after complete remission and 4.2% had sequelae. Lastly, Bacigalupo et al (1988) reported that the Karnofsky's scores (measure of the quality of survival) was quite comparable between SAA patients treated with bone marrow transplantation or immunosuppressive therapy (IST) (92% and 93%, respectively).

Mortality and survival in Patients with an Insufficient Response to Immunosuppressive Therapy

Outcomes are poor for patients who have an insufficient response to IST. Despite significant improvements in standard supportive care treatments (particularly antifungal antimicrobials and other antibiotics), approximately 40% of SAA patients unresponsive to initial IST die from the complications of pancytopenia (infection or bleeding) within 5 years of diagnosis (Valdez et al 2011).

Risk factors for the disease

Acquired aplastic anemia is an uncommon bone marrow disorder. Laboratory and clinical observations have suggested an immunological etiopathogenesis. Both environmental and individual host factors have been hypothesized to determine risk. The disorder has been associated with exposure to chemical agents (benzene, pesticides) and drugs. It can also follow viral infections, as post-seronegative hepatitis, and it is a rare complication of pregnancy and other immunological diseases. However, most often aplastic anemia is considered idiopathic with no identifiable cause.

Main treatment options

The standard definitive treatment for SAA is either intensive immunosuppressive therapy (IST) with horse anti-thymocyte globulin and cyclosporine (ATG/CsA) or haematopoietic stem cell transplantation (HSCT). The choice between HSCT and IST as definitive treatment is dependent upon age, comorbidities and availability of a matched sibling donor. Supportive care with red cell and platelet transfusions is essential for patients with SAA to maintain a safe blood count. Iron overload can cause significant problems in heavily transfused patients and iron chelation therapy is utilized in such patients. SAA patients receive prophylactic antimicrobial therapy (antibiotics and antifungals) for prevention of infections due to neutropenia.

Important co-morbidities

Gupta et al (2006) found that 19.8% of patients with AA in their UK single center had a paroxysmal nocturnal hemoglobinuria (PNH) clone at diagnosis. The presence of low grade paroxysmal nocturnal hemoglobinuria (PNH) clones in patients with SAA does not alter the choice of treatment. The majority (70% - 80%) of aplastic anemia cases are categorized as idiopathic because their primary etiology is unknown and there are no associated important comorbidities. In approximately 15–20% of adult patients, the disease is constitutional/inherited, where the disease is familial and/or presents with one or more other somatic abnormalities (Alter 1996, Marsh et al 2009). There are no specific markers or characteristics of idiopathic SAA.

Blood cell counts determine the signs and symptoms of patients with AA. Anemia leads to fatigue, dyspnea, and cardiac symptoms; thrombocytopenia to bruising and mucosal bleeding; and neutropenia to increased susceptibility to infection. At present, the most common causes of death in patients with aplastic anemia are recurrent bacterial sepsis or fungal invasion of critical organs secondary to refractory granulocytopenia (Young 2002).

A known complication of SAA is the appearance of cytogenetic abnormalities in bone marrow cells. Cytogenetic abnormalities have been reported in 15-20% of patients with SAA (Maciejewski et al 2002, Scheinberg et al 2011, Scheinberg et al 2012). The clinical consequences are variable, depending upon the specific abnormality and the presence or absence of clinical sequelae such as dysplasia or worsening cytopenias (Maciejewski et al 2002).

Patients with aplastic anemia are known to be at risk for the development of Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) (Maciejewski and Selleri 2004, Marsh et al 2009).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Cataracts In mice and rats, development of cataracts was dose- and time-dependent with the rapidly developing lens of young mice being more susceptible. There was no evidence of drug accumulation in the lens, and exposure to solar-simulated (UVR) light did not contribute to eltrombopag-induced cataracts in rodents. Exposure at the no observed effect level (NOEL) in mice, the more sensitive species, was 1.2- and 0.6-fold exposure in ITP/HORT and HCV patients, respectively, while exposure at the lowest observed effect level (LOEL) was 3.5- and 1.7-fold clinical exposure, respectively. No cataracts were evident after chronic dosing in dogs (52 weeks) at maximally tolerated doses.	The data from the double-blind and open label ITP and HORT studies, as well as data from the LENS study and the Phase II HCV study did not suggest an increased risk of cataract development in subjects treated with eltrombopag. This conclusion was supported by the blinded, independent ocular safety data review from the Clinical Events Committee (CEC). In the pooled data from the Phase III HCV studies (ENABLE studies), where subjects received up to 57 weeks of eltrombopag at doses up to 100 mg, there was a numerically higher incidence of cataracts in the eltrombopag treatment group compared with the placebo group.
Pregnancy and Lactation Eltrombopag was assessed in reproductive and developmental toxicity studies in rats and rabbits. At a maternally toxic dose (6-fold clinical exposure) in rats, eltrombopag treatment was associated with increased pre-implantation loss and a slight increase in post-implantation loss (embryolethality) in a female fertility and early embryonic development study and a low incidence of cervical ribs in an embryo fetal development study. Reduced fetal body weights were observed in both studies at this maternally toxic dose. There were no other signs of developmental toxicity in rats and rabbits at up to 2-fold and 0.5-fold clinical exposure, respectively. Studies in animals have shown that eltrombopag is likely secreted into milk.	There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Revolade is not recommended during pregnancy and in women of childbearing potential not using contraception. Breast-feeding It is not known whether eltrombopag / metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk; therefore, a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue / abstain from Revolade therapy, taking into account the benefit of breast-feeding for the

	child and the benefit of therapy for the woman.
Renal Tubular Toxicity Renal tubular toxicity, characterized by degeneration and/or necrosis or regeneration, was observed in studies up to 14-days duration in mice and rats and in a 2-year carcinogenicity study in mice at exposures that were generally associated with morbidity and mortality (≥6-fold clinical exposure). At 1.2-fold clinical exposure, regenerative changes were noted in renal tubules of mice on the 2-year study that likely reflect a minimal nephrotoxic effect. No renal tubular toxicity was observed following repeated oral administration to rats for 2 years or dogs for 1 year at exposures up to 4.0- and 2.5-fold clinical exposure, respectively.	The renal tubular toxicity findings observed in nonclinical studies to date have not translated into clinically relevant observations in humans.
Phototoxicity Eltrombopag was phototoxic (3T3 fibroblasts, neutral red uptake assay) and photoclastogenic (CHO cells, chromosomal aberration assay) *in vitro*. *In vitro* photoclastogenic effects were observed at cytotoxic drug concentrations at excessive UVR exposure. There was no evidence of *in vivo* cutaneous phototoxicity in mice or ocular phototoxicity in mice or rats at exposures up to 10-, 9- or 5-fold clinical exposure, respectively.	There was no evidence of *in vivo* cutaneous phototoxicity in mice (10 times the human clinical exposure in ITP subjects at 75 mg/day and 5 times the human clinical exposure in HCV subjects at 100 mg/day based on AUC) or photo-ocular toxicity in mice or rats (up to 11 and 6 times the human clinical exposure in ITP subjects at 75 mg/day and 5 and 3 times the human clinical exposure in HCV subjects at 100 mg/day based on AUC). The *in vitro* phototoxicity findings observed in nonclinical studies to date have not translated into clinically relevant observations in humans.
Haematological Changes At poorly tolerated doses in rats and dogs (>10-fold maximum clinical exposure), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no remarkable effects on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses	The haematologic changes observed in nonclinical studies to date have not translated into clinically relevant observations in humans.

which were 2- to 4-fold maximum clinical exposure.	
Endosteal hyperostosis Endosteal hyperostosis was observed in a 28-week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6-fold maximum clinical exposure). There were no bone changes in mice or rats after lifetime exposure (2 years) at 4-fold maximum clinical exposure.	The endosteal hyperostosis findings observed in nonclinical studies to date have not translated into clinically relevant observations in humans.
Juvenile Toxicity Nonclinical juvenile rat studies have been completed. Data suggest that toxicity is lower in younger rats (dosed on days 4 to 31 post-partum) than in those dosed on days 32 to 63 post-partum, no additional nonclinical information for special population is considered necessary. Higher susceptibility in younger rats was probably based on higher systemic exposure. Systemic exposure in older pups was similar to those in adult animals.	The effects are not deemed to be clinically relevant.

Conclusions:

- There are no important identified risks from non-clinical studies, which would have been confirmed by clinical data
- Important potential risks from non-clinical safety studies, which have not been refuted by clinical data or are of unknown significance include Renal Tubular Toxicity, Phototoxicity and Endosteal hyperostosis. Removal of these important potential risks was endorsed by PRAC (EMEA/H/C/PSUSA/00001205/201809) (Section 8.2)
- There is no missing information identified from pre-clinical safety studies.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Cumulative subject exposure in clinical trials

Approximately 1254 healthy volunteers and 4896 subjects received Promacta/Revolade treatment in Novartis-sponsored investigational clinical trials cumulatively since the Development IBD (DIBD of 29-Oct-2004) till 30-Sep-2021.

Estimates of the cumulative patient exposure, based upon actual exposure data from completed interventional clinical trials and the enrollment and randomization schemes from ongoing interventional clinical trials at time of 30-Sep-2021 cutoff date are provided by indication in Table 4-1Cumulative subject exposure from completed and ongoing clinical trials. Exposure to eltrombopag in trials for other investigational products is also included in Table 4-1Cumulative subject exposure from completed and ongoing clinical trials. Exposure by age, gender and race are provided for completed trials only (i.e., clinical trials for which a Clinical Study Report is available at time of cut-off date, 30-Sep-2021) in Table 4-2 and Table 4-3.

Table 4-1 Cumulative subject exposure from completed and ongoing clinical trials

Study indication	Eltrombopag n (%)	Placebo n (%)
Healthy volunteers	1,126 (22.9)	128 (9.0)
Adult ITP	927 (18.9)	187 (13.2)
Pediatric ITP	171 (3.4)	50 (3.5)
Liver diseases	1,802 (36.7)	647 (45.7)
Solid tumors	227 (4.6)	76 (5.4)
MDS/AML	444 (9.2)	329 (23.2)
Moderate aplastic SAA	146 (2.9)	0 (0.0)
Pediatric SAA	53 (1.0)	0 (0.0)
Total	4896	1,417

AML - Acute Myeloid Leukemia; ITP - Immune ThrombocytoPenia; MDS - MyeloDysplastic Syndrome; SAA- Severe Aplastic Anemia; n= Number of subjects

Note: Subjects are listed under all the treatments that they received.

Completed studies: Healthy Volunteer: 497115/001, 497115/002, 497115/005, TPL116010, TPL111716, TRA102860, TRA102861, TRA102863, TRA103452, TRA104412, TRA104603, TRA104631, TRA105120, TRA105122, TRA105580, TRA106914, TRA110087, TRA111718, 200338, 201583

Adult ITP: TRA100773, TRA102537, TRA105325, TRA108057, TRA108109, TRA112940, TRA113765

Pediatric ITP: TRA108062, TRA115450

Solid Tumors: 497115/003, TRC105499, TRC112765, CHDM201X2101

Liver: TPL102357, TPL103922, TPL104054, TPL108390, TPL111913, TPL116101

MDS/AML: PMA112509, TRC112121, TRC114968, TRC117146; MAA/SAA: ELT112523, 200926, 201793

Ongoing studies- CETB115E2201, CETB115E2202, CETB115E2403, CETB115A2X01B, CETB115J2411, CETB115I2102, CETB115K12101, CETB115JDE01, CETB115L11201, CETB115G2201

Table 4-2 Cumulative subject exposure from clinical trials by age, gender and treatment group

	Eltrombopag N=4,270 Subjects n (%)	**Placebo N=1,417 Subjects n (%)**
Age (years) Total	4,270 (100.0)	1,417 (100.0)
< 18	171 (4.0)	50 (3.5)
18 to 64	3,438 (80.5)	1,040 (73.4)
65 to 74	445 (10.4)	217 (15.3)
≥ 75	216 (5.1)	110 (7.8)
Female (total)	1,846 (43.2)	565 (39.9)
< 18	89 (2.1)	27 (1.9)
18 to 64	1,461 (34.2)	406 (28.7)
65 to 74	212 (5.0)	93 (6.6)
≥ 75	84 (2.0)	39 (2.8)
Male (total)	2,424 (56.8)	852 (60.1)
< 18	82 (1.9)	23 (1.6)
18 to 64	1,977 (46.3)	634 (44.7)
65 to 74	233 (5.4)	124 (8.8)
≥ 75	132 (3.1)	71 (5.0)

N=Total number of subjects; n=number of subjects

Note: Subjects are listed under all the treatments that they received.

Table 4-3 Cumulative subject exposure from clinical trials by race and treatment group

Race	**Eltrombopag N=4,270 Subjects n (%)**	**Placebo N=1,417 Subjects n (%)**
White	2,858 (66.9)	1,012 (71.4)
African American/African	202 (4.7)	40 (2.8)
East Asian/South East Asian/ Japanese	801 (18.8)	244 (17.2)
Central/South Asian	233 (5.5)	72 (5.1)
Other	73 (1.7)	17 (1.2)
Unknown	96 (2.3)	32 (2.3)
Missing	7 (0.1)	0 (0.0)

N=Total number of subjects; n=number of subjects

Note: Subjects are listed under all the treatments that they received.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale *(if not included as missing information)*
Prior history of arterial or venous thrombosis and two or more thrombotic risk factors	In eltrombopag clinical trials thromboembolic events were observed at low and normal platelet counts.	No	Platelet counts above the normal range present a theoretical risk for thrombotic complications. Clinical trials with eltrombopag showed thromboembolic events at low and normal platelet counts. Thus, use caution when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome). In addition, platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels.
Pre-existing cardiovascular disease, or arrhythmia known to increase the risk of thromboembolic events	In eltrombopag clinical trials thromboembolic events were observed at low and normal platelet counts.	No	Clinical trials with eltrombopag showed thromboembolic events at low and normal platelet counts. Thus, use caution when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., cardiovascular disease or arrhythmia).
Female subjects who were nursing or pregnant	It is not known whether eltrombopag is excreted in human milk. Eltrombopag is not recommended for nursing mothers unless the expected benefit justifies the potential risk to the infant. Eltrombopag was not teratogenic when studied in pregnant rats and rabbits but caused a low incidence of cervical ribs (a fetal variation) and reduced fetal body weight at doses that were maternally toxic. There are no adequate and well-controlled studies of eltrombopag in pregnant women. The effect of	No	The effect of eltrombopag on human pregnancy is unknown. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale *(if not included as missing information)*
	eltrombopag on human pregnancy is unknown. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.		
Subjects with secondary immune thrombocytopenia, including HIV infection, anti-phospholipid antibody syndrome, chronic hepatitis B infection, hepatitis C virus infection, active hepatitis	Eltrombopag administration can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity, and potentially fatal liver injury. Chronic HCV patients with cirrhosis may be at risk for hepatic decompensation, some with fatal outcomes, when receiving alpha interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, ALT or AST > 3 x ULN were reported in 34% and 38% of the eltrombopag and placebo groups, respectively. Eltrombopag administration in combination with peginterferon/ ribavirin therapy is associated with indirect hyperbilirubinemia. Total bilirubin ≥1.5 x ULN was reported in 76% and 50% of the eltrombopag and placebo groups, respectively. Safety findings suggestive of hepatic decompensation were reported more frequently in the eltrombopag arm (13%) than in the placebo arm (7%). Subjects with low albumin levels (< 3.5 g/dL) or Model for End-Stage Liver Disease (MELD) score ≥ 10 at baseline had a greater risk of hepatic decompensation. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation. Novartis conducted a program wide hepatic evaluation to identify all cases fulfilling Hy`s law criteria. Five cases were identified: two within the approved indication of cITP, and three in clinical trials for MDS and AML patients. The elevation of laboratory values typically occurred within 3 months of initiation (30 days to 81 days)	No	With the exception of hepatitis C virus-associated thrombocytopenia, the indications have not been studied, and would be considered off label.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale *(if not included as missing information)*
	except in 1 case, where the elevation occurred on Day 97, during the 4th cycle of chemotherapy. In all five cases, the event resolved following eltrombopag discontinuation (i.e., with a positive dechallenge); no patient died or required transplantation. One of the five patients also had a positive rechallenge. These factors represent a likely causal relationship to eltrombopag.		
Subjects planning to have cataract surgery	Cataracts were observed in toxicology studies of eltrombopag in rodents. Therefore, routine monitoring of patients for cataracts is recommended	No	The current label includes a warning regarding the previous observation of progression of pre-existing cataract or incident cataracts in eltrombopag-treated patients

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Further details on these types of adverse reactions are provided in Table 5-2 below.

Table 5-2 Limitations of ADR detection common to clinical trial development programs

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	An estimated 4463 subjects in total have been exposed to eltrombopag in Novartis-sponsored ongoing and completed interventional studies.	As per the "rule of three" if no events of a particular type are observed in a study of X individuals, then one can be 95% certain that the event occurs no more often than 3/X. According to this guidance, any event which is not observed in this population occurs less often than 3 in 4463 exposed individuals, or has an incidence of less than 0.000067 (or 6.7 per 10000).
Due to prolonged exposure	Some patients were observed up to seven years in clinical trials.	The safety profile for patients with more than 12 months of exposure appeared to be similar and consistent with the overall safety profile of eltrombopag observed in patients treated less than 12 months.

Due to cumulative effects	Eltrombopag did not show unexpected accumulation in blood and tissues after multiple dosing.	Not applicable
Which have a long latency	Due to the well-known inherent limitations of clinical trial development programs in general adverse drug reactions with a long latency period are often not detected.	Long latency adverse drug reactions are defined as adverse drug reactions (ADRs) which occur six months or more after initial exposure (Fletcher and Griffin 1991). Based on the review of the safety profile for patients with more than six months of exposure there is no evidence for eltrombopag induced long latency adverse drug reactions so far.
Source: Fletcher and Griffin 1991		

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-3 Exposure of special populations included or not in clinical trial development programs

Type of special population	**Exposure**
Pregnant women (adult ITP, paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia)	Not included in the clinical development program
Breastfeeding women (adult ITP, paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia)	Not included in the clinical development program
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment	Not included in the clinical development program
Population with relevant different ethnic origin East Asian populations (adult ITP, paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia) Other Asian population (HCV-associated thrombocytopenia)	Data on patients of different racial and/or ethnic origins is limited
Subpopulations carrying relevant genetic polymorphisms • 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 to 9) • Safety and efficacy of eltrombopag in combination with new direct acting agents (telaprevir/boceprevir) (Chronic HCV-associated thrombocytopenia)	Data on populations with relevant genetic polymorphisms is limited
Other	
Elderly patients (≥ 65 years)	Data is limited
Very elderly patients (≥ 75 years of age) (adult ITP, paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia)	Data is limited

Paediatric patients (<18 years of age) (HCV-associated thrombocytopenia and SAA)	Not included in the clinical development program
Paediatric patients (<1 years of age) in ITP	Not included in the clinical development program

Source: RMP version 54.0 Attachment to Annex 7 - Table 5-3

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in no. of unit sold during the reporting interval. One unit per day is considered as Defined Daily Dose (DDD) for patient exposure calculation. The estimated patient exposure was calculated based on the following formula.

Patient exposure in patient treatment years (PTY) = No of units sold/(1 × 365)

6.1.2 Part II Module SV.1.2. Exposure

Table 6-1 Cumulative estimate of eltrombopag tablets sold and patient-years

Cumulative 20-Nov-2008 to 30-Sep-2021		
Strength	**Cumulative period tablets sold**	**Patient years**
12.5 mg	31,555,510	86,453
25 mg	59,470,125	162,932
50 mg	38,974,454	106,779
75 mg	58,26,724	15,964
Grand Total	135,826,813	372,128
Source: Promacta PSUR (Reporting Period: 01-Oct-2018 to 30-Sep-2021)		

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

A potential for misuse for illegal purposes or abuse has not been identified for eltrombopag and is considered unlikely from the knowledge of eltrombopag to date.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable; the Risk Management Plan (RMP) was already approved.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns and reclassification with this RMP submission.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 SVII.3.1. Presentation of important identified risks and important potential risks

Table 8-1 Important Identified risk: Hepatotoxicity

Risk: **Hepatotoxicity**

Frequency with 95% CI

Adult ITP

	RAISE		TRA100773 A and B		OPEN LABEL	
	Placebo n=61	Epag n=135	Placebo n=67	Epag 50mg* n=106	REPEAT n=66	EXTEND n=299
Parameters	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
≥ 3x ULN# AT[a] & >1.5x ULN Bili	0	0	0	1 (1)	0	5 (2)
≥ 20x ULN ALT[c]	1 (2)	0	0	1 (1)	0	0
≥ 10x ULN ALT	1 (2)	2 (1)	1 (2)	2 (2)	0	1 (<1)
≥ 5x ULN ALT	1 (2)	4 (3)	1 (2)	4 (4)	0	5(2)
≥ 3x ULN ALT	2 (3)	9 (7)	1(2)	6 (6)	1 (2)	11 (4)
>2x ULN Bili	0	4 (3)	2 (3)	4 (4)	0	5 (2)
>1.5x ULN Bili	0	5 (4)	4 (6)	4 (4)	1 (2)	16 (5)

Source: Table SDAP 8.200
* Pooled data from TRA100773 A and B
# ULN= upper limit of normal
[a]AT = Aminotransferases
Bili = Total bilirubin
ALT = Alanine aminotransferase

Paediatric ITP:

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

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

m5.3.5.3 ISS Section 2.1.5.2

Risk	Hepatotoxicity

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

- Denominator is number of subjects with ALT and/or AST ≥3xULN and Total Bili. ≥ 1.5xULN.

e. Denominator is number of subjects with Total Bili. ≥ 2xULN.
f. Denominator is number of subjects with Total Bili. ≥ 1.5xULN.

In the eltrombopag treated population, there were additional 7 subjects with ALT ≥3x ULN from those previously reported in the Safety Population. Of these 7, there were 5 subjects who had increases in ALT ≥5x ULN, which met the protocol defined liver chemistry stopping criteria. There were 2 events of concurrent elevations in ALT ≥3x ULN and bilirubin ≥1.5x ULN. The laboratory abnormalities were not indicative of drug induced liver injury (DILI) as the bilirubin was primarily unconjugated.
All the HBLAs resolved while on study treatment or after discontinuation of study treatment. Overall, these findings were mostly mild, reversible, and not accompanied by impaired liver function.

Refractory Severe aplastic anaemia

On-therapy hepatobiliary laboratory abnormalities in Study ELT112523 (ETB115AUS28T) (safety population)

	Eltrombopag N=43[a]
ALT or AST >3xULN and Total Bilirubin >2xULN	0
ALT or AST >3xULN and Total Bilirubin >1.5xULN	2 (5)
ALT or AST >10xULN	0
ALT or AST >5xULN	4 (9)
ALT or AST >3xULN	9 (21)
ALT >10xULN	0
ALT >5xULN	4 (9)
ALT >3xULN	8 (19)
AST >10xULN	0
AST >5xULN	2 (5)
AST >3xULN	5 (12)
Total Bilirubin >2xULN	0
Total Bilirubin >1.5xULN	6 (14)
ALP >1.5xULN	5 (12)
Data Source: ELT112523 (ETB115AUS28T) CSR Section 7.6.1.1	
Subjects may be counted in more than 1 category of the criteria.	

Seriousness/outcomes	**Adult ITP** Many medications have the potential to induce liver injury, which can range from a transient, self-limited increase in aminotransferases to a severe liver injury and liver failure. Hepatotoxicity was assessed because of evidence of liver toxicity in non-clinical studies. There were no direct hepatobiliary-related deaths and no lasting clinical sequelae. The majority of events recovered prior to the clinical cut-off date, in most cases despite continuation of treatment. Indirect bilirubin increases were found in several patients, most likely due to

Risk	Hepatotoxicity

inhibition of the OATP1B1 transporter (Summary of Clinical Pharmacology (m2.7.2)). These elevations of indirect bilirubin are considered of little clinical significance.

An analysis has been completed to investigate if there is any relationship between the dose of eltrombopag and the occurrence of HBLA. The focus on the results of this analysis is on ALT >3xULN since it is clinically the most important laboratory parameter for hepatotoxicity. There are several possible ways to retrospectively analyse a potential dose toxicity relationship of eltrombopag in the clinical trials. The first occurrence and the maximum occurrence of ALT elevations by the modal dose for the five days leading up to the event were reviewed. No significant difference between the first occurrence and the maximum occurrence by modal dose was observed.

No relationship to dose was found in studies TRA100773B and REPEAT. In RAISE the number of patients with ALT >3x ULN was similar in both 50 mg and 75 mg modal doses. In EXTEND, however, with a number of patients on 25, 50, and 75 mg dose, no patients on <25 mg, 2 on 50 mg, and 7 on 75 mg had ALT >3x ULN. Based on this data in EXTEND, a relationship between dose and occurrence of ALT > 3x ULN cannot be ruled out with the specific methodology used (five day prior to modal dose).

Paediatric ITP (Pooled PETIT and PETIT 2 data):

Summary of Subjects Meeting Hepatobiliary Laboratory Abnormality Criteria at Any Post-Baseline Visit (All Eltrombopag Treated Population)

	Eltrombopag (N=171)
Subjects with events meeting at least one criterion, n (%)	**21 (12.3)**
ALT and/or AST ≥ 3xULN and Total Bili. ≥ 2xULN	0
Direct Bilirubin >35% Total Bilirubin	0
ALT and/or AST ≥ 3xULN and Total Bili. ≥ 1.5xULN	2 (1.2)
Direct Bilirubin >35% Total Bilirubin [a]	0
ALT+AST ≥ 10xULN	0
ALT+AST ≥ 5xULN	2 (1.2)
ALT+AST ≥ 3xULN	5 (2.9)
ALT ≥ 20xULN	0
ALT ≥ 10xULN	2 (1.2)
ALT ≥ 5xULN	7 (4.1)
ALT ≥ 3xULN	12 (7.0)
AST ≥ 10xULN	0
AST ≥ 5xULN	3 (1.8)
AST ≥ 3xULN	7 (4.1)
Total Bili. ≥ 2xULN	0
Direct Bilirubin >35% Total Bilirubin	0
Total Bili. ≥ 1.5xULN	6 (3.5)
Direct Bilirubin >35% Total Bilirubin [b]	1 (16.7)
Alk. Phos. ≥ 1.5xULN	4 (2.3)
m5.3.5.3 ISS Section 2.1.5.2	

Risk	Hepatotoxicity
	Note: Based on Guidance for Drug-Induced Liver Injury: Premarketing Clinical Evaluation [FDA, 2009]. Abnormality criteria applied on lab value/ULN calculated to 1 decimal place where criteria are multiple of ULN, otherwise direct comparison of lab value to ULN is performed. [a]Denominator is number of subjects with ALT and/or AST ≥ 3xULN and Total Bili. ≥ 1.5xULN. [b]Denominator is number of subjects with Total Bili. ≥ 1.5xULN. The laboratory abnormalities were not indicative of drug induced liver injury as the bilirubin was primarily unconjugated. All the HBLAs resolved while on study treatment or after discontinuation of study treatment. Overall, these findings were mostly mild, reversible, and not accompanied by impaired liver function. **Chronic hepatitis C virus (HCV)-associated thrombocytopenia** Eltrombopag is metabolised in the liver, therefore a comprehensive analysis of hepatobiliary events and assessments is recommended. A is indicated because. Equally important, in these studies subjects were treated with peginterferon, which is known to have hepatobiliary side effects. During the double blind phase on-treatment plus 30-day follow-up period, a higher proportion of eltrombopag subjects reported hepatobiliary adverse events overall, grade3/ grade 4, and drug-related hepatobiliary adverse events in particular compared with placebo subjects (Data Source: Table 8.1312 and Table 8.1341). The proportion of adverse events (AEs) that led to withdrawal from study or were considered serious were similar for eltrombopag and placebo subjects. The majority of AEs resolved in both treatment groups. Hyperbilirubinemia and blood bilirubin increased accounted for a substantial portion of the imbalance in hepatobiliary AEs between eltrombopag and placebo. The hyperbilirubinemia was largely due to increases in indirect bilirubin. (Data Source: Table 8.1302) Hepatobiliary laboratory parameters reported during the study were evaluated according to the FDA Guidance for Industry entitled “drug-induced liver injury (DILI): Premarketing Clinical Evaluation (Jul-2009)”. However, there are important limitations to this analysis in a liver disease population. In fact, the FDA guidance states the predictive value of transaminase elevations and bilirubin elevations for drug induced liver disease may be different in patients with liver disease (i.e., HCV) or in patients on drugs that inhibit bilirubin glucuronidation. Therefore, the following analyses are complicated by the fact that indirect hyperbilirubinemia is a consequence of treatment with eltrombopag and 78% of the subjects in the study population had elevated ALT at baseline The results do not indicate eltrombopag as a cause for DILI in this study. 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. (Data Source: Table 8.2103 and Table 8.3163).

	Bilirubin Median total bilirubin levels at the antiviral Baseline were similar for the eltrombopag and placebo treatment groups, and the values were similar to baseline for the open label Phase (~22 μmol/L; Data Source Tables 8.2000 and 8.2003). Median total bilirubin levels increased during treatment with IP in the eltrombopag group in the DB treatment phase (Data Source Figure 18.2037). Values dropped sharply following the end of treatment. In the placebo group, median total bilirubin levels transiently increased during treatment with IP, but returned to baseline by Week 8. To better characterise these results, median indirect and median direct bilirubin levels were analysed for the DB phase. Median indirect and direct bilirubin levels at the antiviral baseline were similar to the values at baseline for the OL Phase (indirect: ~15 μmol/L; Data Source Figure 18.2032; direct: ~6 μmol/L; Data Source Figure 18.2034). Median indirect bilirubin levels increased in the eltrombopag group during IP treatment in a pattern similar to that observed for median total bilirubin. In contrast, median direct bilirubin levels remained unchanged during treatment with IP in the eltrombopag group, demonstrating that the increase in total bilirubin was due to indirect hyperbilirubinaemia. **Severe aplastic anaemia** In Study ELT112523 (ETB115AUS28T), the profile of eltrombopag in hepatobiliary AEs and laboratory parameters is consistent with the information described in the current labeling for the approved indications of eltrombopag. Hepatobiliary laboratory parameters reported during Study ELT112523 (ETB115AUS28T) were evaluated according to the FDA Guidance for Industry entitled "drug-induced liver injury (DILI): Premarketing Clinical Evaluation (Jul-2009)". As stated in this guidance, there are some limitations to this analysis in patients on drugs known to inhibit bilirubin glucuronidation. Two subjects in Study ELT112523 (ETB115AUS28T) (Subject [redacted] and Subject[redacted] had ALT or AST >3x the ULN concurrent with total bilirubin >1.5xULN. In both cases, bilirubin elevations were due to indirect bilirubin. Four subjects (Subjects [redacted] and [redacted]) had either elevated ALT >5xULN or elevated ALT and AST >5xULN. All four subjects had elevations in ALT and/or AST at study entry. One of the subjects (Subject [redacted]) was diagnosed with acute hepatitis B during the study. Six subjects had total bilirubin elevation >1.5xULN. In all subjects, bilirubin elevations were due to indirect bilirubin, with direct fractions ≤ 25%. Hepatobiliary AEs were reported for 16 subjects. Thirteen subjects had no changes to eltrombopag dosing; two subjects (Subjects [redacted] and [redacted]) had treatment interrupted due to elevated Liver function tests (LFTs) and one subject (Subject[redacted]) discontinued treatment due to acute hepatitis B. CTCAE grades were not documented in the National Institute of Health (NIH) source records for the majority of AEs reported during the study. For that reason, hepatobiliary laboratory elevations (ALT, AST, and bilirubin levels) were examined during the treatment period to determine the maximum toxicity grade for all subjects with a hepatobiliary AE reported. Eleven of the 16 subjects had a maximum laboratory toxicity grade of grade 1 (five subjects) or grade 2 (six subjects). Seven of the 11 subjects with grade 1 or grade 2 elevations had a history of elevated LFTs or entered the study with elevated LFTs.

Risk	Hepatotoxicity
	Four subjects had a laboratory toxicity grade of grade 3 ALT or AST reported during the study (Subjects [redacted] and [redacted]. One additional subject (Subject [redacted]) had CTCAE grade 3 AEs of elevated ALT and AST reported. All four subjects with grade 3 hepatobiliary laboratory values had prior history of transaminase elevations and/or elevations at baseline (Data Source: ELT112523 (ETB115AUS28T) CSR Section 7.6.1.2). As of the clinical cut-off date of 31-Mar-2014, no hepatobiliary serious adverse events (SAEs) had been reported in either Study ELT116826 (ETB115AUS18T) (Data Source: Study ELT116826 (ETB115AUS18T) Short Study Summary) or Study ELT116643 (ETB115AUS01T) (Data Source: ELT116643 (ETB115AUS01T) Short Study Summary).
Severity and nature of risk	**Adult and paediatric ITP** Reports of occurrence of ALT > 3x ULN were mostly mild (grade 1-2), reversible and not accompanied by clinically significant symptoms that would impair liver function. **HCV-associated thrombocytopenia** See above **Severe aplastic anaemia** See above
Background incidence/prevalence	**Adult ITP** Drug-induced liver injury (DILI) is a common cause of liver disease. It accounts for approximately one-half of the cases of acute liver failure and can present as diverse forms of acute and chronic liver disease. An estimated 1000 drugs have been implicated in causing liver disease on more than one occasion. A population-based case-control study using the UK-based General Practice Research Database to look for drug induced liver injury determined the crude incidence rate of nonfatal, clinically relevant, acute liver disease to be 2.4 (95%CI: 2.0, 2.8) per 100 000 person-years in the study population. **Paediatric ITP** Clinical trials and long term safety studies (over 5 years) for romiplostim, IVIg and anti-D in children reported no drug induced hepatotoxicities (Bussel et al 2014, Bussel et al 2011, Dash et al 2014, ElAlfy et al 2006, Marquinez-Alonso et al 2014, Mokhtar et al 2012, Rodeghiero et al 2013). In a retrospective analysis of the safety of romiplostim and eltrombopag in children treated outside of clinical trial settings, there were no reported hepatotoxicities associated with either drugs (Ramaswamy et al 2014). **HCV-associated thrombocytopenia** GSK sponsored a large observational data collection of HCV-associated thrombocytopenia in five European countries (UK, Germany, France, Spain and Italy). The study was a retrospective chart review collecting details about laboratory results, antiviral treatment, co-morbidities and concomitant medications for 911 HCV patients at 60 sites covering a period of 2.5 years (Jan-2005 to Jul-2007). (WEUKSTV1115 Study, 2010) The tables below provide information regarding three HBLAs: ALT, AST and Bilirubin among these patients, restricted to those who did not receive anti-viral treatment during the observational window and who had a platelet count of <75000/Gi/L. The platelet count is the lowest recorded during the observational window that also had a liver enzyme recorded within 6 month of the platelet reading.

<table>
<tr><th>Risk</th><th>Hepatotoxicity</th></tr>
<tr><td></td><td>
Prevalence of hepatobiliary laboratory abnormalities: ALT and AST
<table>
<tr><th colspan="3">Distribution of elevated ALT and AST among HCV patients with platelet count <75000/Gi/L</th></tr>
<tr><th></th><th>ALT (N=87)</th><th>AST (N=91)</th></tr>
<tr><td>>20xULN:</td><td>0%</td><td>0%</td></tr>
<tr><td>>10xULN</td><td>1%</td><td>1%</td></tr>
<tr><td>>5xULN:</td><td>8%</td><td>10%</td></tr>
<tr><td>>3xULN</td><td>18%</td><td>37%</td></tr>
<tr><td colspan="3">ULN for ALT was defined as 40 U/L
ULN for AST was defined as 35 U/L
Source: GlaxoSmithKline WEUKSTV1115 Study, 2010</td></tr>
</table>
Prevalence of hepatobiliary laboratory abnormalities: Bilirubin
<table>
<tr><th colspan="2">Distribution of elevated bilirubin among HCV patients with platelet count <75000/Gi/L</th></tr>
<tr><th></th><th><75,000 (N=90)</th></tr>
<tr><td>Bilirubin >2xULN</td><td>17%</td></tr>
<tr><td>Bilirubin >1.5xULN:</td><td>43%</td></tr>
<tr><td colspan="2">ULN for Bilirubin was defined as 1.0 mg/dl
Source: GlaxoSmithKline WEUKSTV1115 Study, 2010</td></tr>
</table>
</td></tr>
<tr><td>Risk groups or risk factors</td><td>
Adult ITP
A trend was observed towards a higher frequency of elevated aminotransferases/bilirubin in Asian subjects compared to Caucasians, although it did not reach statistical significance in any study.
Paediatric ITP
The incidence of ALT and AST increases was reported in a higher proportion of East Asian subjects. The HBLAs resolved either while still on treatment or after discontinuation of study treatment.
HCV-associated thrombocytopenia
Overall, there was no difference in aminotransferase levels between eltrombopag and placebo treated subjects. 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.
</td></tr>
<tr><td>Potential mechanisms</td><td>
Adult and paediatric ITP
The observed elevations of aminotransferases do not have a comprehensive explanation at this time.
Pharmacogenetic analyses have identified the UGT1A1*28 polymorphism to be associated with increased bilirubin while receiving eltrombopag. This same association has been described for other drugs. Patients with this polymorphism are more likely to experience hyperbilirubinemia, which is not a clinically relevant safety risk, and thus no screening is necessary.
</td></tr>
</table>

Risk	Hepatotoxicity
	HCV-associated thrombocytopenia Eltrombopag is known to inhibit UGT1A1, the enzyme responsible for glucuronidation of bilirubin in humans. Inhibition of UGT1A1 can cause elevation of indirect bilirubin. In addition, eltrombopag is also an inhibitor of OATP1B1, which is one of the hepatic transporters for bilirubin. Therefore, eltrombopag-mediated inhibition of OATP1B1 may additionally contribute to an elevation of indirect bilirubin in subjects treated with the drug. Furthermore, hyperbilirubinemia is also an expected finding in subjects treated with ribavirin, which induces hemolytic anemia in up to 40% of HCV patients receiving antiviral therapy. Of note, the exposure to ribavirin was greater in eltrombopag-treated subjects than in placebo-treated subjects in the ENABLE studies. **Severe aplastic anaemia** See above
Preventability	**Adult and Paediatric ITP** In the SmPC, a warning regarding the potential for abnormal liver function is included in Section 4.4 (Special warnings and precautions for use). Also, increased ALT, AST, hyperbilirubinaemia, hepatic function abnormal are included in Section 4.8 (Undesirable effects). The analyses performed show that treatment with eltrombopag can be associated with abnormal liver function. **HCV-associated thrombocytopenia** In the SmPC, a warning regarding the potential for HBLAs (ALT, AST, bilirubin,) is included in Section 4.4 (Special warnings and precautions for use). Also, preferred terms related to hepatobiliary disorders are included in Section 4.8 (Undesirable effects). **Severe aplastic anaemia** In the SmPC Section 4.8 (Undesirable effects), transaminases increased is listed as very common hepatobiliary disorders, while blood bilirubin increased (hyperbilirubinemia) and jaundice are listed as common hepatobiliary disorders.
Impact on individual patient	None known
Potential public health impact of safety concern	Potential public health impact is considered to be low.
Impact on the benefit-risk balance of the product	Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a moderate impact on the benefit-risk balance in this indication.
Evidence source	Supporting data are referenced in the RAISE, TRA100773B, TRA100773A, EXTEND and REPEAT Clinical Study Reports (see m5.3.5.1 and m5.3.5.2, respectively) Supporting data are referenced in the PETIT and PETIT2, Clinical Study Reports (m5.3.5.1 and m5.3.5.2, respectively), Summary of Clinical Safety (SCS) (m2.7.4) and Integrated Summary of Safety (m5.3.5.3). Integrated Safety and Summary (m5.3.3.3). Study [GlaxoSmithKline Document Number XM2008/00042/00] - East Asian Ethnicity and Eltrombopag Pharmacokinetics, Pharmacodynamics, Efficacy and Safety

Risk	Hepatotoxicity
	Study [GlaxoSmithKline Document Number RM2008/00112/00] - Genetic Investigation of Association with Elevations in Total Bilirubin Observed in Subjects with Chronic Idiopathic Thrombocytopenic Purpura Exposed to Eltrombopag Supporting data are referenced in the TPL102357, TPL103922 (ENABLE 1) and TPL108390 (ENABLE 2), Clinical Study Reports (m5.3.5.1) and Integrated Summary of Safety. Supporting data are referenced in the Clinical Study Report for ELT112523 (ETB115AUS28T) and the Short Study Summaries for the Study ELT116826 (ETB115AUS18T) and Study ELT116643 (ETB115AUS01T), PSUR, Clinical Overview.
MedDRA terms	SMQ (broad): Drug related hepatic disorders - comprehensive search MedDRA v.20.0

Table 8-2 Important Identified risk: Thromboembolic events

Risk	Thromboembolic events
Frequency with 95% CI	**Adult ITP** A total of 20 subjects across the ITP studies experienced thromboembolic events at the time of reporting with a frequency of 4.5%; this is consistent with published literature for patients with chronic ITP. No placebo treated subject experienced such an event. Comparative exposure 584 patient-years for eltrombopag and 35 patient-years for placebo.

Frequency of subjects with TEE across the eltrombopag ITP studies

Study	Treatment (n)		TEE (n, subjects)	
	Placebo	Eltrombopag	Placebo	Eltrombopag
TRA100773A	29	88	0	1 (venous)
TRA100773B	38	76	0	0
TRA102537/RAISE	62	135	0	3 (venous)
TRA108057/REPEAT (Open label)	NA	66	NA	0
TRA105325/EXTEND (Open label)	NA	302	NA	22 (6 venous, 13 arterial, 3 both)
TRA108109 (Japanese) [b]	8	23	0	1 (arterial)

NA: Not applicable.
a=TRA108109 had a 7-week randomized, double-blind period, followed by an open-label treatment period. All subjects were treated with eltrombopag for a total of 26 weeks.

Incidence rate (95% CI) of TEEs (on-therapy plus 30 days) in eltrombopag ITP studies

Study	Placebo	Eltrombopag

Risk	Thromboembolic events

TRA100773A, TRA100773B, TRA102537/RAISE	-	3.78/100PYs (1.03, 9.69)
TRA108057/REPEAT (Open label)	NA	-
TRA105325/EXTEND (Ongoing, open label)	NA	3.17/100PYs (1.81, 5.15)
Pooled eltrombopag exposed [a]	NA	3.14/100PYs (1.92, 4.85)
TRA108109 (Japanese) [b]	-	8.3/100PYs (0.2, 46.1)

NA: Not applicable.

a=Includes TRA100773A, TRA100773B, TRA102537, TRA108057, and TRA105325. One subject in TRA102537 experienced 2 DVTs, 222 and 337 days post-therapy.

b=TRA108109 had a 7-week randomized, double-blind period, followed by an open-label treatment period. All subjects were treated with eltrombopag for a total of 26 weeks.

TEE Frequency in the US REMS Program

From Dec-2008 to Jan-2012 US Risk Evaluation and Mitigation Strategies (REMS) program (i.e. PROMACTA CARES), a total of 2855 patients had ITP alone or in conjunction with other conditions listed as the diagnosis on the baseline enrollment form. Based on pharmacy authorization data, the cumulative eltrombopag exposure of these patients was 1626 patient-years. Given that a total of 56 of the 2855 patients experienced a TEE, the estimated incidence rate for TEEs in this ITP population is 3.44 per 100 patient years. This incidence rate is similar to the rate seen in the eltrombopag ITP studies as displayed in the table above (incidence rate (95% CI) of TEEs (on-therapy plus 30 days) in eltrombopag ITP Studies). The table below displays the overall frequency of TEE in these 2855 patients sub-classified according to age, sex, length of ITP disease, splenectomy, major co-morbidities, prior ITP medications and risk factors for TEEs.

Incidence rates (95% CI) of thromboembolic events from PROMACTA CARES

	Population	Number at risk	Cumulative patient-years exposure for number at risk[1]	Number with Event	Incidence rate (95% CI) per 100 patient years
Overall	Total	2855	1626	56	3.44 (2.602, 4.472)
Age at enrolment	Age:<18 yrs	55	36	0	-
	Age: 18-49yrs	756	402	14	3.48 (1.904, 5.843)

Risk	Thromboembolic events					
		Age: 50-64yrs	812	485	12	2.47 (1.278, 4.322)
		Age: 65-74yrs	515	311	12	3.86 (1.994, 6.740)
		Age>=75yrs	596	341	13	3.81 (2.030, 6.519)
		Age: Unknown	121	52[1]	5	9.62 (3.122, 22.439)
	Gender	Gender: Male	1297	736	21	2.85 (1.766, 4.362)
		Gender: Female	1516	859	35	4.07 (2.838, 5.667)
		Gender: Not specified	42	31	0	-
	Length of ITP at enrolment	Newly Diagnosed (<3m)	504	220	10	4.55 (2.180, 8.359)
		Persistent (3-12m)	486	258	10	3.88 (1.859, 7.128)
		Chronic (>12m)	1308	880	26	2.95 (1.930, 4.329)
		Unknown	557	268	10	3.73 (1.789, 6.862)
	Splenectomy	Splenectomy: Yes	785	465	23	4.95 (3.135, 7.422)
		No	1794	1023	26	2.54 (1.660, 3.724)
		Unknown	276	138	7	5.07 (2.039, 10.451)
	Number Prior ITP Medications	0	225	95	6	6.32 (2.318, 13.747)
		1	525	294	5	1.70 (0.552, 3.969)
		2	793	436	11	2.52 (1.259, 4.514)
		3	700	399	14	3.51 (1.918, 5.887)
		4	343	207	10	4.83 (2.317, 8.884)
		>4	269	195	10	5.13 (2.459, 9.431)
	Risk Factors for TEE	Present	303	171	12	7.02 (3.626, 12.258)
		Absent	2117	1217	29	2.38 (1.596, 3.422)
		Unknown	435	238	15	6.30 (3.527, 10.395)
	Previous TEE	Yes	255	142	14	9.86 (5.390, 16.542)

Risk	Thromboembolic events

	No	2211	1266	29	2.29(1.534, 3.290)
	Unknown	389	218	13	5.96 (3.175, 10.197)
Major comorbiditie s	Present	388	198	15	7.58 (4.240, 12.495)
	Absent/Unkn own	2467	1428	41	2.87 (2.060, 3.895)

[1]For some categories, cumulative patient-years exposure for number at risk may not add up to 1626 patient-years due to rounding

Paediatric ITP

No TEEs have been reported during treatment in PETIT or PETIT2.

Summary of subjects who experienced TEEs in the ELEVATE study

Eight subjects experienced 10 TEEs: 2 subjects (3 events) in the placebo group and 6 subjects (7 events) in the eltrombopag group (OR [95% CI] = 3.04 [0.62, 14.82]). Nine of the 10 events were of the portal venous system, including all the events in the eltrombopag-treated subjects. Seven of the events were considered by the Investigator to be related to investigational product and were of grade 3/4 severity.

Five of the six eltrombopag-treated subjects who had a TEE, experienced the event at the maximum platelet count (>200000 /Gi/L) within two weeks after completing eltrombopag dosing. The median time (range) to onset since the first dose of eltrombopag was 21.5 days (15-53 days) and the median time (range) since the last dose was 8.5 days (1-38 days). One of the 2 placebo-treated subjects and 4 of the 6 subjects on eltrombopag either had a malignancy diagnosed prior to study entry or were diagnosed with a suspected malignancy during the study.

Severe aplastic anaemia

No TEEs have been reported during treatment in Study ELT112523 (ETB115AUS28T), Study ELT116826 (ETB115AUS18T), or in Study ELT116643 (ETB115AUS01T).

One (Subject [redacted] out of 43 subjects in ELT112523 (ETB115AUS28T) had an unrelated SAE of deep vein thrombosis which was reported 14 months after discontinuation of treatment with eltrombopag.

Seriousness/outcomes	**Adult ITP** No thromboembolic AEs were reported in the REPEAT study. In the EXTEND open label study (n=302), 22 patients experienced 28 TEE (6 patients had venous events, 13 had arterial events, and 3 had both), including 3 events which occurred two, three and 23 days after end of treatment. The majority of the events were serious (19), and grade 2 (12); 5 events were grade 1, 9 were grade 3 and 2 were grade 4. Twenty-four of the 28 events resolved, 3 were unresolved at the end of study, and one (grade 2 DVT) was reported having a fatal outcome. In the Japanese ITP study TRA108109, one case of suspected transient ischemic attack has been reported in a subject with a medical history

<table>
<tr><td>Risk</td><td>Thromboembolic events</td></tr>
<tr><td></td><td>significant for osteoporosis and hyperlipidemia and a platelet count of 120 Gi/L at the time of the event. Study medication was discontinued and the event resolved.

Paediatric ITP
None reported.

Thromboembolic events in subjects with chronic liver disease
Thromboembolic events in subjects with chronic liver disease - (ELEVATE study)
<table>
<tr><th rowspan="2">Subject</th><th rowspan="2">Event Verbatim Term</th><th colspan="2">Platelet Count (Gi/L)</th><th rowspan="2">Time to Onset/Since Last Dose (Days)</th><th rowspan="2">Outcome</th><th rowspan="2">Malignancy</th></tr>
<tr><th>Baseline</th><th>At Event</th></tr>
<tr><td colspan="7">Placebo group</td></tr>
<tr><td>[redacted]</td><td>Non occlusive mesenteric and portal thrombosis</td><td>32</td><td>Unknown</td><td>142/128; 276/272</td><td>Not Resolved</td><td>None</td></tr>
<tr><td>[redacted]</td><td>Acute myocardial infarction</td><td>8</td><td>83</td><td>33/20</td><td>Not resolved</td><td>Rectal adeno-carcinoma</td></tr>
<tr><td colspan="7">Eltrombopag group</td></tr>
<tr><td>[redacted]</td><td>Portal vein thrombosis</td><td>34</td><td>33</td><td>53/38</td><td>Not Resolved</td><td>None</td></tr>
<tr><td>[redacted]</td><td>Spleno-portal vein thrombosis</td><td>48</td><td>241</td><td>27/14</td><td>Resolved</td><td>Hepatocellular carcinoma</td></tr>
<tr><td>[redacted]</td><td>Thrombosis mesenteric vessel/mesenteric thrombosis</td><td>37</td><td>289</td><td>22/9</td><td>Resolved</td><td>Hepatocellular carcinoma</td></tr>
<tr><td rowspan="2">[redacted]</td><td>Portal vein thrombosis</td><td rowspan="2">47</td><td rowspan="2">417</td><td rowspan="2">15/1</td><td rowspan="2">Resolved</td><td rowspan="2">Brain tumour</td></tr>
<tr><td>Superior mesenteric vein thrombosis</td></tr>
<tr><td>[redacted]</td><td>Upper mesenteric vein thrombosis</td><td>37</td><td>232</td><td>21/8</td><td>Not Resolved</td><td>Suspected lymphoma</td></tr>
<tr><td>[redacted]</td><td>Portal vein thrombosis</td><td>26</td><td>288</td><td>19/5</td><td>Not Resolved</td><td>None</td></tr>
<tr><td colspan="7">TEE event in Subject [redacted] was reported to GSK post study suspension/closure.</td></tr>
</table>
</td></tr>
<tr><td>Severity and nature of risk</td><td>See above</td></tr>
</table>

Risk	Thromboembolic events
Background incidence/prevalence	**Adult ITP** Data in the literature indicate that subjects with ITP have a higher risk of developing thromboembolic complications compared to subjects without ITP; (Bennett et al 2008b). The reported frequency in the eltrombopag program of 3% is in accordance with the literature for the ITP population, and with the observed incidence of thromboembolic events in the published GSK sponsored epidemiology study, which is 6.9% (Bennett et al 2008b). Additionally, the frequency of thromboembolic events was examined in the ITP population enrolled in eltrombopag clinical trials, comparing the frequency of events prior to and after receiving the first dose of study medication. Prior to initiation of study medication (including placebo or eltrombopag), 16/493 (3.2%) subjects experienced a total of 19 thromboembolic events. Additionally, in GSK supported Study (UK ITP Adult Registry), a sub analysis revealed that the baseline prevalence of TEs in ITP patients was as the following: nineteen patients (5.8%; 95% CI, 3.5-8.9%) had experienced a prior TE, with 16 (4.9%; 95% CI, 2.8%-7.8%) having suffered an arterial TE and 4 (1.2%; 95% CI, 0.3%-3.1%) a venous TE. Over a mean follow-up time of 7.2 ± 7.0 years, 10 (3.25% [95% CI, 1.27%-5.23%]) first arterial, 4 (1.30% [95% CI, 0.03%-6.47%]) first venous, and 13 (4.22%; [95% CI, 1.97%-6.50%]) first combined incident TEs were recorded. The IR of combined TEs was 60.25 (95% CI, 34.99-103.77) per 10000 patient-years. Corresponding rates for arterial and venous TEs were 45.39 (95% CI, 24.42-84.36) and 17.81 (95% CI, 6.68-47.45) per 10000 patient-years, respectively. **Paediatric ITP** In a retrospective analysis of the safety of romiplostim and eltrombopag in children treated outside of clinical trial settings, one patient on eltrombopag experienced a provoked deep-vein thrombosis at the site of ankle fracture) out of 12 children treated for 23-53 months, and no children treated with romiplostim for 6-44 months experienced a TEE (Ramaswamy et al 2014). Retrospective analysis of 13 clinical trials (n=653) to assess the long term (5 years) effects of romiplostim in adults and children reported overall incidences of myocardial infarction as 0.5per 100 patient years, deep vein thrombosis as 0.2 per 100 patient years, pulmonary embolism as 0.2 per 100 patient years (Rodeghiero et al 2013). Statistics for adult's vs paediatrics were not reported across the pooled clinical trials. Long term studies of IVIg and anti D in children with chronic ITP reported no TEE (ElAlfy et al 2006).
Risk groups or risk factors	**Adult ITP** Every subject who experienced a thromboembolic event had risk factors that increased the risk of such complications, including: use of corticosteroids (six subjects), hospitalization without prophylactic anticoagulation prior to the event (four subjects), and treatment with IVIg 5-8 days before the event (three subjects). Thorough analysis of the available information has not revealed a common factor that explains a majority of the cases. As of the cut-off date for this report, 12 of 20 subjects with TEE had platelet counts below the normal range at the time of the event, and six out of the 11 had a count below 50 Gi/L. Platelet counts proximal to the event (the most proximal count) ranged between 14 Gi/L and 482 Gi/L. Of 84 subjects across the program who experienced platelet counts >400 Gi/L, six (8%) experienced a thromboembolic event, but only two out of six had the event at their

Risk	Thromboembolic events
	maximum platelet count achieved on study. Data from the eltrombopag trials show no evidence to support the hypothesis that increased platelet counts constitute a risk factor for thromboembolic events. **Paediatric ITP** Incidence of thrombosis in paediatrics is associated with a clinical prothrombotic risk factor (e.g., venous catheters, exogenous estrogen, decreased mobility, obesity, oral contraception use) and/or an underlying hypercoagulable state (e.g., antiphospholipid antibodies, acquired or congenital anticoagulant deficiencies, factor V Leiden, or prothrombin G20210A mutations) (Goldenberg and Bernard 2010, Goldenberg 2005). In adolescents, patient characteristics associated with acute myocardial infarction include substance abuse, tobacco use, and male sex (Mahle et al 2007). **Chronic liver disease** **Baseline and other potential predictors of TEEs in ELEVATE study** To further understand the patient population at risk of TEE in the ELEVATE study, eltrombopag-treated subjects who experienced TE were compared to those who did not. The median age of eltrombopag-treated subjects who reported a TE (60.5 years) was higher than the subjects who did not (51 years). All of the eltrombopag treated subjects who reported a TEs were male (6/6). Sixty-six percent of the non-TE populations were male. Eltrombopag-treated subjects both with and without a TE were predominantly White (TE: 59%; non TE: 75%). TE events occurred in Child Pugh A and B eltrombopag-treated subjects, with no TE events observed in any Child Pugh C subject. The non-TE eltrombopag-treated population had (11, 8%) Child Pugh C subjects. Eltrombopag treated subjects with a TE had a lower median (range) MELD score (10 [7-18]) than those with no TE (12 [6-23]). There was a significant association between platelets counts ≥ 200000/µl and the occurrence of TE. Even though all subjects experiencing TEs had risk factors for TEs, no specific patient risk factor has been identified that allows a differentiation between those subjects who experienced a TE and those who did not. However, a significant association between maximum post-baseline platelet count and TE was identified. The TEE findings in the ELEVATE study are unlikely to be relevant to the ITP patient population due to the rare overlap of the two diseases and the distinct differences in the phenotype of TEEs observed in the two populations. The data presented do not suggest that eltrombopag increases the risk of TEEs associated with hemostatic challenges in patients with ITP. However, it is recognised that a risk may exist for a very small proportion of patients with ITP that subsequently develop CLD.
Potential mechanisms	**Adult ITP** Based on the data in the literature, epidemiological findings, and comparison to pre-treatment history, the data seem to indicate that patients with ITP may be pre-disposed to TEE. A relationship between TEE and platelet count has not been established. **Paediatric ITP**

Risk	Thromboembolic events
	No TEEs were reported.
Preventability	Patients with known risk factors for TEE should use eltrombopag only after careful benefit/risk consideration and under close clinical monitoring. Based on the current data, there is no evidence that contraindicates initiation or continuation of prophylactic anticoagulation or anti-aggregation, if clinically indicated. Risk Minimisation will focus on informing prescribers and patients of the risks through the SmPC and package leaflet. **Adult ITP** 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 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 hepatic impairment, the starting dose must be 25 mg once daily. A warning is included in Section 4.4 (Special warnings and precautions) of the SmPC stating that thromboembolic events may occur in patients with ITP and eltrombopag should be used with caution in patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, etc). Thromboembolic events are included in Section 4.8 (Undesirable effects). **Paediatric ITP** See above **Chronic Liver Disease** 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. <u>Suspension of ELEVATE trial (Chronic Liver Disease)</u> ELEVATE, a Phase III study, was designed to determine the efficacy and safety of eltrombopag in reducing the proportion of thrombocytopenic subjects with CLD who require a platelet transfusion to undergo a planned invasive procedure. Subjects were randomized to receive 75 mg QD of eltrombopag or placebo for 14 days. On 08-Sep-2009, GSK received a recommendation from the ELEVATE independent data monitoring committee (IDMC) to suspend recruitment and dosing in ELEVATE due to an increased incidence of thromboembolic events (TEE) in the eltrombopag treatment arm compared to placebo. The IDMC recommendation was specific only to the target patient population in ELEVATE, and did not extend to other indications or patient populations under study. On 11-Sep-2009, GSK suspended enrolment and dosing in the ELEVATE study and a decision was made to terminate the study on 03-Nov-2009 to allow a full analysis of the safety and efficacy data to take place. This finding has been broadly communicated to investigators in eltrombopag clinical trials and to all relevant regulatory authorities. **Severe Aplastic Anaemia** See above.
Impact on individual patient	None known

<table>
<tr><th>Risk</th><th>Thromboembolic events</th></tr>
<tr><td>Potential public health impact of safety concern</td><td>
Adult and Paediatric ITP
Potential public health impact is considered to be low for the ITP population.

Chronic liver indication
For the chronic liver indication, the potential public impact is currently under evaluation.

HCV-associated thrombocytopenia
Potential public health impact is considered to be low for the HCV population.
Number needed to harm (NNH)

<table>
<tr><th></th><th>Placebo + IFN/RBN (N=484)</th><th>Eltrombopag + IFN/RBN (N=955)</th><th>Total (N=1439)</th><th>NNH</th><th>95% CI for NNH</th></tr>
<tr><td>Thromboembolic Adverse Event</td><td>16 (3%)</td><td>62 (6%)</td><td>78 (5%)</td><td>31</td><td>18.46, 104.71</td></tr>
</table>
Table 8.9022
Number needed to harm (NNH)
<table>
<tr><th></th><th>Placebo + IFN/RBN (N=484)</th><th>Eltrombopag + IFN/RBN (N=955)</th><th>Total (N=1439)</th><th>NNH</th><th>95% CI for NNH</th></tr>
<tr><td>Portal Vein Thrombosis</td><td>2 (<1%)</td><td>15 (2%)</td><td>17 (1%)</td><td>86</td><td>46.92, 544.81</td></tr>
</table>
Table 8.9106

Severe aplastic anaemia
Potential public health impact is considered to be low for the SAA population.
</td></tr>
<tr><td>Impact on the benefit-risk balance of the product</td><td>Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a moderate impact on the benefit-risk balance in this indication.</td></tr>
<tr><td>Evidence source</td><td>Supporting data are referenced in the RAISE, TRA100773B, TRA100773A, EXTEND and REPEAT Clinical Study Reports (see m5.3.5.1 and m5.3.5.2, respectively).
Supporting data are referenced in the PETIT and PETIT2, Clinical Study Reports (m5.3.5.1 and m5.3.5.2, respectively), Summary of Clinical Safety (m2.7.4) and Integrated Summary of Safety (m5.3.5.3).
Supporting data are referenced in the TPL102357, TPL103922 (ENABLE 1) and TPL108390 (ENABLE 2), Clinical Study Reports (see m5.3.5.1) and Integrated Summary of Safety.
Supporting data are referenced in the Clinical Study Report for ELT112523 (ETB115AUS28T) Study and the Short Study Summaries for the Study ELT116826 (ETB115AUS18T) and Study ELT116643 (ETB115AUS01T).
PSUR, Clinical Study Report for HCV-Target (ETB115A2408)</td></tr>
<tr><td>MedDRA terms</td><td>SMQ (broad): Embolic and thrombotic events - MedDRA version 20.0</td></tr>
</table>

Table 8-3 Important Identified risk: Hepatic decompensation (Chronic HCV associated thrombocytopenia only)

<table>
<tr><th>Risk</th><th>Hepatic decompensation</th></tr>
<tr><td>Frequency with 95% CI</td><td>
Events of hepatic decompensation are presented, as determined by the external adjudication panel, and as requested, by trial and treatment group, during the on-treatment plus 6-month follow-up period.
The external adjudication panel assessment showed a higher proportion of subjects experienced an event suggestive of hepatic decompensation in the eltrombopag treatment group compared to the placebo group (pooled study results for any hepatic decompensation event: eltrombopag 11%, placebo 6%, results for the individual studies are shown in the table below). The difference between treatment groups was mainly due to a higher frequency of ascites and hepatic encephalopathy events in the eltrombopag arm compared to the placebo arm (pooled study results: ascites, eltrombopag 7%, placebo 4%; encephalopathy, eltrombopag 3%, placebo 2%). Importantly, both ascites and hepatic encephalopathy are conditions for which effective medical therapy exist.

Externally adjudicated decompensation events during double blind (safety DB population)
<table>
<tr><th rowspan="3"></th><th colspan="4">Number of Subjects (%)</th></tr>
<tr><th colspan="2">ENABLE 1</th><th colspan="2">ENABLE 2</th></tr>
<tr><th>Placebo N=232</th><th>Eltrombopag N=449</th><th>Placebo N=252</th><th>Eltrombopag N=506</th></tr>
<tr><td>Any Event</td><td>18 (8)</td><td>60 (13)</td><td>13 (5)</td><td>48 (9)</td></tr>
<tr><td>Ascites</td><td>10 (4)</td><td>36 (8)</td><td>7 (3)</td><td>32 (6)</td></tr>
<tr><td>Hepatic encephalopathy</td><td>3 (1)</td><td>16 (4)</td><td>2 (<1)</td><td>14 (3)</td></tr>
<tr><td>Variceal haemorrhage</td><td>3 (1)</td><td>12 (3)</td><td>4 (2)</td><td>4 (<1)</td></tr>
<tr><td>Spontaneous bacterial peritonitis</td><td>3 (1)</td><td>7 (2)</td><td>0</td><td>3 (<1)</td></tr>
<tr><td>Other decompensation events[a]</td><td>1 (<1)</td><td>13 (3)</td><td>0</td><td>4 (<1)</td></tr>
</table>
Data Source: TPL103922 Table 8.9019;TPL108390 Table 8.9019
Other decompensation events included hepatic failure, hepatorenal syndrome, hepatitis alcoholic, hepatic cirrhosis, and hepatic function abnormal

Similar results were seen when events suggestive of hepatic decompensation included death and HCC and follow-up was 30 days.
Events suggestive of hepatic decompensation on-treatment plus 30 days follow-up during the DB Phase (external-adjudication) (safety DB population)
<table>
<tr><th></th><th>Number of Subjects (%)</th></tr>
</table>
</td></tr>
</table>

Risk	Hepatic decompensation

	Placebo + IFN/RBN (N=484)	Eltrombopag+ IFN/RBN (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)

Data Source: Table 8.1810, Table 8.9018, and Table 8.9023

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

In the ENABLE TEE follow-up study (WWE116951; An Observational Follow-up Study of Patients who Experienced Thromboembolic Events in the ENABLE studies), information was collected through medical record review of the five-year post-event period.

Twenty-two of the 45 eligible patients with TEE in the ENABLE trials were enrolled in this study, where 19 (86%) had been randomised to eltrombopag and three to placebo. In the overall ENABLE trial population, the ratio of patients randomised to eltrombopag to placebo was 2:1.

Among 21 patients (one patient was lost to follow-up), 19 patients experienced hepatic decompensation events, 16 patients in the eltrombopag group and all three patients in the placebo group. The specific type of hepatic decompensation event was not recorded for one eltrombopag patient; thus, this patient was not included in the analysis of hepatic decompensation events. Thirteen patients overall (11 eltrombopag and 2 placebo) had 1-2 hepatic decompensation events, three patients (all eltrombopag) had 3-4 decompensation events, and two patients (1 eltrombopag and 1 placebo) had 5 or more decompensation events.

Event types comprising hepatic decompensation were not mutually exclusive, and the numbers of these events were as follows. Among the 15 patients experiencing a specific type of hepatic decompensation event in the eltrombopag arm, there were a total of 32 events (10 hepatic encephalopathy events, 5 ascites, 4 variceal haemorrhages, 3 cases of sustained increase in CTP score, 2 hepatocellular carcinomas, and 8 deaths. Among the three patients who experienced a hepatic decompensation event in the placebo group there were a total of ten events (3 cases of hepatic encephalopathy, 3 ascites, 1 variceal haemorrhage, 1 spontaneous bacterial peritonitis, 1 hepatocellular carcinoma, and 1 death).

In summary, eltrombopag patients were less likely to experience any of the other liver disease-related outcomes (hepatic decompensation,

<table>
<tr><td>Risk</td><td>Hepatic decompensation</td></tr>
<tr><td></td><td>hospitalisation, receipt of liver transplantation, liver disease-related mortality, and all-cause mortality) than placebo patients. However, the interpretability of these results is limited by the small number of patients enrolled (19 eltrombopag and 3 placebo) as well as the number of patients with the clinical outcomes of interest, which resulted in wide confidence intervals around the HRs.

Study ETB115A2408 was an observational study in HCV patients treated with eltrombopag in combination with interferon, ribavirin and a direct-acting antiviral (triple therapy). Overall, the incidence of hepatic decompensation was low. After enrollment in the study, 4 out of 61 patients (6.5%) developed hepatic decompensation. One of the 4 patients who developed decompensation on study, had prior evidence of decompensation.

A total of seven events corresponding to Hepatic Decompensation were reported in these 4 patients; Hepatic encephalopathy (n=5) was the most frequently reported decompensating event followed by ascites (n=2). One patient each discontinued the study due to anasarca, ascites, hepatic encephalopathy, cerebral hemorrhage and conjunctival hemorrhage. Further information on whether these events were in patients with decompensation or whether these events were suspected due to anti -virals or eltrombopag is not available. These and other events could occur in this patient population or could be associated with therapies used.
No patient had a decompensation event beyond Day 100 (days on antiviral therapy in conjunction with eltrombopag). No deaths related to decompensation events were reported in the study.</td></tr>
<tr><td>Seriousness/outcomes</td><td>HCV-associated thrombocytopenia
A comprehensive analysis of hepatobiliary events and assessments is indicated because eltrombopag is metabolised in the liver. Equally important, in these studies subjects were treated with peginterferon, which is known to have hepatobiliary side effects, including hepatic decompensation in patients with cirrhosis.
Relevant related AEs were collected to facilitate clinical review and to identify patterns of events. A blinded independent review of these events was conducted by hepatology experts external to the company.
During the DB Phase on-treatment plus 30 day follow-up period, a higher proportion of eltrombopag subjects reported drug-related events suggestive of hepatic decompensation compared with placebo subjects (Table 43, ISS). The proportion of events that were fatal and led to IP discontinuation were lower for eltrombopag compared with placebo subjects. The majority of AEs resolved in both treatment groups.
Characteristics of events suggestive of hepatic decompensation on-treatment plus 30 days follow-up (safety DB population)
<table>
<tr><th></th><th>Placebo + IFN/RBN (N=484)</th><th>Eltrombopag + IFN/RBN (N=955)</th></tr>
<tr><td>Number (%) of subjects with events</td><td>35 (7)</td><td>125 (13)</td></tr>
<tr><td>Event characteristics by subject, n (%)</td><td></td><td></td></tr>
<tr><td>Serious</td><td>31 (57)</td><td>115 (58)</td></tr>
<tr><td>Drug-related</td><td>8 (15)</td><td>52 (26)</td></tr>
<tr><td>Leading to withdrawal from study</td><td>15 (28)</td><td>40 (20)</td></tr>
<tr><td>DAIDS grade 3/grade 4</td><td>28 (52)</td><td>109 (55)</td></tr>
</table></td></tr>
</table>

Risk	Hepatic decompensation

Fatal	15 (28)	44 (22)
Number of events	54	198
Outcome, n (%)		
Recovered/resolved	22 (41)	105 (53)
Recovering/resolving	0	4 (2)
Not recovered/not resolved	13 (24)	33 (17)
Recovered/resolved with sequelae	4 (7)	12 (6)
Fatal	15 (28)	44 (22)

Data Source: Table 8.1314

Analysis of the DB exposure was conducted to determine if there was a relationship between the dose of eltrombopag and events suggestive of hepatic decompensation. Exposure to DB treatment was calculated for subjects with and without events. For subjects with events, DB exposure was calculated up to the time of the event. The results do not show a clear relationship between DB exposure and events suggestive of hepatic decompensation (Table 44, ISS). In addition, in these studies subjects were treated with peginterferon, which is known to have hepatobiliary side effects, including hepatic decompensation in patients with cirrhosis.

Of the four patients with events of hepatic decompensation in the HCV-Target study (ETB115A2408), two patients discontinued prematurely due to ascites and lack of efficacy respectively, one patient was lost to follow-up and the remaining patient completed the study treatment. No deaths related to decompensation events were reported in the study.

Severity and nature of risk	See above
Background incidence/prevalence	Development of hepatic decompensation including HCC and death among patients with cirrhosis is increased in patients with lower platelets. In a study by (Dienstag et al 2011) more than 1000 HCV patients with advanced fibrosis or cirrhosis were followed for eight years. The annualized incidence of HCC, decompensation (variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy) and death was 3.6%, 6.0% and 7.5%, respectively, among HCV patients with <100000/Gi/L. The same rates were found to be 1.0%, 2.0% and 2.4% among patients with platelet count between 150000 and 200000/Gi/L. Annual incidence: Death (all death or liver transplantation) 7.3% Any decompensation event (excluding death) 7.9%
Risk groups or risk factors	Patients with more advanced liver impairment are at higher risk for hepatic decompensation during antiviral therapy with interferon/ribavirin. The model for end-stage liver disease (MELD) score is a function of serum bilirubin, serum creatinine, and the INR for prothrombin time. Patients with a MELD score ≥10 have been shown to have poorer outcomes (Kamath et al 2001). Serum albumin is a measure of hepatic synthetic function and low albumin is known to be an independent predictor of hepatic decompensation and death (Ghany et al 2009). In the ENABLE studies, a baseline MELD score ≥ 10 or albumin ≤35 g/L were associated with a 2-3-fold higher rate of progression to decompensated liver

<table>
<tr><td>Risk</td><td>Hepatic decompensation</td></tr>
<tr><td></td><td>disease in comparison to a baseline MELD score <10 or albumin >35 g/L (see tables below). This pattern was observed for both the placebo and the eltrombopag treatment groups. For the baseline MELD score <10 and albumin >35 g/L subgroups, the safety profile was similar between the placebo and eltrombopag treatment groups. These findings indicate again that the degree of liver impairment at baseline is a major predictive factor for the safety and tolerability of the higher intensity peginterferon and ribavirin treatment that is facilitated by eltrombopag.
Adverse events of special interest by baseline MELD score (safety DB population)
<table>
<tr><td></td><td colspan="4">Number of subjects (%)</td></tr>
<tr><td></td><td colspan="2">Grouping: baseline MELD score <10</td><td colspan="2">Grouping: baseline MELD score ≥10</td></tr>
<tr><td></td><td>Placebo + IFN/RBN (N=264)</td><td>Eltrombopag + IFN/RBN (N=541)</td><td>Placebo+ IFN/RBN (N=213)</td><td>Eltrombopag + IFN/RBN (N=400)</td></tr>
<tr><td>Events suggestive of hepatic decompensation[a]</td><td>11 (4)</td><td>38 (7)</td><td>24 (11)</td><td>85 (21)</td></tr>
<tr><td colspan="5">Data Source: ISS Section 6.1.2
On-treatment plus 30 days follow-up</td></tr>
</table>
Adverse events of special interest by baseline albumin (safety DB population)
<table>
<tr><td></td><td colspan="4">Number of subjects (%)</td></tr>
<tr><td></td><td colspan="2">Grouping: baseline albumin ≤35 g/L</td><td colspan="2">Grouping: baseline albumin >35 g/L</td></tr>
<tr><td></td><td>Placebo + IFN/RBN (N=139)</td><td>Eltrombopag + IFN/RBN (N=275)</td><td>Placebo + IFN/RBN (N=345)</td><td>Eltrombopag + IFN/RBN (N=680)</td></tr>
<tr><td>Events suggestive of hepatic decompensation[a]</td><td>14 (10)</td><td>69 (25)</td><td>21 (6)</td><td>56 (8)</td></tr>
<tr><td colspan="5">Data Source: ISS Section 6.1.3
On-treatment plus 30 days follow-up</td></tr>
</table></td></tr>
<tr><td>Potential mechanisms</td><td>Potential mechanism is unknown</td></tr>
<tr><td>Preventability</td><td>In the SmPC, a warning regarding the potential for hepatic decompensation is included in Section 4.4 (Special warnings and precautions for use).</td></tr>
<tr><td>Impact on individual patient</td><td>None known</td></tr>
<tr><td>Potential public health impact of safety concern</td><td>Potential public health impact is considered to be low.
Number needed to harm (NNH)
<table>
<tr><td></td><td>Placebo + IFN/RBN (N=484)</td><td>Eltrombopag + IFN/RBN (N=955)</td><td>Total (N=1439)</td><td>NNH</td><td>95% CI for NNH</td></tr>
<tr><td>Externally Adjudicated Progression of Liver</td><td>31 (6%)</td><td>108 (11%)</td><td>139 (10%)</td><td>20</td><td>12.71, 51.58</td></tr>
</table>
Table 8.9022</td></tr>
</table>

Risk	Hepatic decompensation
Impact on the benefit-risk balance of the product	Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a moderate impact on the benefit-risk balance in this indication.
Evidence source	Supporting data are referenced in the TPL102357, TPL103922 (ENABLE 1) and TPL108390 (ENABLE 2), Clinical Study Reports (m5.3.5.1), ETB115A2408, Summary of Clinical Safety and Integrated Safety and Summary (m5.3.5.3), PSUR
MedDRA terms	MedDRA PTs: Hepatic Failure, Ascites, Hepatic encephalopathy, Gastric varices haemorrhage, Oesophageal varices haemorrhage, Splenic varices haemorrhage, Anorectal varices haemorrhage. MedDRA version 20.0

Table 8-4 Important Potential risk: Increased bone marrow reticulin formation

Risk	Increased bone marrow reticulin formation

Frequency with 95% CI	**Adult ITP**
	The requirements for bone marrow (BM) examinations were modified during the conduct of the EXTEND study, with biopsies indicated as follows:
	• Prior to enrolment into the study, for subjects who had not responded to prior ITP therapies with a platelet count ≥ 100 Gi/L or who had not had a BM examination consistent with a diagnosis of ITP within 3 years;
	• At baseline, per protocol amendment 03, evaluation of BM status was added for any new subjects entering the study. During treatment:
	  • Per protocol amendment 02, a bone marrow biopsy was requested for patients treated with eltrombopag for longer than one year in the study.
	  • Per protocol amendment 03, all subjects were instructed to have a BM biopsy performed annually while on study.
	  • Bone marrow biopsy was performed for subjects who had immature or dysplastic cells in the white blood cell (WBC) differential that were confirmed by peripheral blood smear microscopy and not deemed typical for chronic ITP.
	  • At any time at the investigator's discretion.
	• Post-treatment; per protocol amendment 03, subjects withdrawn due to BM findings, or who had an on-treatment bone marrow finding of myelofibrosis grade (MF)-2 or -3 on the EU consensus scale or grade 3 or 4 on the Bauermeister scale had a BM biopsy performed at the 6-month follow-up visit to evaluate reversibility of the reticulin or collagen fiber deposition. This 6-month BM biopsy assessment was only performed on subjects who had not taken eltrombopag or any other TPO-R agonist after the last dose of study medication in EXTEND.
	• Pre-treatment biopsies: of the 418 biopsies from 179 subjects, 15 biopsies from 15 subjects were taken prior to treatment with eltrombopag. Nine of these biopsies were stained and graded for reticulin, using the EU Consensus Scale. Of these 9 biopsies, 8 were graded myelofibrosis grade (MF)-0 and 1 was graded MF-1.
	• On-treatment biopsies: these were defined as one performed during treatment and up to 7 days after the last dose of eltrombopag in the study. A total of 387 on-treatment biopsies, reviewed centrally and/or locally, were collected from 177 subjects. Of these, 352 biopsies from 166 subjects were graded for reticulin/collagen using the EU consensus scale.

Risk	Increased bone marrow reticulin formation

None of the on-treatment BM biopsies were prompted by an abnormal peripheral blood smear or done at the investigator's discretion for clinical symptoms suggestive of BM dysfunction. All but four of the biopsies were performed following the study protocol requirement for annual BM biopsies. The four BM examinations performed at investigator's discretion are presented below.

- Subject [redacted] had a BM exam on D57 due to recent diagnosis of diffuse large B-cell lymphoma. No infiltration of the BM was found (MF-0, centrally graded).
- Subject [redacted] had two BM examinations on D335 (MF-2, locally graded) and D432 (not graded). The first was performed per protocol after 1 year of eltrombopag and the second was performed on suspicion of loss of efficacy that led to early withdrawal.
- Subject [redacted] had two BM examinations on D41 (MF-1, locally graded) and D847 (MF-0, centrally graded). The first was performed due to failure to respond to study medication. The subject subsequently achieved platelet counts >50 Gi/L and continued on treatment for more than 2 years. The second biopsy was performed as per protocol: 4 days after the subject completed the study.
- Subject [redacted] had two BM examinations on D147 (MF-0, locally graded) and D371 (MF-0, locally graded). The first biopsy was performed due to an increase in hemoglobin and presumptive diagnosis of polycythemia vera which was ruled out. The subject continued on study and the second biopsy was performed per protocol following 1 year of eltrombopag treatment, and confirmed no sign of polycythemia vera. Additional per protocol biopsies performed on Days 734, 1262, 1499 and 1885 were all graded MF-0, per local review.

Maximum reticulin grade

The majority of samples (93%) were graded as either MF-0 or MF-1. Thirteen biopsies in 11 (7%) subjects were reported as MF-2 and one biopsy at 24 months was graded MF-3. Eleven subjects with grade MF-2 were reported in the study (subjects [redacted]). One of these subjects [redacted] had grade MF-3 at 24 months. In addition, subject [redacted] had a BM biopsy that stained positive for collagen despite the local grading being MF-1. No apparent relationship to the modal dose of eltrombopag was observed. None of the 11 subjects who had a grade ≥ MF-2 or presence of collagen in the bone marrow biopsy had clinical symptoms typical of bone marrow dysfunction or abnormalities of clinical concern reported in the WBC or peripheral blood smear.

Maximum MF grade at each on-treatment time interval

Maximum MF[a] grade at each on-treatment time interval[b] (safety population[b]) on treatment assessment interval	Pre-12 month (<10 months) n=15	12 month (10 - <22 months) n=150	24 month (22 - <34 months) n=76	36 month (34 - <46 months) n=55	48 month n=32	60 month n=17	72 month n=5

Risk	Increased bone marrow reticulin formation

MF grade 0, n (%)	12 (80)	97 (65)	63 (83)	44 (80)	21 (66)	11 (65)	5 (100)
MF grade 1, n (%) Collagen reported, n	3 (20)	43 (29) 1	11 (14)	10 (18)	10 (31)	6 (35)	0
MF grade 2, n (%) Collagen reported, n	0 0	10[c] (7) 3	1[c] (1) 0	1[c] (2) 0	1[c] (3)	0	0
MF grade 3, n (%)	0	0	1[c] (1) 0	0	0	0	0

a=European Consensus Scale, MF. MF-0: Scattered linear reticulin with no intersections corresponding to normal bone marrow; MF-1: Loose network of reticulin with many intersections, especially in perivascular areas; MF-2: Diffuse and dense increase in reticulin with extensive intersections, occasionally only focal bundles of collagen and/or focal osteosclerosis; MF-3: Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

B=The numbers presented reflect the number of subjects with assessments at each time-interval. If a subject had more than 1 biopsy during a time-interval, only the maximum MF grade is included. A subject will be counted in more than 1 time interval when a bone marrow biopsy was done during each interval.

c= Subject [redacted] had MF-2 at 12 months, had MF-3 at 24 months, and was MF-2 at 36 and 48 months. The findings for two subjects (Subjects [redacted] and [redacted] were considered staining artifacts by the central pathologist, who after re-processing the biopsies graded the samples as MF-0.

Shifts in MF grade between the first on-treatment bone marrow biopsy in EXTEND and the subsequent on-treatment biopsies were evaluated for the 105 subjects with 2 or more biopsies performed (Data Source: 2013 TRA105325 Table 8.157 from the CSR). These data are presented below considering the time elapsed between the initial and subsequent on-treatment bone marrow assessment.

- Less than 10 months between first and subsequent bone marrow assessments (n=5):
  - 2 subjects had MF-0 on both assessments
  - 2 subjects shifted from MF-0 to MF-1
  - 1 subject had MF-1 on both assessments
- 10 to <22 months between first and subsequent bone marrow assessments (n=74):
  - 48 subjects had MF-0 on both assessments
  - subjects shifted from MF-0 to MF-1
  - 1 subject had MF-1 on both assessments
  - 13 subjects shifted from MF-1 to MF-0
  - 3 subjects shifted from MF-2 to MF-0
  - 1 subject shifted from MF-2 to MF-3
- 22 to <34 months between first and subsequent bone marrow assessments (n=54):
  - 22 subjects had MF-0 on both assessments
  - 6 subjects shifted from MF-0 to MF-1
  - 1 subject shifted from MF-0 to MF-2
  - 4 subjects had MF-1 on both assessments.

Risk	Increased bone marrow reticulin formation

- 16 subjects shifted from MF-1 to MF-0
- 1 subject had MF-2 on both assessments
- 3 subjects shifted from MF-2 to MF-0
- 1 subject shifted from MF-2 to MF-1

- 34 to <46 months between first and subsequent bone marrow assessments (n=26):
  - 9 subjects had MF-0 on both assessments
  - 6 subjects shifted from MF-0 to MF-1
  - 4 subjects had MF-1 on both assessments.
  - 4 subjects shifted from MF-1 to MF-0
  - 1 subject had MF-2 on both assessments
  - 2 subjects shifted from MF-2 to MF-0
- 34 to <46 months between first and subsequent bone marrow assessments (n=13):
  - 2 subjects had MF-0 on both assessments
  - 2 subjects shifted from MF-0 to MF-1
  - 2 subjects had MF-1 on both assessments.
  - 7 subjects shifted from MF-1 to MF-0

Among the 105 subjects who had 2 or more biopsies during the study, 97 (92%) subjects remained MF-0, MF-1 or had a mild change within MF-0 to MF-1 band over the on-treatment period. One subject with MF-0 increased to MF-2. Of seven subjects whose first on-treatment biopsy was graded MF-2, 6 decreased to either MF-0 or MF-1, while one MF-2 increased to MF-3 over the on-treatment period. Overall, no pattern of increased reticulin deposition after a longer treatment period was apparent in these subjects, however, given that increased reticulin has been observed in healthy subjects as well as chronic ITP patients who have never been treated with thrombopoietin receptor agonists, the clinical significance of this finding in the bone marrow remains to be determined.

Paediatric ITP

No adverse events indicative of bone marrow fibrosis were reported.

Severe aplastic anaemia

One subject had a current medical condition of 'reticulin fibrosis 3+' reported at baseline.

Subject	Condition	Status at Baseline
[redacted]	Reticulin fibrosis 3+	Current

Listing of Medical Conditions 30.0030

During the ELT112523 (ETB115AUS28T) study, no AEs or SAEs regarding reticulin or fibrosis in the bone marrow were reported.

In the bone marrow pathology reports, three subjects had mention of reticulin or fibrosis mentioned in the baseline bone marrow. Four subjects had mention of reticulin in at least one bone marrow report during treatment with eltrombopag.

Based upon available data, there does not appear to be any worsening of bone marrow reticulin upon treatment with eltrombopag in SAA.

Risk	Increased bone marrow reticulin formation

Subject	Study Day	Verbatim
[redacted]	-44	Reticulin is focally slightly increased.
	-42	There is no increase in reticulin fibers.
	-36	Focal areas of mild marrow fibrosis.
	456	Reticulum staining was unchanged from the study of [redacted]2010 (On [redacted]-2010 Day 257 bone marrow report had no mention of reticulin)
	1349	Mild reticulin fibrosis (Subsequent marrow from Day 1692 had no mention of reticulin or fibrosis)
	1181	Minimal reticulin fibrosis
	649	Reticulin fibrosis appears focally and minimally increased (1+) but the degree of fibrosis cannot be assessed adequately in this sample due to severe artifact.
	266	Mild reticulin fibrosis

Listing 30.0070

Seriousness/outcomes

Adult ITP

Deposition of reticulin fibres in the bone marrow could potentially replace the bone marrow and cause a clinical situation similar to primary myelofibrosis. Clinical signs would be anaemia, leukocytosis, thrombocytopenia, hepato-/splenomegaly, and blood smear abnormalities such as nucleated red blood cells.

Paediatric ITP

No adverse events indicative of bone marrow fibrosis were reported.

HCV-associated thrombocytopenia

Patients in the ENABLE studies were treated for up to 48 weeks with eltrombopag, peg-interferon, and ribavirin. Overall, abnormalities in the hematology parameters were balanced between treatment groups with the exception of increases to Division of AIDS (DAIDS) grade 4 lymphocytes, which occurred more frequently with eltrombopag than placebo subjects. These comprehensive CBCs did not show any evidence for reticulin formation by virtue of declining counts. If blood abnormalities suggestive of bone marrow reticulin formation had occurred during these studies, a bone marrow biopsy would have been obtained as part of the evaluation. Since there was no clinical evidence suggestive of bone marrow reticulin formation, no bone marrow biopsies were needed or performed.

Severe aplastic anaemia

Based upon available data, there does not appear to be any worsening of bone marrow reticulin upon treatment with eltrombopag in SAA.

Risk	**Increased bone marrow reticulin formation**
Severity and nature of risk	See above
Background incidence/prevalence	**Adult ITP** Reticulin grades 0, 1, and 2 (Bauermeister scale) have been reported in healthy volunteers in 7%, 73%, and 20%, respectively. A Danish study of 187 chronic ITP patients never treated with thrombopoietin receptor agonists (TPO-RA) showed that 60% had MF-0, 38% MF-1, and ~2% MF-2 or MF-3 (European Consensus scale). In healthy individuals grade 1 reticulin has been reported in 27-70% of bone marrow biopsies, while grade 2 has been reported in 4-20% (Hultdin et al 2007, Beckman and Brown 1990, Bauermeister 1971). The presence of grade 1-2 reticulin has been described in the bone marrow of patients with ITP in up to 67% of patients before the introduction of thrombopoietin agonists). This mild to moderate presence of reticulin fibres in the bone marrow of healthy volunteers and patients with chronic ITP complicates the analysis of a potentially drug-induced deposition of reticulin/collagen fibres in the bone marrow. (Kuter et al 2007) **Paediatric ITP** Retrospective analysis of 13 clinical trials (n=653) to assess the long term (5 years) effects of romiplostim in adults and children reported 1.8% or an overall incidence of 1.3 events of increase in bone marrow reticulin per 100 patient years (Rodeghiero et al 2013). Statistics for adults vs paediatrics were not reported. Long term studies of IVIg and anti D in children with chronic ITP reported no effects on bone marrow reticulin (ElAlfy et al 2006).
Risk Groups or risk factors	No specific risk factor has been identified during clinical trials.
Potential mechanisms	Chronic stimulation of megakaryocytes with thrombopoietin receptor agonists might lead to a pathological increase of reticulin or collagen fibres in the bone marrow. Currently, it is unclear whether the presence of reticulin in some patients in EXTEND is due to the underlying disease, treatment with eltrombopag, or a combination of both. Analysis of bone marrow biopsy data in both the EXTEND and Bone Marrow study (TRA112940) do not suggest that eltrombopag is associated with a clinically relevant increase in bone marrow reticulin or collagen fibers. Limited data from pre-treatment bone marrow assessments from the RAISE study confirm that reticulin is found in the bone marrow of patients with chronic ITP regardless of treatment with a TPO-R agonist.
Preventability	**Adult and paediatric ITP:** Risk Minimisation will focus on informing prescribers and patients through the SmPC and package leaflet. Monitoring of the bone marrow function should take place in a step-wise fashion, including a pre-treatment blood smear to establish a baseline level of cellular morphologic abnormalities. Periodic complete blood counts and white blood cell counts with differential shall also be performed, and peripheral blood smears examined if immature or dysplastic cells are observed. If new or worsening cytopenia(s) or morphological abnormalities were identified (e.g., teardrop and nucleated red blood cells, immature white blood cells), a bone marrow would be indicated, including staining for reticulin and collagen fibres. A warning is in Section 4.4. (Special warnings and precautions) of the SmPC informing prescribers to monitor for immature or dysplastic cells.

Risk	Increased bone marrow reticulin formation
	HCV-associated thrombocytopenia Current text in SmPC addresses increased bone marrow reticulin formation in the patient population with HCV Associated thrombocytopenia **Severe aplastic anaemia** Current text in SmPC addresses increased bone marrow reticulin formation.
Impact on individual patient	None known
Potential public health impact of safety concern	Potential public health impact is considered to be low.
Impact on the benefit-risk balance of the product	Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a moderate impact on the benefit-risk balance in this indication.
Evidence source	Supporting data are referenced in the EXTEND Clinical Study Reports (see m5.3.5.2) PMA112509 Clinical Study Report Supporting data are referenced in the PETIT and PETIT2, Clinical Study Reports (m5.3.5.1 and m5.3.5.2, respectively), Summary of Clinical Safety (m2.7.4) and Integrated Summary of Safety (m5.3.5.3). Supporting data are referenced in the Clinical Study Report for Study ELT112523 (ETB115AUS28T) and the Short Study Summaries for the Study ELT116826 (ETB115AUS18T) and Study ELT116643 (ETB115AUS01T). TRA112940 (ETB115B2401) Bone marrow study report PSUR
MedDRA terms	MedDRA version 20.0 PTs: Bone marrow reticulin fibrosis' and 'Myelofibrosis'

Table 8-5 Important Potential risk: Haematological malignancies

Risk	Haematological malignancies
Frequency with 95% CI	**Adult ITP** **Subjects with Haematologic Malignancies in Eltrombopag Studies**

Study	Placebo n/N (%)	Eltrombopag n/N (%)
TRA100773A, TRA100773B, TRA102537/RAISE	1/128 (1)	0/299 (0)
TRA108057/REPEAT (open-label)	NA	0/66 (0)
TRA105325/EXTEND (ongoing, open-label)	NA	2/299 (<1)
Pooled eltrombopag exposed [a]	NA	2/446 (<1)
TRA108109 (Japanese) [b]	0/8 (0)	0/23 (0)

NA: Not applicable
a=Includes TRA100773A, TRA100773B, TRA102537, TRA108057, and TRA105325
b=TRA108109 had a 7-week randomized, double-blind period, followed by an open-label treatment period. All subjects were treated with eltrombopag for a total of 26 weeks.

Incidence rate (95% CI) of haematologic malignancies in eltrombopag ITP studies

ITP Study	Placebo	Eltrombopag
TRA100773A, TRA100773B, TRA102537/RAISE	2.09/100PYs (0.05, 11.63)	-
TRA108057/REPEAT (open label)	NA	-
TRA105325/EXTEND (ongoing, open label)	NA	0.39/100PYs (0.05, 1.41)
Pooled eltrombopag exposed [a]	NA	0.31/100PYs (0.04, 1.12)
TRA108109 (Japanese) [b]	-	-

NA: Not applicable
a=Includes TRA100773A, TRA100773B, TRA102537, TRA108057 and TRA105325
b=TRA108109 had a 7-week randomized, double-blind period, followed by an open-label treatment period. All subjects were treated with eltrombopag for a total of 26 weeks.

The incidence of malignancies in subjects treated with eltrombopag across the ITP program (2010 update) is 1.73/100 PY (95% CI [0.86, 3.09]), which is similar to the incidence rate observed in the 2009 update (1.65/100 PY, 95% CI [0.66, 3.40]). The incidence rate observed in the eltrombopag treated subjects is similar to the incidence in subjects treated with placebo (2.09/100 PY, 95% CI [0.05, 11. 63]).

Paediatric ITP

No adverse events indicative of haematologic malignancies were reported.

Study in MDS/AML

PMA112509 Study

Study PMA112509 was a double-blind, randomized, placebo-controlled Phase I/II study of eltrombopag in thrombocytopenic subjects with advanced MDS or AML who were relapsed, refractory or ineligible to receive standard treatment. The primary objective of this study was to evaluate the safety and tolerability (including changes in bone marrow blast counts from baseline) of single-agent eltrombopag versus placebo. In the PMA112509 study, the majority of subjects in the eltrombopag treatment group (53/64 [83%]) and the placebo treatment group (31/34 [91%]) prematurely discontinued treatment. The most common reasons for premature discontinuation in both groups were disease progression (assessed by the Investigator) and AEs. Approximately 30% of subjects in both treatment groups discontinued treatment due to disease progression (21/64 [33%] eltrombopag; 10/34 placebo [29%]).

Disease response and diseases progression results are different depending on the criteria used for their determination. Disease response and progression was assessed by an external Independent Review Committee (IRC) through review of blinded subject data using two definitions of disease progression. The protocol-defined disease progression criteria was assessed by the IRC for all subjects based on bone marrow blasts (<20% for MDS or ≥ 20% for AML). A modified version of the IWG definition of disease progression was used by the IRC for the subset of subjects with MDS with baseline (<20% bone marrow blasts). The results of the IRC assessments using both the protocol-defined and the modified IWG criteria are shown in the tables below. The IRC determined that 9% and 15% of eltrombopag and placebo treated subjects respectively were not evaluable for the protocol definition of disease progression and 39% and 57% of eltrombopag and placebo treated subjects respectively were not evaluable for the modified IWG definition of disease progression.

MDS subjects (baseline bone marrow blast <20%)

Definition of disease progression	Eltrombopag (N= 18[a])	Placebo (N= 14)
Protocol-defined disease progression, n (%)	9 (50%)	8 (57%)
Median progression free survival	16.1 weeks	7.7 weeks
IWG definition of disease progression, n (%)	7 (39%)	5 (36%)
Best response of disease progression[b], n (%)	9 (50%)	6 (43%)

a=One eltrombopag subject is present under both MDS and AML subject sections because the baseline bone marrow blast percentage from the screening sample could determine only that the blasts were between 10% and 50% (exact count not provided).
b=Best response of progressive disease represents the IRC-adjudication at any time during the study. Note that a subject may have had a positive disease response (e.g. stable disease or partial response etc.) and later progress.

AML subjects (baseline bone marrow blast ≥ 20%)

Definition of disease progression	Eltrombopag (N= 47[a])	Placebo (N= 20)
Protocol-defined disease progression, n (%)	32 (68%)	14 (70%)
Median progression free survival	8.1 weeks	6.4 weeks
Best response of disease progression[b], n (%)	30 (64%)	11 (55%)

a=One eltrombopag subject is present under both MDS and AML subject sections because the baseline bone marrow blast percentage from the screening sample could determine only that the blasts were between 10% and 50% (exact count not provided).
b=Best response of progressive disease represents the IRC-adjudication at any time during the study. Note that a subject may have had a positive disease response (e.g. stable disease or partial response etc.) and later progress.

In addition to the IRC assessment of progression, thirteen subjects identified as having MDS at baseline, eight of 15 eltrombopag subjects (53%) and five

<table>
<tr><td></td><td>of 11 placebo subjects (45%), had an increase in local bone marrow and/or peripheral blood blasts from <20% to ≥ 20%.

Severe aplastic anaemia
One subject enrolled in Study ELT112523 (ETB115AUS28T) had a change in diagnosis to MDS prior to treatment with eltrombopag. This subject was not treated with eltrombopag and was not included in the Safety Population.
Three subjects of the 43 treated subjects (7%) in Study ELT112523 (ETB115AUS28T) were diagnosed by the Investigator with MDS following treatment with eltrombopag
• One subject with baseline bone marrow dysplasia developed monosomy 7 at the 3-4 month primary response assessment and subsequently died of MDS >6 months after the last dose of eltrombopag.
• The diagnosis in one subject was based solely on monosomy 7 without evidence of dysplasia on bone marrow or worsening peripheral blood counts at the 3-4 month primary response assessment; the subject received a transplant.
• One subject was a responder for 13 months, developed deletion of chromosome 13 with <5% ringed sideroblasts, and received a transplant.
As of the clinical data cut-off date (31-Mar-2014), the development of MDS or AML had not been reported in Study ELT116826 (ETB115AUS18T).
In Study ELT116643 (ETB115AUS01T), one subject (Subject [redacted]) who did not respond after three months and developed monosomy 7-associated dysplasia consistent with MDS and discontinued treatment.</td></tr>
<tr><td>Seriousness/outcomes</td><td>Adult ITP
A comprehensive presentation of all malignancies is provided. Twelve subjects in the eltrombopag trials (11 on eltrombopag, one on placebo) have been diagnosed with malignancies. In the eltrombopag group, five subjects have undergone or are undergoing treatment for the malignancy and continued treatment with eltrombopag and four were withdrawn when the malignancy was diagnosed. Two subjects were diagnosed with a malignancy after more than 90 days off therapy. Two subjects reporting a malignant event already had a reported malignancy during the eltrombopag trials.
Among these cases, two cases of hematological malignancy were reported in the eltrombopag group and one in the placebo, across all studies.

<table>
<tr><th colspan="3">Haematological Malignancies</th></tr>
<tr><td>Subject [redacted]
RAISE
Placebo</td><td>[redacted]
23 years</td><td>• Transformation of myelodysplastic syndrome to acute leukaemia
• After 173 days post therapy</td></tr>
<tr><td>Subject [redacted]
EXTEND
Eltrombopag
50 mg</td><td>[redacted]
77-years</td><td>• Persistent fatigue and anaemia
• After 63 days in study presented with posterior neck and chest wall masses
• Biopsy confirmed a diffuse large B cell lymphoma.
• No follow up information was provided as the patient withdrew [redacted] consent</td></tr>
<tr><td>Subject [redacted]
EXTEND</td><td>[redacted]
64-years</td><td>Grade 2 Hodgkin's lymphoma, diagnosed 1094 days after the first dose of eltrombopag in EXTEND. At the</td></tr>
</table>
</td></tr>
</table>

Eltrombopag 75 mg		time of the diagnosis the subject had been off eltrombopag for >18 months (559 days after the last dose).

Malignancies/		
Subject [redacted] RAISE Eltrombopag 50-75 mg	[redacted] 59-years	• After 91 days on study rectal bleeding • Colonoscopy and surgery confirmed a Stage I rectosigmoid adenocarcinoma • Patient treated and subsequently enrolled in EXTEND
Subject [redacted] REPEAT Eltrombopag 50-75 mg	[redacted] [redacted]-years	• Intermittent abdominal pain eight months before the study • Presented with jaundice and weight loss after four months in study • After four months on study, a computerised tomography (CT) scan and guided aspiration confirmed a non-resectable pancreatic body carcinoma. • Died due to malignancy
Subject [redacted] EXTEND Eltrombopag 50-75 mg	[redacted] 51-years	• Forehead skin lesion • Biopsy showed basal cell carcinoma • Uneventful surgical resection/resolved
Subject [redacted] EXTEND Eltrombopag 75 mg	Female [redacted]-years	• Ovarian carcinoma diagnosed after 288 days on study • Uneventful surgical resection • Completed chemotherapy, continued on eltrombopag • Breast cancer diagnosed after 722 days on study. Underwent chemotherapy and continued treatment with eltrombopag until study completion.
Subject [redacted] EXTEND Eltrombopag 75 mg	Male 49-years	• Constipation and abdominal discomfort on Day 306 of eltrombopag • Intramucosal adenocarcinoma diagnosed after 421 days on study • Treated with chemotherapy and surgery, initially continued eltrombopag • Diagnosed with metastatic disease to the lungs after 445 days on study. Withdrawn from study • Died due to metastatic disease
Subject [redacted] TRA100773B Eltrombopag 50mg	[redacted] [redacted]-years	• Exposed to eltrombopag 20 days, withdrawn for platelet count >200 Gi/L • Colon carcinoma in situ after 102 days off therapy • No follow up information available

	Subject [redacted] EXTEND Eltrombopag 75 mg	[redacted] 62-years	• Incidental finding of low grade papillary urothelial carcinoma (transitional cell carcinoma) of the bladder, diagnosed during a laparotomy for a colonic resection (polyps). History of bladder transitional cell carcinoma treated before enrolling in the eltrombopag trials • Diagnosed after 874 days of treatment • Fully resected • Continued on study until completion
	Subject [redacted] EXTEND Eltrombopag 75 mg	[redacted] 65-years	• Basal cell carcinoma of the lower palpebra of left eye, after 609 days of treatment in EXTEND • Resected with no need for additional ITP treatment/resolved • Continued on study
	Subject [redacted] EXTEND Eltrombopag 25 mg	[redacted] 75-years	• Grade 2 squamous cell carcinoma on right hand, after 348 days of treatment. • Resected with no need for additional ITP treatment/resolved • Continued on study

Paediatric ITP

No adverse events indicative of haematologic malignancies were reported.

HCV-associated thrombocytopenia

Of the 1520 subjects in the ENABLE studies, there were two reports of hematological malignancies.

In ENABLE 1, Subject [redacted] was diagnosed post-study with myelodysplastic/myeloproliferative neoplasm, unclassifiable; six months after radiotherapy for non-small cell lung cancer (NSCLC) and 13 months after last dose of study medication

In ENABLE 2, there was one report of hematological malignancy in Subject [redacted] who was treated with eltrombopag for 28 days before being randomized into the placebo group. He had a history of neutropenia and relative lymphocytosis prior to treatment and had a diagnosis of acute leukemia on Day 208 (175 days post-treatment) and died of progressive multi-organ failure on Day 210. The Investigator did not report the hematological malignancy as an AE.

Severe aplastic anaemia

See section above (frequency with 95% CI)

Severity and nature of risk	Ongoing non-clinical studies with leukemic (AML/MDS) cell lines have shown that there is no excess proliferation of the malignant cells when exposed to eltrombopag. Pre-clinical GSK research with multiple cancer cell-lines: Study UH2007/00074/00 investigating the response of nine solid tumour cell lines to eltrombopag in a proliferation assay has been completed and reported. The cell lines investigated include four lung cancer cell lines, two prostate tumour lines and three ovarian carcinoma cell lines. There was no increase in proliferation of any of the cell lines assays after 72 h of treatment with eltrombopag.

Background incidence/prevalence	**Adult ITP:** In GSK sponsored epidemiology study (GlaxoSmithKline WEUKSTV1116 Study), the risk of haematologic malignancies among patients with chronic ITP (N=3131) compared to a non-ITP population (N=9392) was examined. The analysis used eligibility and medical claims collected during 2000-2006 from a large US health insurance plan. In the statistical modeling, after adjusting for age, gender and other variables, the adjusted incidence rate ratio (IRR) for lymphoma was 3.88 (95% CI: 1.43, 10.56), for non-Hodgkin's lymphoma was 5.03 (95% CI: 1.84, 13.75), and for leukaemia was 32.71 (95% CI: 7.58, 141.14). Although the confidence intervals were wide, all adjusted IRRs were elevated and statistically significant. The study found an association of an increased risk for select blood cancers for patients with chronic ITP compared to the non-ITP population. **Paediatric ITP** The literature on hematalogic malignancies in children with ITP is limited to a few case reports. Reports of the overall prevalence of cancer comorbidity in this population is estimated at 0.2% (Kuhne et al 2011); suggesting the incidence of haematologic malignancies is low. Retrospective analysis of 13 clinical trials (n=653) to assess the long term (5 years) effects of romiplostim in adults and children reported haematological malignancies in 0.8% of patients (0.7 events per 100 patient-years) Statistics for adults vs. paediatrics were not reported (Rodeghiero et al 2013). **HCV-associated thrombocytopenia** The research around a possible association between HCV and hematological malignancies has been primarily focused on Non-Hodgkin's lymphoma (NHL). Two meta-analysis report pooled relative risk estimates of 2.5 (95% CI 2.1, 3.0) and 5.70 (95% CI 4.09, 7.96) for the risk of NHL among HCV patients compared to patients without HCV infection (Dal Maso and Francheschi 2006, Matsuo et al 2004). There is no clear evidence that HCV is associated with other hematological malignancies, although some results suggest HCV patients may be at increased risk for multiple myeloma (Duberg et al 2005). In a GSK sponsored study using medical claims data from a large U.S. health plan affiliated with i3 Drug Safety (GlaxoSmithKline WEUKSTV1116 Study) an increased risk for NHL was found for both HCV patients (4.38 95% CI: 2.45-7.83) and for patients with cirrhosis (8.67 95% CI:4.58-16.41), compared to patients without HCV or cirrhosis. In that study HCV and cirrhosis patients were defined between 01-Jan-2000 and 20-Sep-2006 with follow-up through 31-Dec-2006. Comparison cohorts were matched on age and gender. The HCV cohort included all stages of liver disease and the cirrhosis cohort included all underlying aetiologies, including HCV. All patients were followed up with respect to occurrence of lymphoma, leukaemia and chronic lymphoid leukaemia (CLL). The only additional increase in risk was found for the overall leukemia estimate in the HCV cohort (2.51 95%CI 1.15-5.48). No increase was found for the cirrhosis cohort or the subgroup CLL. The incidence and prevalence from the GSK sponsored study among patients with HCV and cirrhosis are presented below. **Incidence of condition, 95% CI per 10000 person years**

	HCV cohort	Cirrhosis cohort
Non-Hodgkin's lymphoma	7.2 (4.8-10.2)	17.3 (12.5-23.4)

	<table><tr><td>Leukaemia</td><td>2.9 (1.5-5.0)</td><td>3.5 (1.7-6.7)</td></tr><tr><td>Chronic lymphoid leukaemia</td><td>0.5 (0.2-1.0)</td><td>1.3 (0.4-3.5)</td></tr></table> Source: GlaxoSmithKline WEUKSTV1116 Study, 2008 **Prevalence of condition, %** <table><tr><th></th><th>HCV cohort</th><th>Cirrhosis cohort</th></tr><tr><td>Non-Hodgkin's lymphoma</td><td>0.3%</td><td>0.5%</td></tr><tr><td>Leukaemia</td><td>0.2%</td><td>0.3%</td></tr><tr><td>Chronic lymphoid leukaemia</td><td><0.1%</td><td><0.1%</td></tr></table> Source: GlaxoSmithKline WEUKSTV1116 Study, 2008
Risk Groups or risk factors	**Adult ITP** The association of ITP and hematological malignancies has been widely recognized (Soderberg et al 2006, Stern et al 2007). **Paediatric ITP** No evidence of an association documented in the literature. **HCV-associated thrombocytopenia** The association of HCV and NHL has been described above. **Severe aplastic anaemia** Patients with aplastic anaemia are known to be at risk for the development of MDS and AML (Maciejewski and Selleri 2004, Marsh et al 2009).
Potential mechanisms	None known for eltrombopag
Preventability	Risk minimisation will focus on informing prescribers and patients through the SmPC and package leaflet. Patient follow-up will include clinical symptoms, clinical chemistry and hematological parameters (CBC, WBC and differential, blood smears and bone marrow biopsy as warranted). A warning is included in Section 4.4. (Special warnings and precautions) of the SmPC informing prescribers that a theoretical risk exists that TPO agonists may stimulate progression of existing hematological malignancies. **Adult and paediatric ITP** Section 4.4 of the SmPC (Special warnings and precautions) states that the diagnosis of ITP in adults and elderly patients should have been confirmed by the exclusion of other clinical entities with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs. **Severe aplastic anaemia** Section 4.8 of the SmPC (Undesirable effects) states that in the single-arm, open label trial in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (Study ELT116826 (ETB115AUS18T) and Study ELT116643 (ETB115AUS01T), 1/28 (4%) and 1/62 (2%) subject has been diagnosed with MDS or AML in each study.
Impact on individual patient	None known

Potential public health impact of safety concern	Potential public health impact is considered to be low.
Impact on the benefit-risk balance of the product	Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a moderate impact on the benefit-risk balance in this indication.
Evidence source	Supporting data are referenced in the RAISE, TRA100773B, TRA100773A, EXTEND and REPEAT Clinical Study Reports (see m5.3.5.1 and m5.3.5.2, respectively) Study UH2007/00074/00 In vitro and ex vivo studies evaluating potential effects on leukaemic AML/MDS cells Supporting data are referenced in the TPL102357, TPL103922 (ENABLE 1) and TPL108390 (ENABLE 2), Clinical Study Reports (m5.3.5.1) and Integrated Summary of Safety. Supporting data are referenced in the PETIT and PETIT2, Clinical Study Reports (m5.3.5.1 and m5.3.5.2, respectively), Summary of Clinical Safety (m2.7.4) and Integrated Summary of Safety (m5.3.5.3). Integrated Safety and Summary (m5.3.3.3) PMA112509 Clinical Study Report Supporting data are referenced in the Clinical Study Report for ELT112523 (ETB115AUS28T) Study and the Short Study Summaries for the Study ELT116826 (ETB115AUS18T) and Study ELT116643 (ETB115AUS01T). PSUR
MedDRA terms	Malignant or unspecified tumors' and 'Blood premalignant disorders - SMQ (Broad) MedDRA version 20.0

Table 8-6 Important Potential risk: Cytogenetic abnormalities in severe aplastic anaemia

Risk	**Cytogenetic abnormalities in severe aplastic anaemia**
Frequency with 95% CI	Consistent with the known occurrence of cytogenetic abnormalities in SAA, 7% of subjects in Study ELT112523 (ETB115AUS28T) had a cytogenetic abnormality present at baseline. In Study ELT112523 (ETB115AUS28T), eight subjects (19%) had a new cytogenetic abnormality detected after treatment. In Study ELT116826 (ETB115AUS18T) there were 2 of 15 subjects (13%) at the 3-month response assessment with cytogenetic abnormalities. In Study ELT116643 (ETB115AUS01T) there were 2 of 44 subjects (5%) at the 3-month response assessment with cytogenetic abnormalities.
Seriousness/outcomes	Eight subjects (19%) had a new cytogenetic abnormality detected after treatment in Study ELT112523 (ETB115AUS28T). Testing for cytogenetic abnormalities is performed in all SAA studies conducted by the NIH. • Of these eight subjects, five subjects had cytogenetic abnormalities affecting the structure or number of chromosome 7; all five were non-responders to eltrombopag and the cytogenetic abnormality was detected at the Primary Response Assessment. • One of these five subjects (Subject [redacted]) had insufficient bone marrow aspirate at baseline so it is unknown whether the cytogenetic abnormality was present in the bone marrow prior to treatment with eltrombopag.

Risk	Cytogenetic abnormalities in severe aplastic anaemia
	• In one subject (Subject [redacted]), the monosomy 7 was transient and was not present on the repeat bone marrow 21 days later. • The three remaining subjects had trisomy 8 (Subject 8) and deletion of chromosome 13 (Subject [redacted] and [redacted]. • Six of the subjects did not respond to eltrombopag, and the cytogenetic abnormality was detected at the primary response visit (12 to 16 weeks). The two subjects (Subjects [redacted] and [redacted]) who responded to treatment with eltrombopag had the cytogenetic abnormality detected 13.7 and 9.6 months after initiating treatment with eltrombopag and had eltrombopag treatment discontinued. • Three of the eight subjects with a cytogenetic abnormality detected after treatment had evidence of dysplasia in their bone marrow examinations. • A total of three subjects' cytogenetic abnormalities were considered to have MDS. Of note, one subject (Subject [redacted]) with 'mild dyserythropoiesis' noted on the bone marrow report was not reported to have had MDS by the Investigator. • Outcomes of these eight subjects were as follows: five subjects were transplanted, one subject is awaiting transplant, one subject died and one subject is being under observation (Desmond et al 2013). In Study ELT116826 (ETB115AUS18T), cytogenetic abnormalities affecting chromosome 7 (Subject [redacted], non-responder) and 13 (Subject [redacted] non-responder), respectively, were detected post-baseline in two of 15 subjects (13%) at the 3-month response assessment. Both subjects were discontinued from eltrombopag treatment. Neither subject was considered to have developed MDS or AML. In Study ELT116643 (ETB115AUS01T), cytogenetic abnormalities affecting chromosome 7 (Subject [redacted] non-responder) and chromosome 13 (Subject [redacted] complete remission), respectively, were detected post-baseline in two of 44 subjects (5%) at the 3-month response assessment. Eltrombopag was discontinued in both subjects. Subject [redacted] had a repeat bone marrow examination one month later showed evidence of dysplasia and an increase in blasts consistent with development of myelodysplastic syndrome.
Severity and nature of risk	There is no literature on the incidence of cytogenetic abnormalities in the heavily pretreated population studied in the pivotal trial; however, the 5-19% incidence of cytogenetic abnormalities in the SAA studies of eltrombopag appear in line with published literature. The clinical consequences are variable, depending upon the specific abnormality and the presence or absence of clinical sequelae such as dysplasia or worsening cytopenias (Maciejewski et al 2002). Physicians who treat SAA are familiar with the management of cytogenetic abnormalities and current treatment guidelines recommend patients with SAA and cytogenetic abnormalities be treated and managed in the same fashion as SAA patients without cytogenetic abnormalities, with the exception of patients with monosomy 7. In patients with monosomy 7, the preferred treatment option is HSCT (Marsh et al 2009, Scheinberg et al 2012b).
Background incidence/prevalence	Cytogenetic abnormalities have been reported in 15-20% of patients with SAA (Maciejewski et al 2002, Scheinberg et al 2011, Scheinberg et al 2012).
Risk Groups or risk factors	A known complication of SAA is the appearance of cytogenetic abnormalities in bone marrow cells in 15-20% of patients (Maciejewski et al 2002, Scheinberg et al 2011, Scheinberg et al 2012). This risk is thought to be higher

Risk	Cytogenetic abnormalities in severe aplastic anaemia
	in heavily pretreated patients with insufficient response to immunosuppressive therapies than in earlier lines of therapy (Desmond at el 2013).
Potential mechanisms	Cytogenetic abnormalities have been postulated to be associated with SAA patients who have telomeres in the shortest age adjusted quartile (Scheinberg et al 2010).
Preventability	Treatment should not be initiated when the patient has existing cytogenetic abnormalities of chromosome 7. For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and every 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate.
Impact on individual patient	None known
Potential public health impact of safety concern	Potential public health impact is considered to be low.
Impact on the benefit-risk balance of the product	Presently, a causal relationship between cytogenetic abnormalities and eltrombopag treatment has not been confirmed and therefore, this risk has no impact on benefit-risk balance.
Evidence source	Supporting data are referenced in the Clinical Study Report for Study ELT112523 (ETB115AUS28T) and the Short Study Summaries for the Study ELT116826 (ETB115AUS18T) and Study ELT116643 (ETB115AUS01T).
MedDRA terms	High Level Terms (Chromosomal abnormalities, Chromosome analyses) and Preferred Term 'Clonal evolution', MedDRA 20.0.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

Patients with hepatic impairment

Name of missing information	Details
Evidence source	The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult subjects with liver cirrhosis (hepatic impairment). Following the administration of a single 50 mg dose, the AUC(0-inf) of eltrombopag was increased by 41% (90% CI: 13% decrease, 128% increase) in subjects with mild hepatic impairment, 93% (90% CI: 19%, 213%) in subjects with moderate hepatic impairment, and 80% (90%: CI: 11%, 192%) in subjects with severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between subjects with hepatic impairment and healthy volunteers. The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population PK analysis in 28 healthy adults and 79 subjects with chronic liver disease. Based on estimates from the population PK analysis, subjects with liver cirrhosis (hepatic impairment) had higher plasma eltrombopag AUCtau values as compared to healthy volunteers, and AUCtau increased with increasing Child-Pugh score. Compared to healthy volunteers, subjects with mild hepatic

Name of missing information	Details
	impairment had approximately 87% to 110% higher plasma eltrombopag AUCtau values and subjects with moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag AUCtau values. A similar analysis was also conducted in 28 healthy adults and 635 subjects with HCV. A majority of subjects had Child Pugh score of 5-6. Based on estimates from the population PK analysis, subjects with HCV had higher plasma eltrombopag AUCtau values as compared to healthy subjects, and AUCtau increased with increasing Child-Pugh score, HCV subjects with mild hepatic impairment had approximately 100 to 144% higher plasma eltrombopag AUCtau compared with healthy subjects. For patients with HCV, initiate eltrombopag at a dose of 25 mg once daily (see Dosage and Administration).
Anticipated risk/ consequence of the missing information:	While the prescribing information provides a guidance for patients with hepatic impairment in all indications, the concern is that the safety profile may be worse due to increased exposure despite the dose reduction, in the presence of the known risk of hepatotoxicity.

Table 8-7 Use in pediatric SAA population

Name of missing information	Details
Evidence source	Two pediatric subjects were enrolled in the refractory SAA study; both were aged ■■years.
Anticipated risk/ consequence of the missing information:	Two adolescent patients were enrolled in the refractory SAA study therefore the safety profile in this population is unknown.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	**Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia and severe aplastic anaemia** • Hepatotoxicity • Thromboembolic events **HCV-associated thrombocytopenia** • Hepatic decompensation
Important potential risks	**Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia** • Increased Bone Marrow Reticulin Formation • Haematological malignancies **Severe aplastic anaemia** • Cytogenetic abnormalities
Missing information	**Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia** • Patients with hepatic impairment

	Severe aplastic anaemia • Use in paediatric population

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective risks

The following adverse event follow-up checklists are used to collect additional data for eltrombopag:

- Hepatobiliary laboratory abnormalities
- Hepatic decompensation
- Thrombotic and thromboembolic events
- Worsening thrombocytopenia and bleeding
- Hematological malignancy
- Bone Marrow Reticulin / Bone Marrow Fibrosis

These checklists are provided in Annex 4 of the RMP.

Other forms of routine pharmacovigilance activities for risks

Not applicable.

10.2 Part III.2. Additional pharmacovigilance activities

Study RAD200936 (CETB115E2201)

Title: A phase II, open-label, non-controlled, intra-patient dose escalation study to characterize the pharmacokinetics after oral administration of eltrombopag in paediatric patients with refractory, relapsed or treatment naïve severe aplastic anemia or recurrent aplastic anemia

Rationale and Study Objectives:

This study will evaluate eltrombopag treatment in paediatric patients who have either refractory/relapsed SAA or recurrent aplastic anemia after immunosuppressive therapy (IST) for SAA (Cohort A), or who have SAA, previously untreated with IST. This study will fulfill a requirement agreed upon in the paediatric Investigational Plan for SAA (EMEA-000170-PIP03-13).

Primary Objective: To characterize the PK of eltrombopag at steady state after oral administration in paediatric patients with SAA.

Secondary Objective:

- To determine the safety and tolerability of eltrombopag given orally in paediatric patients with SAA.

- To assess the efficacy defined as overall response (ORR).

Study design:

This Phase II, open-label, non-controlled, intra-patient dose-escalation study will evaluate pharmacokinetics, safety, activity and acceptability/palatability of eltrombopag in combination with immunosuppressive therapy in children from 1 to less than 18 years of age with severe aplastic anemia that is relapsed/refractory or aplastic anemia that is recurrent after immunosuppressive therapy for SAA, or with severe aplastic anemia previously untreated with immunosuppressive therapy.

Study population:

This target population of this study will be paediatric patients (1 to <18 years) who have been diagnosed with severe aplastic anemia and are not suitable or eligible candidates for hematopoietic stem cell transplantation.

Milestones:

- Primary study report submission: 24-Nov-2022.
- Final study report submission: 26-Nov-2025.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Study RAD200936 (CETB115E2201) Ongoing	Safety of eltrombopag in paediatric SAA	Paediatrics	Primary Study Report submission	24-Nov-2022
			Final Study Report submission	26-Nov-2025

11 Part IV: Plans for post-authorization efficacy studies

No post authorisation efficacy studies are planned or ongoing.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

12.1 Part V.1. Routine risk minimization measures

Description of routine risk minimization measures by safety concern

Table 12-1 Risk minimization measures for Hepatotoxicity

Safety concern	Hepatotoxicity
Routine risk minimization measures	**Routine risk communication** Section 4.4 and 4.8 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk** Serum alanine aminotransferase (ALT), aspartate aminotrasferase (AST) and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. **Other routine risk minimization measures beyond the Product Information** None

Table 12-2 Risk minimization measures for Thromboembolic events

Safety concern	Thromboembolic events
Routine risk minimization measures	**Routine risk communication** Section 4.2, Section 4.4 and Section 4.8 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk** Dose of eltrombopag to be decreased or stopped according to platelet count elevation. Patients should be closely monitored for signs and symptoms of TEE. **Other routine risk minimization measures beyond the Product Information** None

Table 12-3 Risk minimization measures for Hepatic decompensation

Safety concern	Hepatic decompensation
Routine risk minimization measures	**Routine risk communication** Section 4.4 and Section 4.8 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk**

	Monitoring is required in patients with low albumin levels (≤35 g/l) or with a MELD score ≥10 at baseline. **Other routine risk minimization measures beyond the Product Information** None

Table 12-4 Risk minimization measures for Increased bone marrow reticulin formation

Safety concern	Increased bone marrow reticulin formation
Routine risk minimization measures	**Routine risk communication** Section 4.4 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** None

Table 12-5 Risk minimization measures for Haematological malignancies

Safety concern	Haematological malignancies
Routine risk minimization measures	**Routine risk communication** Section 4.4 and Section 4.8 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk** The diagnosis of ITP or SAA in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. 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 such as increased peripheral blast cells. **Other routine risk minimization measures beyond the Product Information** None

Table 12-6 Risk minimization measures for Cytogenetic abnormalities in severe aplastic anaemia

Safety concern	Cytogenetic abnormalities in severe aplastic anaemia
Routine risk minimization measures	**Routine risk communication**

	Section 4.2, 4.4 and 4.8 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk** For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate. **Other routine risk minimization measures beyond the Product Information** None

Table 12-7 Risk minimization measures for Patients with hepatic impairment

Safety concern	Patients with hepatic impairment
Routine risk minimization measures	**Routine risk communication** Section 4.2 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** None

Table 12-8 Risk minimization measures for Use in paediatric SAA patients

Safety concern	Use in paediatric SAA patients
Routine risk minimization measures	**Routine risk communication** Section 4.2 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** None

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V12.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3 Summary of risk minimization measures

Table 12-9 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hepatotoxicity	Section 4.4 and Section 4.8 of the SmPC.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for adverse reaction Additional pharmacovigilance activities: None
Thromboembolic events	Section 4.2, Section 4.4 and Section 4.8 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for adverse reaction Additional pharmacovigilance activities: None
Hepatic decompensation	Section 4.4 and Section 4.8 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for adverse reaction Additional pharmacovigilance activities: None
Increased bone marrow reticulin formation	Section 4.4 of the SmPC.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for adverse reaction Additional pharmacovigilance activities: None

Haematological malignancies	Section 4.4 and Section 4.8 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for adverse reaction Additional pharmacovigilance activities: None
Cytogenetic abnormalities in severe aplastic anaemia	Section 4.2, 4.4 and 4.8 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with hepatic impairment	Section 4.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in paediatric SAA patients	Section 4.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study RAD200936 (CETB115E2201) /Paediatric SAA study

13 Part VI: Summary of the risk management plan for Revolade

This is a summary of the risk management plan (RMP) for eltrombopag. The RMP details important risks of eltrombopag, how these risks can be minimized, and how more information will be obtained about eltrombopag's risks and uncertainties (missing information).

Eltrombopag's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how eltrombopag should be used.

This summary of the RMP for eltrombopag should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of eltrombopag's RMP.

13.1 Part VI: I. The medicine and what it is used for

Revolade® contains eltrombopag as the active substance and it is used for in the following indications:

- **Immune thrombocytopenia:**

Revolade is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

Revolade is indicated for the treatment of paediatric patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

- **HCV-associated thrombocytopenia:**

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.

- **Severe aplastic anaemia:**

Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation.

Dosing requirements

- **Immune (primary) thrombocytopenia**

Adults and paediatric population aged 6 to 17 years: The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East-/Southeast-Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), eltrombopag should be initiated at a reduced dose of 25 mg once daily.

Paediatric population aged 1 to 5 years: The recommended starting dose of eltrombopag is 25 mg once daily.

- **Chronic hepatitis C (HCV) associated thrombocytopenia:**

The recommended starting dose of eltrombopag is 25 mg once daily. No dosage adjustment is necessary for HCV patients of East-/Southeast-Asian ancestry or patients with mild hepatic impairment.

- **Severe aplastic anaemia:**

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily. The treatment should not be initiated when the patient has existing cytogenetic abnormalities of chromosome 7.

Further information about the evaluation of eltrombopag's benefits can be found in eltrombopag's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of eltrombopag, together with measures to minimize such risks and the proposed studies for learning more about eltrombopag's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of eltrombopag, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of eltrombopag is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of eltrombopag are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of eltrombopag. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information

List of important risks and missing information	
Important identified risks	**Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia and severe aplastic anaemia** • Hepatotoxicity • Thromboembolic events **HCV-associated thrombocytopenia** • Hepatic decompensation
Important potential risks	**Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia** • Increased Bone Marrow Reticulin Formation • Haematological malignancies **Severe aplastic anaemia** • Cytogenetic abnormalities
Missing information	**Adult ITP, Paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia** • Patients with hepatic impairment **Severe aplastic anaemia** • Use in paediatric population

13.2.2 Part VI - II B: Summary of important risks

Table 13-1 Important identified risks

Risk	What is known	Preventability
Liver laboratory abnormalities (hepatotoxicity)	Revolade can increase some blood markers indicating liver damage.	Patients will have blood tests to check liver function before starting Revolade and at intervals while taking it. Patients may need to stop taking Revolade if the amount of these substances increases too much, or if physical signs of liver damage appear. Patients should tell their doctor immediately if they have any of these signs and symptoms of liver problems: • yellowing of the skin or the whites of the eyes (jaundice) • unusually dark-coloured urine

		• right upper stomach area pain.
Liver abnormalities in patients with hepatitis C who are receiving antiviral medication (hepatic decompensation) (risk for HCV-associated thrombocytopenia)	Revolade can increase some blood markers indicating liver damage. When patients are given certain interferon-based antiviral treatments together with Revolade for the treatment of thrombocytopenia due to hepatitis C virus (HCV) infections some liver problems can get worse.	Patients will have blood tests to check liver function before starting Revolade and at intervals while taking it. Patients may need to stop taking Revolade if the amount of these substances increases too much, or if physical signs of liver damage appear. Patients should tell their doctor immediately if they have any of these signs and symptoms of liver problems: • yellowing of the skin or the whites of the eyes (jaundice) • unusually dark-coloured urine • right upper stomach area pain.
High platelet counts and higher chance for blood clots (thromboembolic events {TEE})	If a patient has very high blood platelet counts, this may increase the risk of blood clotting, however, blood clots can occur with normal or even low platelet counts.	A doctor can adjust the dose of Revolade to ensure that the platelet count does not become too high. Patients should tell their doctor immediately if they have any of these signs and symptoms of a blood clot: • swelling, pain or tenderness in one leg (deep vein thrombosis) • sudden shortness of breath especially when accompanied with sharp pain in the chest and/or rapid breathing (pulmonary embolism) • abdominal pain, enlarged abdomen, blood in stool (portal vein thrombosis)

Table 13-2 Important potential risks

Risk	What is known
Cytogenetic Abnormalities (risk for severe aplastic anaemia)	A known complication of SAA is the development of changes in the chromosome(s). These changes have been reported in 15-20 out of every 100 patients with SAA. The importance of these chromosomal changes depends on the type of changes and any abnormal results to the blood cells.
Bone marrow abnormalities (increased bone marrow reticulin formation)	People with thrombocytopenia may have problems with their bone marrow. Medicines like Revolade could make this problem worse. Signs of bone marrow changes may show up as abnormal results in blood tests. A doctor may also carry out tests to directly check a patient's bone marrow during treatment with Revolade.
Worsening of blood cell cancers cells (worsening haematological malignancies)	Revolade belongs to a group of medicines called thrombopoietin receptor agonists. For TPO-R agonists there is a concern that they may worsen already existing blood cell cancers. Ongoing studies have not shown increased growth of these cells when exposed to Revolade. Patients should tell their doctor if they have ever been diagnosed with a blood cell cancer.

Table 13-3 Missing information

Risk	What is known
Children	With the exception of paediatric ITP, there is limited experience with the use of Revolade in children
Patients with decreased liver function (hepatic impairment)	If the use of eltrombopag is considered necessary for adult and paediatric ITP patients with decreased liver function, the starting dose must be 25 mg once daily. No dose adjustment is needed for thrombocytopenic patients with chronic HCV and decreased liver function. Thrombocytopenic patients with chronic HCV should initiate eltrombopag at a dose of 25 mg once daily.Severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily.

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of eltrombopag.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-4 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study RAD200936 (CETB115E2201): A phase II, open-label, non-controlled, intra-patient dose escalation study to characterize the pharmacokinetics after oral administration of eltrombopag in paediatric patients with refractory, relapsed or treatment naïve severe aplastic anemia or recurrent aplastic anemia	This study will evaluate eltrombopag treatment in paediatric patients who have either refractory/relapsed SAA or recurrent aplastic anemia after immunosuppresive therapy (IST) for SAA (Cohort A), or who have SAA, previously untreated with IST. This study will fulfill a requirement agreed upon in the Paediatric Investigational Plan for SAA (EMEA-000170-PIP03-13). Primary Objective: To characterize the PK of eltrombopag at steady state after oral administration in paediatric patients with SAA. Secondary Objective: To determine the safety and tolerability of eltrombopag given orally in paediatric patients with SAA. To assess the efficacy defined as overall response (ORR).

14 Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

This annex contains the specific adverse event targeted follow-up checklists used to collect additional data for the following eltrombopag RMP risks:

- Hepatobiliary laboratory abnormalities
- Hepatic decompensation
- Thrombotic and thromboembolic events
- Worsening thrombocytopenia and bleeding
- Hematological malignancy
- Bone Marrow Reticulin / Bone Marrow Fibrosis

Targeted Follow-up Checklists

Hepatobiliary Laboratory Abnormalities

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

- Date of the event(s) _____
- Date when eltrombopag was started: _____
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event? _____mg
- If NO, what were the last dose and the date? _____mg Date _____

Current Liver Function Laboratory Tests

Please provide the following regarding the current liver function laboratory test for this event.

Tests	Lab Value	Date	Reference range
Alanine Aminotransferase(ALT)			
Aspartate Aminotransferase(AST)			
Total Bilirubin			
Direct Bilirubin			
Alkaline Phosphatase (Alk Phos)			

Was a liver biopsy performed? ☐ Yes ☐ No

If YES, what were the results?

You may attach anonymized copy of these reports, if available. ☐ **Check this box, if attached.**

Diagnostic imaging

Were any of the following diagnostic imaging tests of the hepatobiliary system performed?

Yes	No	
☐	☐	Liver Ultrasound
☐	☐	CAT Scan
☐	☐	MRI Scan
☐	☐	Endoscopic/Magnetic Retrograde Cholangiopancreatography (ERCP) / (MRCP)
☐	☐	

Other_____

You may attach anonymized copy of these reports, if available. ☐ **Check this box, if attached.**

Liver Function Laboratory Tests - Peak and Return to Baseline Values

Please provide the following information regarding the peak and return to baseline liver function laboratory tests, if available.

Tests	Peak Value	Date of peak	Value at Return to baseline	Date of Return to baseline	Reference range
Alanine Aminotransferase (ALT)					
Aspartate Aminotransferase (AST)					
Total Bilirubin					
Direct Bilirubin					
Alkaline Phosphatase (Alk Phos)					

You may attach anonymized copy of these reports, if available. ☐ **Check this box, if attached**

Patient history

Does the patient have a history of drug allergies? YES ☐ NO ☐

Any concomitant medication(s)? YES ☐ NO ☐ NONE ☐
If YES, please list the concomitant medication(s) if patient was taking any at the time of event?

_____

_____

Please list concurrent disease(s)

_____

_____

Hepatic Decompensation

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

- Date of the event(s) _____
- Date when eltrombopag was started: _____
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event? _____mg
- If NO, what were the last dose and the date? _____mg Date _____

Patient history

	YES	**NO**
Does the patient have right side heart failure?	☐	☐
Is there a history of prior liver disease (e.g., hepatitis A, B, C, fatty liver, hepatic failure, cirrhosis)?	☐	☐
Is there a history of Gilbert's Disease?	☐	☐
Is there a history of recent travel to a developing country?	☐	☐
Does the patient have autoimmune disease?	☐	☐

If yes, please specify:-

_____

Does the patient have a history of any of the following?

☐ Active gall bladder disease ☐ Active pancreatitis ☐ Alcohol use ☐ NSAID use ☐ IV drug use

☐ acetaminophen consumption in patients with chronic alcohol exposure – please state number of g/day taken:

If diabetic, has the patient taken any of the following?

☐ Avandia/ Avandamet ☐ Sulfonylureas ☐ Metformin ☐ Insulin ☐ Alpha-glucosidase inhibitors ☐ Repaglinide ☐ Troglitazone

If yes, please give start and stop dates and dose:

_____

_____

_____

Description of the Event

Is the patient symptomatic? ☐ Yes ☐ No

If yes, please indicate all that apply.

☐ RUQ pain ☐ abdominal pain ☐ fever ☐ hepatic encephalopathy / confusion

☐ nausea ☐ jaundice ☐ anorexia ☐ variceal bleeding (please specify site)

☐ ascites

☐ other (please specify:_____

Please describe the results for the following or provide anonymized hard copy of results

1. Did the patient have any triggers for the hepatic decompensation (e.g., infection, medication)?
   ☐ Yes ☐ No

   If yes, please specify._____

_____

_____

2. Were any diagnostic imaging tests performed e.g. CT or MRI scan abdomen/ liver, abdominal ultrasound of liver/ hepatobiliary tree? ☐ Yes ☐ No

   If yes, please describe results or provide anonymized hard copy of results:

_____

3. Was an Endoscopic/Magnetic Retrograde Cholangiopancreatography (ERCP) / (MRCP) performed?
☐ Yes ☐ No
If yes, please attach anonymized copy of report.

4. Was a liver biopsy performed?
☐ Yes ☐ No
If yes, please describe results or provide anonymized copy of results:

5. Are liver enzymes (ALT/SGPT, AST/SGOT, Alkaline Phosphatase, LDH, GGT or bilirubin (total, direct, or indirect bilirubin) elevated?
☐ Yes ☐ No

If yes, please provide anonymized copies of results, including baseline and normal ranges

Liver Function Laboratory Tests - Peak and Return to Baseline Values

Tests	Value at peak	Date of Peak	Value after Return to baseline	Date of Return to baseline	Reference range
Alanine Aminotransferase (ALT)					
Aspartate Aminotransferase (AST)					
Total Bilirubin					
Direct Bilirubin					
Alkaline Phosphatase (Alk Phos)					

You may attach anonymized copy of these reports, if available. ☐ Check this box, if attached

Please specify if additional liver studies were obtained?

Please specify or attach anonymized copy of tests if serology for Hepatitis A, B, and C was done

Please specify or attach anonymized copy of tests Prothrombin time/International Normalized Ratio, Thrombin time, Partial thromboplastin time, Albumin, Total protein, if available?

Does the patient have a history of drug allergies? ☐ Yes ☐ No

Please list the concomitant medication(s) if patient was taking any at the time of event?

Has the patient had close contact with a person with active hepatitis? ☐ Yes ☐ No

Did the patient receive treatment for liver disease? ☐ Yes ☐ No
If yes, please describe:

Thrombotic and Thromboembolic Events

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Please provide detailed information regarding the following:

- History of the event(s)
- Date of the event(s) _____
- Date when eltrombopag was started: _____
- Is the patient still taking eltrombopag? Yes No
- If YES, what was the dose of eltrombopag at the time of the event? _____mg
- If NO, what were the last dose and the date? _____mg Date _____
- What is the platelet count most proximal to this event?

Unit _____Normal range _____Date _____

- What was the platelet count after this event? _____ Date _____

Diagnostic tests

Were any of the following diagnostic tests performed? **Check all that apply. Please specify which test(s), providing dates and results. Please provide anonymized copy of these reports, if available.**

☐ CT scan _____

☐ ECG _____

☐ Phlebography_____

☐ Blood gas analysis _____

☐ Doppler\ ultrasound_____

☐ Echocardiography_____

☐ V\P scintigraphy_____

Other tests? Please specify

_____

Please provide anonymized copy of these reports, if available.

Thrombophilic Laboratory Profile (You may attach anonymized copy of these reports, if available.

☐ **Check this box, if attached)**

Status	Normal	Abnormal	Not done

Lupus anticoagulants ☐ ☐ ☐

Antiphospholipid antibodies ☐ ☐ ☐

Anti-prothrombin antibodies ☐ ☐ ☐

Beta 2 glycoprotein antibodies ☐ ☐ ☐

Factor VIII ☐ ☐ ☐

Protein C ☐ ☐ ☐

Protein S ☐ ☐ ☐

Serum homocysteine ☐ ☐ ☐

Anti-thrombin III ☐ ☐ ☐

Factor V Leiden mutation ☐ ☐ ☐
☐**Heterozygous** ☐**Homozygous** ☐**Unknown**

Prothrombin mutation ☐ ☐ ☐
☐**Heterozygous** ☐**Homozygous** ☐**Unknown**

MTHFR-Polymorphism ☐ ☐ ☐
☐**Heterozygous** ☐**Homozygous** ☐**Unknown**

Patient History: Does the patient have a history of any of the following conditions? **Check all that apply. Please specify date of onset**

☐ Hypertension ☐ Diabetes Mellitus

☐ Hyperlipidemia ☐ Cardiovascular disease

☐ Thromboembolic event ☐ Family history of thromboembolism

☐ Varicose Vein(s)

Risk Factors

Was there trauma prior to the event? ☐Yes ☐No

Was the patient immobilized /hospitalized prior to this event (e.g. surgical procedures)? ☐Yes ☐No

If YES, was prophylactic anticoagulation administered? ☐Yes ☐No

If female, is the patient taking oral contraceptives? ☐Yes ☐No

If female, has the patient taken hormone replacement therapy? ☐Yes ☐No

Evidence of any autoimmune disease at any time other than ITP (e.g. IBD, SLE, RhA, etc.)? ☐Yes ☐No

If YES, please describe:_____

Please list past or concomitant medication(s) (e.g. IVIg, diuretics, corticosteroids, aminocaproic acid, antifibrinolytic agents, or any recent exposure to drugs associated with TEEs)

☐None

Worsening Thrombocytopenia and Bleeding

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Please provide detailed information regarding the following:

- Date when eltrombopag was started:
- Is the patient still taking eltrombopag?
- If YES, what was the dose of eltrombopag at the time of the event?
- If NO, what were the last dose and the date?
- What is the platelet count most proximal to this event? unit _____Normal range _____
- Describe any bleeding symptoms during the event?

_____

- Was a transfusion required to maintain the baseline hemoglobin? ☐Yes ☐No

If yes, how many? _____Please provide the date(s) _____

- Outcome of the event(s)_____

Please provide up to the last four platelet counts before the first day of treatment with eltrombopag.

☐ Date _____ Platelet count _____ Normal range_____

☐ Date _____ Platelet count _____ Normal range_____

☐ Date _____ Platelet count _____ Normal range_____

☐ Date _____ Platelet count _____ Normal range_____

You may attach anonymized copy of these reports, if available. ☐ Check this box, if attached

Medical Information

1. Were there any similar bleeding events prior to therapy with eltrombopag?☐Yes☐No

If YES, please describe:_____

2. Has the patient experienced bleeding symptoms on discontinuation of other treatments for ITP?

☐Yes ☐No

If YES, please describe:_____

3. Were there any changes to the concomitant therapy(ies) for ITP prior to this event?

☐Yes ☐ No

If YES, please specify:_____

Data Source: Table 8.9066, Table 8.9081, and Table 28.9081.
a=Includes terms renal failure and acute renal failure.

Please list concurrent medication(s) (e.g. anti-platelet medications, NSAIDs)
☐ None

Hematological malignancy

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Please provide detailed information regarding the following:

- History of the event(s)_____
- Date of the event(s) _____
- Date when eltrombopag was started: _____
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event? _____ mg
- If NO, what were the last dose and the date? _____mg Date _____

Diagnosis:
Please select one choice regarding this event:
☐ **New diagnosis** ☐ **Relapse of previous malignancy** ☐ **Unknown**

Please select one diagnosis from this list:
☐ Under investigation ☐ MDS (IPSS score):

☐ AML (FAB subtype): ☐ Lymphoma (specify):

☐ Myeloproliferative Disease (MPD)
Please specify: CMLIMFPVET

☐ **Other,** (specify): _____

Is the peripheral blood smear abnormal? ☐ Yes ☐ No

☐ Bone marrow biopsy/Trephine Date_____
Findings_____

☐ Bone marrow aspiration Date_____ Findings
_____

☐ Immunophenotype? Date _____
Findings_____

☐ Cytogenetics? Date _____
Findings_____

You may attach anonymized copy of these reports, if available. ☐ Check this box, if attached

Please provide any additional information on stage, treatment planned, pathology, and x-ray findings.

What clinical features were present at the time of diagnosis? Check all that apply

- ☐ Anemia
- ☐ Pallor
- ☐ Fatigue
- ☐ Fever/night sweats
- ☐ Bone pain
- ☐ Hepatosplenomegaly
- ☐ Thrombocytopenia
- ☐ Granulocytopenia
- ☐ Lymphadenopathy
- ☐ Increased bruising/bleeding
- ☐ Recurrent infection/poor wound healing
- ☐ Abdominal pain and /or weight loss

Patient History:

Does the patient have any of the following past or present conditions that may predispose them to malignancies?

Yes	No	
☐	☐	Family History of malignancy
☐	☐	Smoking
☐	☐	Occupational exposure (e.g. benzene)
☐	☐	Monoclonal gammopathy
☐	☐	History of chemotherapy or radiation therapy
☐	☐	Other (please specify)_____

What are the concomitant medications? (check all that apply)

☐ None

- ☐ Azathioprine
- ☐ Cyclophosphamide
- ☐ Interferon alpha
- ☐ Corticosteroids
- ☐ Danazol
- ☐ IVIg

☐ Rituximab ☐ Romiplostim

Other (please specify):_____

Bone Marrow Reticulin / Bone Marrow Fibrosis

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

- Date of the event(s) _____
- Date when eltrombopag was started: _____
- Is the patient still taking eltrombopag? ☐ Yes ☐ No
- If YES, what was the dose of eltrombopag at the time of the event? _____mg
- If NO, what were the last dose and the date? _____mg Date _____

Adverse Event description

a. Was the Peripheral Blood Smear Abnormal? ☐ Yes ☐ No
b. Date of this smear: ____ / ____ / ____

c. If YES, were any of the following cells present in the peripheral blood smear?
   1. Increased peripheral blast cells ☐Yes Please provide the % _____
   2. Increased nucleated red blood cells ☐Yes Please provide the % _____
   3. Tear drop erythrocytes ☐Yes

Were any of the following diagnostic tests performed? Check all that apply and specify which test(s), dates and results

☐ Bone marrow aspiration Date_____
Findings_____

☐ Bone marrow biopsy/Trephine Date_____
Findings_____

☐ Immunophenotype Date_____
Findings_____

☐ Cytogenetics Date_____
Findings_____

What clinical features were present at the time of the event? (check all that apply)

☐ Recent decrease in hemoglobin
☐ Recent decrease in platelet counts
☐ Newly diagnosed splenomegaly
☐ Increased nucleated red blood cells
☐ Newly diagnosed hepatomegaly
☐ Change in white blood cells, (please specify) _____

Please quantify the degree of bone marrow reticulin/collagen using the Bauermeister scale.
(Select only one)

0 ☐ No reticulin fibers demonstrable
1 ☐ Occasional fine individual fibers and foci of a fine fiber network
2 ☐ Fine fiber network throughout most of the section; no coarse fibers
3 ☐ Diffuse fiber network with scattered thick coarse fibers but no mature collage (negative trichrome stain)
4 ☐ Diffuse, often coarse fiber network with areas of collagenization (positive trichrome stain)
☐ Other (please describe)

_____

You may attach anonymized copy of the bone marrow report, if available. ☐ Check this box if attached

Medical History - Baseline Assessments

Please complete baseline information on any of the assessments below indicating that any of the following procedures were performed prior to the patient being treated with eltrombopag?

☐ Bone marrow aspiration Date_____
Findings_____

☐ Bone marrow biopsy/Trephine Date_____
Findings_____

☐ Immunophenotype Date_____
Findings_____

☐ Cytogenetics Date_____
Findings_____

<u>At baseline</u> Please quantify the degree of bone marrow reticulin/collagen using the Bauermeister scale. (Select only one)

0 ☐ No reticulin fibers demonstrable
1 ☐ Occasional fine individual fibers and foci of a fine fiber network
2 ☐ Fine fiber network throughout most of the section; no coarse fibers
3 ☐ Diffuse fiber network with scattered thick coarse fibers but no mature collage (negative trichrome stain)
4 ☐ Diffuse, often coarse fiber network with areas of collagenization (positive trichrome stain)

☐ Other (please describe) _____

<u>Patient History:</u>

Does the patient have a history of any of the following prior to the start of the suspect drug?
Check all that apply and provide details as applicable

☐ Infection ☐ UV exposure, PUVA/UVB

☐ Smoking ☐ Alcohol abuse

☐ Personal history of malignancy ☐ Family history of malignancy

☐ Immunosuppression condition (e.g. HIV, transplantation) ☐ Immunosuppression therapy

☐ Exposure to carcinogens (environmental, occupational) ☐ Radiation therapy

☐ Autoimmune disease (e.g. psoriasis, Sjogren Syndrome, rheumatoid arthritis)

Others (please specify)

_____

_____

Concomitant medications (Check all that apply and provide details as applicable)

☐ Azathioprine
☐ Corticosteroids

☐ Cyclophosphamide
☐ Danazol Interferon alpha
☐ IVIg
☐ Rituximab
☐ Romiplostim
☐ Other (please specify):_____

Please list previous and concurrent disease(s)

_____

_____

_____

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable