EU risk management plan for Doptelet® (avatrombopag)

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- update of relevant milestones related to CLD PASS study

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- update of end of data collection and due date of final study report results for CLD PASS study

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
ALT	alanine aminotransferase
AST	aspartate transferase
ATC	Anatomical Therapeutic Chemical
AUC	area under concentration-time curve
BUN	blood urea nitrogen
CLD	chronic liver disease
CPK	creatinine phosphokinase
CYP	cytochrome P450
ECL	enterochromaffin-like
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
HCV	hepatitis C virus
HIV	human immunodeficiency virus
INN	International Non-proprietary Name
ITP	immune (idiopathic) thrombocytopenic purpura
MAH	marketing authorization holder
MELD	Model for End Stage Liver Disease
MRHD	maximum recommended human dose
NOAEL	no-observed-adverse-effect-level
NSAID	nonsteroidal anti-inflammatory drugs
PASS	Post authorisation safety study
PL	Package Leaflet
PVT	portal vein thrombosis
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
TPO	Thrombopoietin
US	United States

PART I PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) (INN or common name)	Avatrombopag
Pharmacotherapeutic group(s) (ATC Code)	B02BX08
Marketing Authorisation Holder	Swedish Orphan Biovitrum SE-11276 Stockholm Sweden Phone +46 8 697 20 00
Medicinal products to which this RMP refers	Avatrombopag
Invented name(s) in the European Economic Area (EEA)	Doptelet
Marketing authorisation procedure	Centralised
Brief description of the product:	**Chemical class:** Avatrombopag is an orally administered, small-molecule thrombopoietin (TPO) receptor (c-Mpl) agonist that mimics the biological effects of TPO *in vitro* and *in vivo*. **Summary of mode of action:** Avatrombopag stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in the increased production of platelets. Avatrombopag does not compete with TPO for binding to the TPO receptor and has an additive effect with TPO on platelet production. **Important information about its composition:** Avatrombopag is a pale-yellow film-coated tablet with 20 mg of avatrombopag maleate. Each tablet contains lactose monohydrate (120 mg); microcrystalline cellulose; crospovidone type B; silica, colloidal anhydrous; and magnesium stearate as core excipients.
Hyperlink to the Product Information	Product Information

<table>
<tr><td>Indication(s) in the EEA</td><td>Current:
Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobins).</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:

<u>Posology</u>
Treatment should be initiated by and remain under the supervision of a physician who is experienced in the treatment of haematological diseases. Doptelet should be taken at the same time of day (e.g. in the morning or evening) with food, including when taking the dose less frequently than once daily.

<u>Chronic liver disease</u>
Obtain a platelet count prior to the administration of Doptelet therapy and on the day of a procedure to ensure an adequate increase in platelet count, and no unexpectedly high increase in platelet count in the patient populations.

The recommended daily dose of avatrombopag is based on the patient’s platelet count (see Table 1). Dosing should begin 10 to 13 days prior to the planned procedure. The patient should undergo their procedure 5 to 8 days after the last dose of avatrombopag.

Table 1: Daily dose recommendation for avatrombopag

<table>
<tr><th>Platelet count (x 10^9/L)</th><th>Once daily dose</th><th>Duration of dosing</th></tr>
<tr><td>< 40</td><td>60 mg (Three 20 mg tablets)</td><td>5 days</td></tr>
<tr><td>≥ 40 to < 50</td><td>40 mg (Two 20 mg tablets)</td><td>5 days</td></tr>
</table>

Duration of treatment
Due to limited information, avatrombopag should not be taken for more than 5 days.

Missed doses
If a dose is missed, it should be taken as soon as it is remembered. Two doses should not be taken at one time to make up for a missed dose. The next dose should be taken at the usual time the next day.</td></tr>
</table>

Chronic immune thrombocytopenia

Use the lowest dose of Doptelet needed to achieve and maintain a platelet count ≥ 50 x 10^9/L as necessary to reduce the risk for bleeding. Do not use avatrombopag to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 week after starting avatrombopag and decreased within 1 to 2 weeks after discontinuation.

Initial dose regimen

The recommended starting dose of Doptelet is 20 mg (1 tablet) once daily with food.

Monitoring and dose adjustment

After initiating therapy, assess platelet counts at least once weekly until a stable platelet count ≥ 50 x 10^9/L and ≤ 150 x 10^9/L has been achieved. Twice weekly platelet count monitoring should be conducted during the first weeks of therapy in patients receiving avatrombopag only once or twice weekly. Twice weekly monitoring should also be conducted after dose adjustments during the treatment.

Due to the potential risk of platelet counts above 400 x 10^9/L within the first weeks of treatment patients should be carefully monitored for any signs or symptoms of thrombocytosis. After a stable platelet count has been achieved, obtain platelet counts at least monthly. After discontinuation of avatrombopag, platelet counts should be obtained weekly for at least 4 weeks.

Dose adjustments (see Table 2 and Table 3) are based on the platelet count response. Do not exceed a daily dose of 40 mg (2 tablets).

Table 2: Avatrombopag dose adjustments for patients with chronic immune thrombocytopenia

Platelet count (x10^9/L)	**Dose adjustment or action**
< 50 after at least 2 weeks of avatrombopag treatment	• Increase *One Dose Level* per Table 3. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
> 150 and ≤ 250	• Decrease *One Dose Level* per Table 3. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
> 250	• Stop avatrombopag. • Increase platelet monitoring to twice weekly. • When platelet count is less than 100 x10^9/L, decrease *One Dose Level* per Table 3 and reinitiate therapy.
< 50 after 4 weeks of avatrombopag 40 mg once daily	• Discontinue avatrombopag.
> 250 after 2 weeks of avatrombopag 20 mg weekly	• Discontinue avatrombopag.

Table 3: Avatrombopag dose levels for titration in patients with primary chronic immune thrombocytopenia

Dose[≠]	Dose Level
40 mg once daily	6
40 mg three times a week *AND* 20 mg on the four remaining days of each week	5
20 mg once daily*	**4**
20 mg three times a week	3
20 mg twice a week *OR* 40 mg once weekly	2
20 mg once weekly	1

* Initial dose regimen for all patients except those taking moderate or strong dual inducers or moderate or strong dual inhibitors of CYP2C9 and CYP3A4/5, or of CYP2C9 alone.

≠ Patients taking avatrombopag less frequently than once daily should take the medication in a consistent manner from week to week.

Dose Level 3: Three non-consecutive days a week, e.g., Monday, Wednesday, and Friday
Dose Level 2: Two non-consecutive days a week, e.g. Monday and Friday
Dose Level 1: The same day each week, e.g. Monday

In the case of a missed dose, patients should take the missed dose of avatrombopag as soon as they remember. Patients should not take two doses at one time to make up for a missed dose and should take the next dose per the current regimen.

Avatrombopag can be administered in addition to other ITP medicinal products. Platelet counts should be monitored when combining avatrombopag with other medicinal products for the treatment of primary ITP in order to avoid platelet counts outside of the recommended range, and to determine whether the dose of either medication should be reduced.

Discontinuation

Discontinue avatrombopag if the platelet count does not increase to $\geq 50 \times 10^9$/L after 4 weeks of dosing at the maximum dose of 40 mg once daily. Discontinue Doptelet if the platelet count is greater than 250×10^9/L after 2 weeks of dosing at 20 mg once weekly.

Recommended dosage with concomitant moderate or strong dual inducers or inhibitors of CYP2C9 and CYP3A4/5, or of CYP2C9 alone, in patients with chronic immune thrombocytopenia.

The recommended starting doses of avatrombopag in patients with chronic immune thrombocytopenia receiving concomitant medications are summarised in Table 4.

Recommended Dosage with Concomitant Moderate or Strong Dual Inducers or Inhibitors of CYP2C9 and CYP3A4/5, or of CYP2C9 alone, in Patients with Chronic Immune Thrombocytopenia

The recommended starting doses of avatrombopag in patients with chronic immune thrombocytopenia receiving these concomitant medications are summarised below.

	Table 4: Avatrombopag recommended starting dose for patients with primary chronic immune thrombocytopenia based on concomitant medications **Concomitant medications** / **Recommended starting dose** Moderate or strong dual inhibitors of CYP2C9 and CYP3A4/5, or of CYP2C9 alone (e.g., fluconazole) / 20 mg (1 tablet) three times a week Moderate or strong dual inducers of CYP2C9 and CYP3A4/5, or of CYP2C9 alone (e.g., rifampicin, enzalutamide) / 40 mg (2 tablets) once daily
Pharmaceutical form(s) and strengths	**Current:** Film coated tablet 20 mg.
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

EEA = European Economic Area, EU = European Union, TPO = thrombopoietin.

PART II SAFETY SPECIFICATION

Part II Module SI – Epidemiology of the Indication(s) and Target Population(s)

Table 2 Summary of Epidemiology of Chronic Immune Thrombocytopenia

Incidence	Chronic ITP can develop when the immune system mistakenly produces antibodies against a person's own platelets, marking them for destruction and removal by the spleen; the resultant thrombocytopenia leads to excessive bruising and bleeding. ITP is the most common cause of thrombocytopenia and is an acquired hemorrhagic condition that can be considered as a paradigmatic model of autoimmune disease. Isolated thrombocytopenia with a platelet count of $<100\times10^9$/L is the most important, though not sole criterion for the diagnosis of ITP (Cines, 2002). In Europe, the incidence of ITP in adults has been estimated to be between 1 and 4 per 100,000 persons without any obvious seasonal variation (Frederiksen, 1999; Neylon, 2003). When a cut-off platelet count of $<50 \times 10^9$/L was applied, the annual incidence of ITP was estimated to be 2.25 per 100,000 in Denmark (Frederiksen, 1999) and 1.6 per 100 000 in the UK (Neylon, 2003). The EMA estimates that in adults with ITP, the incidence rate is 1.6 to 3.9 cases per 100,000 per year (EMA/CHMP/153191/2013), and in a recent orphan designation decision (EU/3/18/2131) granted by the European Commission (EC) in 2019, it was estimated that ITP affects approximately 2.6 in 10,000 people in the EU.
Prevalence	It is estimated that there are approximately 50,000 individuals with chronic ITP in Europe (Gernsheimer, 2008).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:	Epidemiologic data suggest that the incidence of ITP in adults is approximately equal for the genders except in the mid-adult years (30-60 years), when the disease is more prevalent in women (Neylon, 2003; Segal, 2006;). In chronic ITP (adults), the female-to-male ratio is 2.6:1 (Silverman, 2019). Onset in a patient older than 60 years is uncommon. ITP is usually chronic in adults (Cines, 2002) and the probability of durable remission is 20-40% (Stevens, 2006). Common ITP risk factors include (Feintuch, 2019): • Genetics • Age • Receiving certain vaccines • Infections (HIV, hepatitis, *H. pylori*) • Viral illness (e.g., flu) • Individuals with such diseases as rheumatoid arthritis, lupus, antiphospholipid syndrome and young women (Mayo Foundation for Medical Education and Research).
The main existing treatment options	Conventional treatment options include corticosteroids, intravenous immunoglobulin, and splenectomy. Other treatments include anti-D, steroid-sparing agents (i.e. mycophenolate, mofetil, azathioprine), platelet transfusions, *H. pylori* eradication, thrombopoietin receptor agonists (i.e. romiplostim, eltrombopag), and other agents (i.e. dapsone, rituximab, fostamatinib).

Natural history of the indicated condition in the population, including mortality and morbidity	ITP has no cure, and relapses may occur years after seemingly successful medical or surgical management (Sandler, 2004). The mortality rate due to chronic ITP varies but tends to be higher relative to the general population for any age range. In a study conducted in Great Britain, it was noted that ITP causes an approximately 60 percent higher rate of mortality compared to gender- and age-matched subjects without ITP. This increased risk of death with ITP is largely concentrated in the middle-aged and elderly. Ninety-six percent of reported ITP-related deaths were in individuals 45 years or older. No significant difference was noted in the rate of survival between males and females (Schoonen, 2009). Hemorrhage represents the most serious complication; intracranial hemorrhage is the most significant. The mortality rate from hemorrhage is approximately 5% in adults. In patients with severe thrombocytopenia, predicted 5-year mortality rates from bleeding are significantly raised in patients older than 60 years versus patients younger than 40 years, 47.8% versus 2.2%, respectively. Older age and previous history of hemorrhage increase the risk of severe bleeding in adult ITP (Silverman, 2019). In adults**,** spontaneous remission occurs in 30% of patients in the first year, and up to 75% of patients improve within 5 years (Sailer, 2006). However, many patients have mild and stable disease (i.e., platelet counts > 30,000/mcL) with minimal or no bleeding; they are often discovered by the automated platelet counting now routinely done with CBC. Other patients have significant, symptomatic thrombocytopenia, although life-threatening bleeding and death are rare.
Important co-morbidities	Evidence on ITP-specific comorbidities is sparse and there is little empirical evidence in the literature on the association between ITP and other medical conditions. ITP is associated with a number of medical conditions such as haematological diseases, dermatological conditions, bleeding disorders, and constitutional conditions (e.g. chills, rigors, malaise, lethargy) which may suggest these conditions share similar causal pathways with ITP. There are also other conditions associated with ITP only after ITP diagnosis such as oral conditions, infections, gastrointestinal, and autoimmune disorders. This could indicate ITP being on the causal pathway of these conditions (Feudjo-Tepie, 2009). The results from a study published in 2010 indicate increased risks of diabetes, renal failure, vascular events, lymphoma, and leukemia in ITP patients with persistent or chronic disease compared to patients without ITP disease. In addition, increased mortality was observed during the study period in individuals with ITP, in comparison to a non-diseased cohort (Enger, 2010).

Table 3 Summary of Epidemiology of Thrombocytopenia in Patients with Chronic Liver Disease

Incidence	Thrombocytopenia is a common complication in patients with chronic liver disease (CLD) that puts them at risk of bleeding with each of the multiple invasive diagnostic and therapeutic procedures they routinely undergo over the course of their disease (Abd-Elsalam, 2016; Mitchell, 2016; Giannini, 2015; Gangireddy, 2014; Hanafiah, 2013; Afdhal, 2012; Afdhal, 2008). The incidence of thrombocytopenia ranges from 64% to 84% of patients with cirrhosis or fibrosis, with the extent of thrombocytopenia often worsening with the severity of their disease (Mitchell, 2016).
Prevalence	Approximately 29 million people in the EU region suffer from a chronic liver condition. About 0.1% of the European population is affected by cirrhosis, corresponding to 14 to 26 new cases per 100,000 inhabitants per year (Blachier, 2013). The prevalence of thrombocytopenia varies according to several factors, such as the definition used, the patient population and severity of underlying liver disease (Peck-Radosavljevic, 2017; Afdhal, 2012; Poordad, 2007; Peck-Radosavljevic, 2007). The prevalence of thrombocytopenia in patients affected by CLD is up to 76%, being greater in patients with advanced fibrosis and cirrhosis (Mitchell, 2016; Maan, 2015; Cuker, 2010; Weksler, 2007). The prevalence of thrombocytopenia is higher in patients with liver failure (Giannini, 2015). Based on data from National Health and Nutrition Examination Surveys, the prevalence of thrombocytopenia was 7.6% among hepatitis C virus (HCV)-infected individuals (Tana, 2015).
Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:	Thrombocytopenia is the most common haematological complication encountered in patients with chronic liver disease (Afdhal, 2008). Due to differing cut-off values for defining thrombocytopenia, and the diversity in patient populations with chronic liver disease, the prevalence of thrombocytopenia in different studies ranges from 6% among non-cirrhotic patients with chronic liver disease up to 70% among patients with liver cirrhosis (Maan, 2015). Women are thought to represent less than 40% of all patients with cirrhosis in the United States (US). These estimates are similar to recent data from 23 European countries. The incidence of cirrhosis in women over the age of 50 years in the United Kingdom is estimated at 26 per 100,000 women per year; extended to the US population, this would represent an incidence of over 13,000 cases per year (Allen, 2014). In a large cohort of 102,155 patients with cirrhosis, the average age was 58 years, with 63% male. In this cohort, 57% of patients were white, 17% were Hispanic, and 7% were black (Mellinger, 2015).
	Risk factors for thrombocytopenia in CLD include: • Decreased production from impaired thrombopoietin or bone marrow suppression caused by viruses, alcohol, iron overload, and medications (Mitchell, 2016). • Splenic sequestration (Mitchell, 2016). • Increased rate of platelet destruction from increased shear stress, increased fibrinolysis, bacterial translocation, and infection that result in an increased rate of platelet aggregation, while raised titers of antiplatelet immunoglobulin result in the immunologic destruction of platelets (Mitchell, 2016).

The main existing treatment options	Platelet transfusion, splenic artery embolization, and splenectomy (MaanMaan, 2015;Hayashi, 2014; Violi, 2011).
Natural history of the indicated condition in the population, including mortality and morbidity	Severe thrombocytopenia (<50×10^9/L) in CLD can be associated with significant morbidity, often complicating the medical management of patients with advanced liver disease (Afdhal, 2008; Hayashi, 2014). Patients with CLD frequently undergo medical procedures for diagnosis and treatment, some of which are invasive. These procedures include liver biopsies, banding, paracentesis and thoracentesis for ascites, etc. The presence of thrombocytopenia complicates the management of these patients due to the increased risk of bleeding from such procedures which can increase associated morbidity, length of hospitalisation and the risk of mortality (Poordad, 2007). In addition, the use of the current standard of care, platelet transfusions, to treat the thrombocytopenia before scheduled procedures, can lead to refractoriness to subsequent platelet transfusions, an unintended consequence that itself significantly impacts patients' safety, resulting in the loss of a primary therapeutic modality to address spontaneous, uncontrolled bleeding; for which patients with CLD are already at increased risk as a comorbidity of their liver disease. Further, platelet refractoriness is associated with prolonged hospitalizations, increased bleeding, decreased survival, and higher healthcare costs, and it often leads to the need to delay or even cancel important scheduled procedures for patients with CLD (Schiffer, 2001).
Important co-morbidities	A chronically damaged liver affects almost every bodily process, including the functions of the digestive, hormonal, and circulatory systems. Decompensated cirrhosis increases the risk of serious and potentially life-threatening complications. Once decompensation occurs, mortality rates without liver transplantation can be as high as 85% within 5 years. The most serious complications are those associated with portal hypertension. The important comorbidities found in the target population are: • Ascites • Variceal haemorrhage from portal hypertension • Spontaneous bacterial peritonitis • Hepatic encephalopathy • Liver cancer • Pancreatitis • Hypoalbuminemia • Elevated partial thromboplastin time • Portal vein thrombosis (PVT) • Alcoholism • Drug abuse • Viral hepatitis • Non-alcoholic fatty liver disease

CLD = chronic liver disease, EU = European Union, HCV = hepatitis C virus, PVT = portal vein thrombosis, US = United States.

Part II Module SII – Nonclinical Part of the Safety Specification

Table 4 Key Findings from Non-clinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity		
Key issues identified from acute or repeat dose toxicity studies	Gastrointestinal toxicity: In repeated dose toxicity studies, treatment-related gastric lesions were observed in mice, rats, and cynomolgus monkeys. In these species, avatrombopag caused histopathology changes in the fundic mucosa of the glandular stomach, characterized by degeneration of the glandular epithelium with a decrease in matured parietal cells. This effect was not associated with inflammatory response or any evidence of erosion or ulcer formation. The severity of gastric lesions was dependent on dose and duration of avatrombopag administration and showed a clear trend towards reversibility during the recovery period. The exposures (area under concentration-time curve [AUC]) at doses that showed no gastric lesions across the species were 3 to 33-fold higher than the exposures in humans at the maximum recommended human dose (MRHD). These histologic changes in the stomach were accompanied by elevation of serum gastrin in animals and were reversible even after chronic treatment.	These changes were confirmed by mechanistic studies to be compatible with a "gastrin hypothesis" (Chandra, 2010), associated with hypergastrinemia in repeated dose studies related to gastric mucosal changes similar to the cases of antisecretory agents such as proton pump inhibitors and histamine receptor (H2) blockers, leading to the conclusion that the results are not likely to be relevant to humans. The gastrin hypothesis may be outlined as follows: 1) Inhibition of gastric acid secretion leads to elevated antral pH and, secondarily, to release of gastrin from the antral gastrin cells into the bloodstream. 2) Gastrin causes both general hypertrophy of the oxyntic mucosa and hyperplasia of the enterochromaffin-like (ECL) cells in the oxyntic mucosa. These drug-induced effects are reversible and can be prevented by antrectomy, which supports the hypothesis that hypergastrinemia is a causative event in oxyntic mucosal hypertrophy and ECL cell proliferation. No elevations in gastric biomarker levels were identified in patients with ITP treated with avatrombopag in the clinical programme.
	Skeletal muscle toxicity: Reversible skeletal muscle-related toxicity (degeneration/necrosis) with increases in creatinine phosphokinase (CPK) and aldolase were seen in short-term (up to 4-week) studies in F344 strain rats, but not in longer-term studies including at higher doses. In cynomolgus monkeys, similar changes were reported only in 4-week studies, but not in the 1-week study with higher doses or in any of the other longer-term studies. No such changes were observed in mice, SD rats, or dog repeated dose studies.	There has been no evidence of changes in CPK levels in the clinical programme.

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Reproductive/ developmental toxicity	Avatrombopag has no effect on male and female fertility or early embryogenesis in rats. There were no embryo-foetal effects noted in rats or rabbits that were administered avatrombopag during organogenesis (exposures 35 to 53 -times the human exposure based on AUC). Pre and postnatal development studies in rats showed no embryo-foetal effects, and no effects on postnatal development, although postnatal survival was lower when pups were exposed to avatrombopag both during gestation and lactation. There were no effects on behavioural or reproductive functions in the offspring.	The safety of avatrombopag has not been established in pregnant or lactating human females. There has been 1 reported case of pregnancy in a healthy subject in Phase 1 Study 019 during the use of avatrombopag. The subject delivered a healthy baby boy at 38.5 weeks of gestation via vaginal delivery. There has been no human experience in lactating females. Patients who are pregnant with CLD would not likely undergo procedures required for this treatment.
Safety Pharmacology		
Nephrotoxicity	Reversible renal toxicity was limited to dogs with renal tubular cell necrosis and regeneration with increases in serum blood urea nitrogen (BUN) and creatinine. These effects were observed at high doses and likely associated with maleic acid, the salt moiety of avatrombopag, since dogs are known to be susceptible to maleic acids, causing similar lesions (Everett, 1993; Fiume, 2007). The systemic exposure at no-observed-adverse-effect-level (NOAEL) was 9-fold higher than the human AUC. No nephrotoxicity was observed in mice, rats and cynomolgus monkeys.	There has been no evidence of renal toxicity in clinical studies.
Other Toxicity-Related Information or Data		
Carcinogenicity	In 2-year carcinogenicity studies in mice and rats, neuroendocrine cell (ECL cell) tumours (carcinoids, 60 and 160 mg/kg/d in mice and 160 mg/kg/d in rats) and neuroendocrine cell hyperplasia (rats only, 50 and 160 mg/kg/d) occurred in the stomach. The gastric carcinoids were considered likely due to prolonged hypergastrinemia observed in toxicity studies. Hypergastrinemia-related gastric carcinoids in rodents are generally considered to be of low risk or relevance to humans. No tumours were observed at doses up to 20 mg/kg in mice (14 times the human exposure based on AUC) and 50 mg/kg in rats (48 times the human exposure based on AUC).	These changes were confirmed by mechanistic studies to be compatible with a “gastrin hypothesis” (Chandra, 2010), associated with hypergastrinemia in repeated-dose studies related to gastric mucosal changes similar to the cases of antisecretory agents such as proton pump inhibitors and H2 blockers, leading to the conclusion that the results are not likely to be relevant to humans. In addition to the rodent-specific mechanisms for gastric carcinoids, there were no gastric tumour findings in any of the repeated-dose toxicity studies in animals.

AUC = area under concentration-time curve, BUN = blood urea nitrogen, CLD = chronic liver disease, CPK = creatinine phosphokinase, ECL = enterochromaffin-like, H2 = histamine receptor, MRHD = maximum recommended human dose, NOAEL = no-observed-adverse-effect-level, SD = Sprague Dawley

Part II Module SIII – Clinical Trial Exposure

As of the DLP for this RMP, 1813 participants have been enrolled in the avatrombopag clinical programs and received avatrombopag, placebo, or active comparator.

In the completed clinical studies, a total of 1520 participants have been exposed to avatrombopag, 608 of whom were healthy volunteers and 912 were patients with ITP, chemotherapy-induced thrombocytopenia (CIT), or CLD.

The cumulative subject exposure is provided by gender, age group, and race in completed healthy volunteer studies (Table 5, Table 6), and for patients with ITP, CIT, or CLD) (Table 7, Table 8), below.

Table 5 Cumulative subject exposure to avatrombopag in completed healthy volunteer studies by age and gender

Age range	Number of subjects[a]		
	Male	Female	Total
<18	0	0	0
18 to 65	406	202	608
66 to 75	0	0	0
>75	0	0	0
Total	**406**	**202**	**608**

[a] Includes studies 477-CL-001, 477-CL-002, 501-PK-901, 501-PK-902, E5501-A001-001, E5501-A001-005, E5501-A001-006, E5501-A001-007, E5501-G000-010, E5501-G000-008, E5501-G000-012, E5501-A000-017, E5501-J081-015, E5501-A001-018, E5501-A001-019, AVA-PED-101, AVA-BE-101, and AVA-BE-102.

Table 6 Cumulative subject exposure to avatrombopag in completed healthy volunteer studies by racial group

Racial/ethnic group	Number of subjects[a]
Caucasian	414
Black	99
Asian	78
Other	17
Unknown	0
Total	**608**

[a] Includes studies 477-CL-001, 477-CL-002, 501-PK-901, 501-PK-902, E5501-A001-001, E5501-A001-005, E5501-A001-006, E5501-A001-007, E5501-G000-010, E5501-G000-008, E5501-G000-012, E5501-A000-017, E5501-J081-015, E5501-A001-018, E5501-A001-019, AVA-PED-101, AVA-BE-101, and AVA-BE-102.

Table 7 Cumulative exposure to avatrombopag in completed studies of patients with ITP, CIT, or CLD by age and sex

Age range	Number of subjects[a]		
	Male	**Female**	**Total**
<18	39	36	75
18-65	364	293	657
66-75	71	70	141
>75	19	20	39
Total	**493**	**419**	**912**

Abbreviations: CIT, chemotherapy-induced thrombocytopenia; CLD, chronic liver disease; ITP, immune thrombocytopenia.

[a] Includes completed CLD studies E5501-G000-202, E5501-G000-203, E5501-J081-204, E5501-G000-310, and E5501-G000-311. Includes completed ITP studies 501-CL-003, 501-CL-004, E5501-G000-302, E5501-G000-305, AVA-ITP-CN301, AVA-PED-301, AVA-ITP-307, and AVA-ITP-401. Includes Study AVA-PST-320, which enrolled patients with either ITP or CLD, and Study AVA-CIT-330, which enrolled patients with CIT.

Table 8 Cumulative exposure to avatrombopag in completed studies of patients with ITP, CIT, or CLD by racial group

Racial/ ethnic group	Number of subjects[a]
Asian	236
Black	32
Caucasian	601
Other/Missing	43
Total	912

Abbreviations: CIT, chemotherapy-induced thrombocytopenia; CLD, chronic liver disease; ITP, immune thrombocytopenia.

[a] Includes completed CLD studies E5501-G000-202, E5501-G000-203, E5501-J081-204, E5501-G000-310, and E5501-G000-311. Includes completed ITP studies 501-CL-003, 501-CL-004, E5501-G000-302, E5501-G000-305, AVA-ITP-CN301, AVA-PED-301, AVA-ITP-307, and AVA-ITP-401. Includes Study AVA-PST-320, which enrolled patients with either ITP or CLD, and Study AVA-CIT-330, which enrolled patients with CIT.

Part II Module SIV – Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 9 Important Exclusion Criteria in Pivotal Studies Across the Development Programme

I. Important Exclusion Criteria in Pivotal Studies Across the Chronic Liver Disease (CLD) Development Programme			
Criterion	**Reason for Exclusion**	**Included as Missing Information (Yes/No)**	**Rationale**
History of significant cardiovascular disease	Avatrombopag has not been specifically studied in subjects with cardiac impairment.	No	Thrombotic/thromboembolic complications are included as an important potential risk.
Women of childbearing potential. Pregnant or lactating females	The available scientific data on avatrombopag in pregnant women are insufficient to establish a drug-associated risk of adverse developmental outcomes. There are no adequate and well-controlled studies with avatrombopag in pregnant women. Whether avatrombopag can cause foetal harm when administered to a pregnant woman is not known.	No	Patients who are pregnant with chronic liver disease (CLD) would not likely be undergoing procedures required for this treatment.
Portal vein blood flow velocity rate <10 cm/second	To decrease the risk of portal vein thrombosis (PVT) due to decreased blood flow in the portal veins and portal hypertension.	No	Low portal vein flow could be a predisposing factor for portal vein thrombosis. Portal vein thrombosis is an important potential risk.
Platelet transfusion or receipt of blood products containing platelets within 7 days of screening	Use of platelet transfusions and products containing platelets would interfere with the ability to assess efficacy in clinical studies.	No	This exclusion was solely relevant to the assessment of efficacy in the context of the clinical trials.
Haemoglobin levels ≤8.0 or ≥18.0 g/dL for men and >15 for women at screening, with haematocrit ≥54% for men and ≥45% for women	Anaemia is a common side effect of antiviral therapy, which is a commonly used concomitant medication in CLD. High haemoglobin levels may indicate bone marrow dysfunction.	No	The safety and efficacy of avatrombopag are not expected to differ in subjects whose haematological parameters are not in normal ranges.

Use of interferon within 14 days of screening and erythropoietin stimulating agents within 7 days of screening	Interferons can cause thrombocytopenia. Use of interferon and erythropoietin stimulating agents can therefore interfere with the ability to assess the efficacy of avatrombopag. The effect of these pegylated interferon agents may be more than two weeks, the time defined to abstain from treatment. This exclusion was solely relevant to the assessment of efficacy in the context of the clinical trials. Although the use of interferon is associated with specific toxicities, the safety of avatrombopag is not expected to differ in subjects using interferon and erythropoietin stimulating agents	No	
Use of heparin, warfarin, nonsteroidal anti-inflammatory drugs (NSAID), aspirin, verapamil, and antiplatelet therapy with ticlopidine or glycoprotein Iib/IIIa antagonists (e.g., tirofiban) within 7 days of screening	Risk of bleeding is associated with heparin and warfarin use and the risk of liver and renal toxicity with NSAIDs use. Aspirin can cause alanine aminotransferase (ALT) elevation. A drug interaction study with verapamil, a known P-gp inhibitor, suggests an interaction. Ticlopidine and glycoprotein IIb/IIIa antagonists would interfere with the ability to assess efficacy and ticlopidine can also cause thrombotic thrombocytopenic purpura.	No	This exclusion was solely relevant to the assessment of efficacy in the context of the clinical trials. Risk of bleeding with heparin and warfarin use and the risk of liver and renal toxicity with NSAIDs use are already well established.
History of genetic prothrombotic syndromes	To minimize the potential impact of it on efficacy and safety measurements.	No	Independent risk factor for thrombosis.
History of any primary hematologic disorder (e.g., myelodysplastic syndrome)	To avoid recruiting patients with previous damage to bone marrow to minimize the impact on safety results.	No	Use in this patient population is not expected to add new safety concerns for avatrombopag since other TPOs are used in these populations.
Current malignancy including solid tumours and hematologic malignancies (except hepatocellular carcinoma)	To ensure the quality of the data captured for the specific population to minimize the potential impact on efficacy and safety results.	No	Malignancy is an independent risk factor for thrombosis.

Hepatocellular carcinoma and Barcelona Clinic Liver Cancer staging classification C or D	To ensure a homogenous disease population and interpretability of efficacy and safety results as liver cancer is a serious long-term risk with cirrhosis.	No	Malignancy is an independent risk factor for thrombosis.
Clinically significant acute or active bleeding (gastrointestinal, central nervous system, etc.)	There can be an increased risk of bleeding with prior acute or active bleeding, which can impact the evaluation of bleeding and bleeding events.	No	It is well known that patients with thrombocytopenia have an increased risk of bleeding.
Hepatic encephalopathy that cannot be effectively treated	To ensure a homogenous disease population and interpretability of efficacy and safety results as hepatic encephalopathy is a serious complication associated with portal hypertension.	No	Hepatic encephalopathy is a serious complication associated with portal hypertension.
Subjects with MELD scores > 24	To ensure enrolled patients would have a high probability of survival, complete the trial, and not confound the safety and efficacy analyses of the Phase 3 studies due to early drop out from complications of their advanced liver disease or high mortality rate.	Yes	
Active infection requiring systemic antibiotic therapy within 7 days of screening	To ensure that the evaluation of the safety profile in clinical studies was not affected by active infection and to reduce the risk of antibiotic-induced thrombocytopenia, which may impact the efficacy of avatrombopag.	No	The safety profile of avatrombopag is not expected to differ in subjects with active infection.
Alcohol abuse, alcohol dependence syndrome, drug abuse, or drug dependence within 6 months of the study start or acute alcoholic hepatitis within 6 months	Alcohol use could interfere with adherence to study requirements. Patients with chronic alcoholic hepatitis were allowed in the clinical trials.	No	The safety and efficacy of avatrombopag is not expected to differ in alcohol abuse and alcohol dependent subjects.
Liver transplant subjects	To ensure the evaluation of the safety profile in clinical studies was not affected by other pre-existing diseases.	No	Thrombocytopenia is a common complication in liver transplantation.
HIV positive patients	To ensure the evaluation of the safety profile in clinical studies was not affected by other pre-existing diseases.	No	The safety and efficacy of avatrombopag is not expected to differ in HIV positive patients.

II. Important Exclusion Criteria in Pivotal Studies Across the Chronic Immune Thrombocytopenia (ITP) Development Programme			
Criterion	**Reason for Exclusion**	**Included as Missing Information (Yes/No)**	**Rationale**
History of significant cardiovascular disease	Avatrombopag has not been specifically studied in subjects with significant cardiac impairment.	No	Thrombotic/thromboembolic complications is included as an important potential risk.
Women of childbearing potential. Pregnant or lactating females	The available scientific data on avatrombopag in pregnant women are insufficient to establish a drug-associated risk of adverse developmental outcomes. There are no adequate and well controlled studies with avatrombopag in pregnant women. Whether avatrombopag can cause foetal harm when administered to a pregnant woman is not known.	No	Avatrombopag is not recommended for use during pregnancy and in women of childbearing potential not using contraception.
History of cirrhosis, portal hypertension, and chronic active hepatitis	To decrease the risk of portal vein thrombosis (PVT) due to decreased blood flow in the portal veins and portal hypertension.	No	This exclusion was solely relevant to the assessment of efficacy and safety in the ITP population.
History of pernicious anemia or subjects with vitamin B12 deficiency (defined as <LLN) who did not have pernicious anemia excluded as a cause	Pernicious anemia and ITP have an autoimmune basis and can result in thrombocytopenia	No	This exclusion was solely relevant to the assessment of efficacy in the context of the clinical trials.
Known secondary immune thrombocytopenia (e.g., subjects with known *Helicobacter pylori*-induced ITP, infected with known human immunodeficiency virus [HIV] or hepatitis C virus [HCV] or subjects with known systemic lupus erythematosus)	To ensure the enrolled population was limited to subjects with primary ITP.	No	This exclusion was solely relevant to the assessment of efficacy in the context of the clinical trials.

Subjects with concurrent malignant disease	To ensure the quality of the data captured for the specific indication to minimize the potential impact on efficacy and safety results.	No	Malignancy is an independent risk factor for thrombosis.
History of myelodysplastic syndrome	To avoid recruiting patients with previous damage to bone marrow to minimize the impact on safety results.	No	Use in this patient population is not expected to add new safety concerns for avatrombopag since other TPO-R agonists are used in these populations.
Subjects with clotting disorders or the presence of significant risk factors for thrombosis	Thrombotic risks are associated with TPO-R agonists	No	Thrombotic/thromboembolic risks are listed as an important potential risk.
Splenectomy or recent use of corticosteroids, mycophenolate mofetil, Cyclosporine A, danazol, immunoglobulins, rituximab, romiplostim, or eltrombopag, cyclophosphamide, or vinca alkaloid regimens	To ensure the quality of the data captured for the specific indication, to minimize the potential impact on efficacy and safety results.	No	This exclusion was solely relevant to the assessment of efficacy in the context of the clinical trials.
Prior history of arterial or venous thrombosis (stroke, transient ischemic attack, myocardial infarction, deep vein thrombosis, or pulmonary embolism), and more than 2 of the following risk factors: estrogen-containing hormone replacement or contraceptive therapies, smoking, diabetes, hypercholesterolemia, medication for hypertension, cancer, hereditary thrombophilic disorders (e.g., Factor V Leiden, antithrombin III deficiency, etc.), or any other family history of arterial or venous thrombosis	To ensure the quality of the data captured for the specific indication, to minimize the potential impact on efficacy and safety results.	No	The safety and efficacy of avatrombopag is not expected to differ in these populations.

ALT = alanine aminotransferase, CLD = chronic liver disease, HIV = human immunodeficiency virus, ITP = immune (idiopathic) thrombocytopenic purpura, MELD = Model for End-Stage Liver Disease, NSAID = nonsteroidal anti-inflammatory drug, PVT = portal vein thrombosis, TPO = thrombopoietin.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme with avatrombopag is unlikely to detect rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Chronic liver disease

Only a limited number of Child-Pugh class C subjects were enrolled in the clinical development programme for avatrombopag. Although the safety data accumulated during the development programme do not support a role for avatrombopag in hepatic deterioration or fatal outcomes in Child-Pugh class C patients, hepatic worsening function in patients with Child-Pugh class C liver disease has been included as an important potential risk.

Chronic immune thrombocytopenia

Only male or female subjects 18 years of age or older with a confirmed diagnosis of ITP were eligible to participate in the development programme. In addition, subjects were excluded from the development programme if a physical examination upon subject screening suggested any disease other than ITP might have caused thrombocytopenia.

Due to limited or no information available, the safety of avatrombopag in adult patients with chronic ITP and human immunodeficiency virus [HIV], hepatitis C virus [HCV] or subjects with known systemic lupus erythematosus, acute hepatitis, active chronic hepatitis, cirrhosis, lymphoproliferative disease, myeloproliferative disorders, leukemia, myelodysplasia (MDS), concurrent malignant disease, and significant cardiovascular disease have not been established.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 10 Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Evaluation of avatrombopag exposure versus degree of hepatic impairment assessed by Child-Pugh score and/or model for end-stage liver disease (MELD) score was performed by population pharmacokinetics analysis in Study 202, 203, 310, and 311.
• Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from the inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with a relevant different ethnic origin	Details of the number of patients exposed to avatrombopag in completed clinical studies by race are provided in Module SIII.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.
Other	Not included in the clinical development programme.

MELD = model for end-stage liver disease.

PART II MODULE SV – POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation Exposure

Doptelet is authorised worldwide for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure and for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Additionally, FDA has approved Doptelet for thrombocytopenia in pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia who have had an insufficient response to a previous treatment.

From the IBD for Doptelet® (21 May 2018) through the DLP for this RMP, the cumulative patient exposure for all approved indications in the marketed setting is estimated to be 30 467.9 patient-years.

SV.1.1 Method Used to Calculate Exposure

The post-authorisation exposure is calculated by extrapolating the approximate* overall patient-years from the number of blister pack units leaving Sponsor's control per the calculation below:

Mathematical representation: $\frac{x(A+B)+(CxD)}{365.25} =$ Total patient-years exposure

where:

x = 5-day course of therapy

A = total units of 10 tablet blister packs of DOPTELET leaving Sponsor's control

B = total units of 15 tablet blister packs of DOPTELET leaving Sponsor's control

C = total units of 30 tablet DOPTELET blister packs leaving Sponsor's control

D = 30-day course of therapy, on average

365.25 = # days in a year (the 0.25 accounts for leap years)

* It is recognized that not all product leaving the Sponsor's control has been dispensed and consumed by patients, with some product remaining in stock at wholesalers, hospitals, clinics, and pharmacies. However, this methodology provides a consistent approach in estimating overall patient-years of exposure.

SV.1.2 Exposure

Table 11 Cumulative avatrombopag postmarketing distribution – CLD and ITP indications combined

Region	Sales data			
	Total 20-mg tablets	**Total patient days**	**Patient-years**	**Patients**
EU	3 734 575	2 907 430	7960.1	177 561
US	4 378 440	3 885 695	10 638.4	190 203
China	7 512 050	3 165 715	8667.3	633 143
UK	728 165	650 175	1780.1	31 085
GCC countries	162 770	138 895	380.3	6648
Australia	171 750	171 750	470.2	5725
Russia	84 210	82 245	225.2	3069
Canada	71 660	69 435	190.1	2557
Levant region	40 920	40 920	112.0	1364
Japan	33 790	14 155	38.8	2831
East Asia	1500	540	1.5	108
South America	1440	1440	3.9	48
Total	**16 921 270**	**11 128 395**	**30 467.9**	**1 054 342**

Table 12 Cumulative avatrombopag postmarketing distribution data by indication

Region	CLD indication				ITP indication			
	Total 20-mg tablets	**Total patient days**	**Patient-years**	**Patients**	**Total 20-mg tablets**	**Total patient days**	**Patient-years**	**Patients**
EU	1 311 025	483 880	1324.8	96 776	2 423 550	2 423 550	6635.3	80 785
US	856 800	364 055	996.7	72 815	3 521 640	3 521 640	9641.7	117 388
China	7 512 050	3 165 715	8667.3	633 143	-	-	-	-
UK	134 465	56 475	154.6	11 295	593 700	593 700	1625.5	19 790
GCC countries	36 020	12 145	33.3	2423	126 750	126 750	347.0	4225
Australia	-	-	-	-	171 750	171 750	470.2	5725
Russia	3930	1965	5.4	393	80 280	80 280	219.8	2676
Canada	3680	1455	4.0	291	67 980	67 980	186.1	2266
Levant region	-	-	-	-	40 920	40 920	112.0	1364
Japan	33 790	14 155	38.8	2831	-	-	-	-
East Asia	1500	540	1.5	108	-	-	-	-
South America	-	-	-	-	1440	1440	3.9	48
Total	**9 893 260**	**4 100 385**	**11 226.4**	**820 075**	**7 028 010**	**7 028 010**	**19 241.5**	**234 267**

Part II Module SVI – Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

There is no perceived potential for avatrombopag to be used for illegal purposes due to its mechanism of action. There have also been no reports associated with recreational use or any related misuse since initial product launch in the US on 04-Jun-2018.

Part II Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 13 Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks		
	CLD	ITP	
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated) Known risks that do not impact the risk-benefit profile.	• anaemia • bone pain • fatigue • myalgia • pyrexia	• headache • fatigue • nausea • blood glucose increased • dizziness • platelet count increased • blood glucose decreased • blood triglycerides increased • diarrhoea • epistaxis • thrombocytopenia • vomiting • arthralgia • back pain • pain in extremity • abdominal pain upper • blood lactate dehydrogenase increased • flatulence • hyperlipidaemia • myalgia • platelet count decreased • rash • acne • alanine aminotransferase increased • anaemia • asthenia • blood gastrin increased	• deep vein thrombosis • dehydration • dry skin • dysgeusia • ear pain • ecchymosis • eructation • eye irritation • eye pruritus • eye swelling • furuncle • gastrooesophageal reflux disease • glossodynia • haematuria • haemoptysis • haemorrhoids • heart rate irregular • hepatic enzyme increased • hunger • hyperacusis • hyperhidrosis • hypertriglyceridaemia • hypoaesthesia • increased appetite • iron deficiency • jugular vein thrombosis • lacrimation increased • leukocytosis • limb discomfort • menorrhagia • mood swings • muscle spasms • muscular weakness • musculoskeletal chest pain

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks		
	CLD	ITP	
		• decreased appetite • dyspnoea • head discomfort • hypertension • migraine • musculoskeletal pain • paraesthesia • petechiae • pruritis • splenomegaly • abdominal discomfort • abdominal distension • abdominal pain lower • abnormal sensation in eye • alopecia • anorectal varices • arthropathy • aspartate aminotransferase increased • blood pressure increased • cerebrovascular accident • chest discomfort • cognitive disorder • constipation	• myelofibrosis • myocardial infarction • nasal congestion • nipple pain • ocular discomfort • pain • paraesthesia oral • peripheral swelling • photophobia • pigmentation disorder • portal vein thrombosis • pulmonary embolism • rash pruritic • retinal artery occlusion • sensory disturbance • skin haemorrhage • skin irritation • swollen tongue • Thrombophlebitis septic • tongue disorder • transient ischaemic attack • upper respiratory tract infection • vasoconstriction • vision blurred • visual impairment

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks	
	CLD	ITP
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised).	Potentially clinically important interactions with dual moderate or strong CYP3A4/5 and CYP2C9 inhibitors and inducers	

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 14 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-Benefit Impact
Important Identified Risks	
Thrombotic/Thromboembolic Events	Thrombotic/thromboembolic events are a known concern with the TPO-RA class of products. Patients with chronic liver disease are also known to be at increased risk for thromboembolic events as a comorbidity of their disease. Portal vein thrombosis (PVT) has been reported at an increased frequency in patients with chronic liver disease who had platelet counts >200 x 10^9/L receiving a TPO receptor agonist (Afdhal, 2012). In clinical studies in patients with chronic immune thrombocytopenia, thromboembolic events (arterial or venous) occurred in 7% (9/128) of patients receiving avatrombopag.
Bone marrow fibrosis related to long-term and repeat use	Increased bone marrow reticulin is believed to be a result of TPO receptor stimulation, leading to an increased number of megakaryocytes in the bone marrow. With long-term use, thrombopoietin receptor (TPO-R) agonists may increase the risk for the development or progression of reticulin fibres/fibrosis within the bone marrow. Studies have found that the overexpression of TPO can lead to bone marrow changes in animals and humans (Kuter, 2009; Cuker, 2010). Bone marrow fibrosis has been observed with chronic/long-term use of TPO-RAs in patients with ITP (Ghanima, 2014; Hogan, 2019). For CLD patients undergoing multiple procedures, avatrombopag may be prescribed more than once, but experience with repeat use is limited.

Safety Concern	Risk-Benefit Impact
Important Potential Risks	
Hepatic worsening function in patients with Child-Pugh class C	The data to date do not support a role for avatrombopag in hepatotoxic effects or deterioration in hepatic function, including death, in Child-Pugh class C patients receiving avatrombopag, but it remains an important potential risk.
Haematological malignancies	TPO-RAs are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation, and platelet production. There is a theoretical concern that TPO-RAs may stimulate the development of haematological malignancies.
Missing Information	
Use in patients with MELD scores > 24	Patients with a MELD score >24 were excluded from the chronic liver disease pivotal studies because these patients have such a poor prognosis and high mortality rate, e.g., a MELD score of 24 is associated with a 3-month mortality rate of ~20%. Therefore, these patients were not considered ideal patients to enrol in the clinical trials. However, there is no scientific rationale to suggest these patients would not otherwise benefit from and be considered as candidates for avatrombopag prior to a planned procedure, but definitive information is missing.

PVT = portal vein thrombosis, TPO = thrombopoietin.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

SVII.2.1 Use in splenectomy patients with chronic liver disease, Use in patients receiving interferon products and Safety in patients undergoing invasive procedures.

As per Guideline on good pharmacovigilance practices (GVP) 3 Module V – Risk management systems (Rev 2) the missing information: Use in splenectomy patients with chronic liver disease, Use in patients receiving interferon products and Safety in patients undergoing highly invasive procedures was removed.

No PASS activities or additional pharmacovigilance activities are planned to address the missing information components. These components have been followed in the PSUR, and no relevant safety concerns have been identified since the product has been authorised.

SVII.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 15 Important Identified Risk: Thrombotic/Thromboembolic Events

<table>
<tr><td>Potential mechanisms</td><td>Dose dependent increase in platelet count.</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>As a class, TPO receptor agonists stimulate the production of endogenous platelets and thus may increase the risk of the occurrence of thrombotic / thromboembolic events. In addition, patients with chronic liver disease (CLD) and immune thrombocytopenia (ITP) are also known to be at increased risk for occurrence of these events.
In the clinical development program, 7.0% (9/128) of patients with chronic ITP who were treated with avatrombopag experienced a thromboembolic event. With the exception of cerebrovascular accident which was reported in 1.6% (2/128) patients, there was no clustering of a specific thromboembolic event type, the time to onset varied from greater than 26 weeks to less than 4 weeks after beginning treatment, there was no relationship to drug dose, and the events typically occurred at a platelet count below the upper limit of normal (450,000/μL). In patients with CLD, 0.4% (1/274) experienced a thromboembolic event.</td></tr>
<tr><td colspan="2">Characterisation of the Risk</td></tr>
<tr><td>Frequency</td><td>CLD
<table>
<tr><td></td><td colspan="2">Phase 3 Pivotal Studies Safety Set</td></tr>
<tr><td></td><td>Placebo
N = 156
n (%)</td><td>Avatrombopag
N = 274
n (%)</td></tr>
<tr><td>Subjects Reporting Any Thrombotic/thromboembolic standardised MedDRA query (SMQ) Events – n (%)</td><td>2 (1.3)</td><td>1 (0.4)</td></tr>
<tr><td>95% confidence interval of subject incidence (%)</td><td>(-0.48, 3.05)</td><td>(-0.35, 1.08)</td></tr>
<tr><td></td><td colspan="2">Phase 3 Pivotal Studies Safety Set</td></tr>
<tr><td></td><td>Placebo
N = 156
n (%)</td><td>Avatrombopag
N = 274
n (%)</td></tr>
<tr><td>Subjects Reporting Portal Vein Thrombosis Events – n (%)</td><td>0 (0.0)</td><td>1 (0.4)</td></tr>
<tr><td>95% confidence interval of subject incidence (%)</td><td>(0,0)</td><td>(-0.35, 1.08)</td></tr>
</table>
ITP
In the Avatrombopag Treatment Group, 7.0% (9/128) of subjects reported treatment-emergent AESI in the Thromboembolic Events category; the exposure-adjusted incidence rate per patient-year was 0.124. All Thromboembolic Event AESI were reported in only single avatrombopag-treated subjects (0.8%), except for cerebrovascular accident, which was reported by 2 (1.6%) subjects; there was no clustering of a specific thromboembolic event type, and no safety signal was</td></tr>
</table>

identified. The time of onset of AESI in the Thromboembolic Events category was greater than 26 weeks for 2 subjects, 12 to less than 26 weeks for 4 subjects, 4 to less than 12 weeks for 1 subject, and 1 to less than 4 weeks for 2 subjects.

Severity

CLD

Subjects Reporting Any Thrombotic/Thromboembolic (SMQ) Events – n (%)	Phase 3 Pivotal Studies Safety Set	
	Placebo N = 156 n (%)	Avatrombopag N = 274 n (%)
Grade 1 (Mild)	0 (0.0)	0 (0.0)
Grade 2 (Moderate)	0 (0.0)	0 (0.0)
Grade 3 (Severe)	1 (0.6)	1 (0.4)
Grade 4 (Life-threatening)	0 (0.0)	0 (0.0)
Grade 5 (Fatal)	1 (0.6)	0 (0.0)

Subjects Reporting Portal Vein Thrombosis Events – n (%)	Phase 3 Pivotal Studies Safety Set	
	Placebo N = 156 n (%)	Avatrombopag N = 274 n (%)
Grade 1 (Mild)	0 (0.0)	0 (0.0)
Grade 2 (Moderate)	0 (0.0)	0 (0.0)
Grade 3 (Severe)	0 (0.0)	1 (0.4)
Grade 4 (Life-threatening)	0 (0.0)	0 (0.0)
Grade 5 (Fatal)	0 (0.0)	0 (0.0)

ITP

Subjects Reporting Any Thrombotic/Thromboembolic (SMQ) Events – n (%)	Studies CL-003, CL-004, 302, 305		
	Placebo N = 22 n (%)	Eltrombopag (N=11) n (%)	Avatrombopag N = 128 n (%)
Grade 1 (Mild)	0 (0.0)	0 (0.0)	1 (0.8)
Grade 2 (Moderate)	0 (0.0)	0 (0.0)	3 (2.3)
Grade 3 (Severe)	0 (0.0)	0 (0.0)	4 (3.1)
Grade 4 (Life-threatening)	0 (0.0)	0 (0.0)	3 (2.3)
Grade 5 (Fatal)	0 (0.0)	0 (0.0)	0 (0.0)

Reversibility

Treatment is necessary.

Long-term outcomes

No data on long-term outcomes are available.

Impact on quality of life

Increased morbidity and mortality.

Risk groups and risk factors	CLD Liver disease patients and patients with chronic immune thrombocytopenia are at increased risk for these events as a comorbidity. Some studies indicated that CLD is in fact a risk factor for venous thrombosis with a more than 2-fold increased risk. Patients with cirrhosis are not protected against arterial thrombosis, and the incidence of arterial events is even increased in patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis compared to the general population (Lisman, 2013). ITP A large study in the UK showed an increased risk for thromboembolic events in adult patients with ITP compared to matched disease-free patients. The adjusted hazard ratios for adult ITP patients for venous thromboembolism was 1.58, for arterial thromboembolic events was 1.37, and for combined (arterial and venous) thromboembolic events was 1.41 (Sarpatwari, 2010). Below are the strong or the most well-established risk factors for venous thromboembolism (Tripodi, 2011; Tufano, 2011): • History of deep vein thrombosis, pulmonary embolism, superficial vein thrombosis • Stroke/other neurological disorders associated with paralysis • Recent immobilization (>3 days) • Increasing age • Pregnancy and Puerperium (<8 weeks from delivery) • Cancer (active or occult) • Cancer therapy (chemo/radiotherapy, hormonal, angiogenesis inhibitors) • Acute myocardial infarction and heart failure • Fractures • Oestrogen intake • Surgery
Preventability	CLD The incidence of portal vein thrombosis may be decreased by maintaining platelet count under 200 x 10^9/L and by monitoring portal vein flow (Afdhal, 2012; Chawla, 2015). ITP Use the lowest dose of avatrombopag needed to achieve and maintain platelet count ≥ 50 x 10^9/L.
Impact on the risk benefit-balance of the product	Patients with CLD or ITP are known to be at increased risk for thromboembolic events. Without prompt action, thrombotic/thromboembolic events such as those resulting in pulmonary embolism and/or cerebrovascular accident may be serious and life threatening. Routine risk minimisation measures and routine pharmacovigilance activities of this risk and its potential consequences are considered appropriate.
Public health impact	None identified.

Table 16 Important Identified Risk: Bone Marrow Fibrosis Related to Long-Term and Repeat Use

Potential mechanisms	With long-term use, thrombopoietin receptor agonists (TPO-RAs), including avatrombopag, may increase the risk of development or progression of reticulin fibres/fibrosis within the bone marrow. The clinical importance of this observation is unknown. The pathophysiology remains incompletely understood, however increased bone marrow reticulin is believed to be a result of TPO receptor stimulation, leading to an increased number of megakaryocytes in the bone marrow, which may subsequently release cytokines. Cytokines appear to be necessary for fibrosis to occur (Cuker, 2010).
Evidence source(s) and strength of evidence	Studies have found that the overexpression of TPO can lead to bone marrow changes in animals and humans (Kuter, 2009; Cuker, 2010). However, the clinical importance of this observation is unknown (Kuter, 2010; Bussel, 2009; Leung, 2011; Ghanima, 2011; Kuter, 2009). Avatrombopag, a TPO-RA, requires chronic dosing for use in patients with ITP and may pose a risk for the development of or progression of reticulin fibres/fibrosis within the bone marrow. In the clinical development programme, 1 of 128 (<1%) ITP patients was treated initially with eltrombopag for 56 days, followed by avatrombopag treatment for 161 days. Thirty-one days after avatrombopag therapy was discontinued, a bone marrow biopsy showed a bone marrow reticulin fibrosis of 2+ with focal areas of 3+. This patient also had a pre-treatment elevated bone marrow reticulin fibrosis (1+). For patients with CLD who undergo multiple procedures, avatrombopag may also be prescribed before each procedure is performed, but experience with repeat use is limited.
Characterization of the Risk	
Frequency	In patients receiving therapy with TPO-RAs, the incidence of increased reticulin deposition is unknown, although data from romiplostim and eltrombopag studies suggest that a minority of patients may develop bone marrow fibrosis within a year of initiating TPO-RA therapy (Cuker, 2010). Less than 1% (1/128) of subjects in the ITP avatrombopag treatment groups experienced the treatment emergent adverse event of bone marrow reticulin fibrosis.
Severity	Increased reticulin deposition in the bone marrow (reticulin fibrosis) has been associated with a number of benign and malignant conditions and is frequently reversible (Cuker, 2010; Kuter, 2007).
Reversibility	There is no evidence-based knowledge and very limited experience on how to manage patients who develop increasing fibrosis during long-term treatment with TPO-RAs, although discontinuation of TPO-RAs will allow the degree of reticulin deposition to decrease (Ghanima, 2014).
Long-term outcomes	The long-term consequences of increased bone marrow reticulin deposition are unclear, though it appears to be reversible with drug discontinuation (Imbach, 2011).
Impact on quality of life	None anticipated.

Risk groups and risk factors	No specific risk factor has been identified in clinical trials. Risk groups include patients on long-term treatment with TPO-RAs, those undergoing multiple procedures who receive repeat dosing with a TPO-RA, or patients with myeloproliferative disease or other hematological and nonhematological malignant neoplasms, autoimmune disorders, or endocrine disorders.
Preventability	Prescriber education.
Impact on the risk benefit balance of the product	Routine risk minimisation measures and routine pharmacovigilance activities of this risk and its potential consequences are considered appropriate.
Public health impact	None identified.

Table 17 Important Potential Risk: Hepatic Worsening Function in Patients with Child-Pugh class C

Potential mechanisms	The risk of thromboembolic events might be increased in Child-Pugh class C patients due to the severity of their underlying primary disease. There may also be a potential for hepatotoxic effects/deterioration in hepatic function, including death in Child-Pugh class C patients receiving avatrombopag.
Evidence source(s) and strength of evidence	The overall incidence of treatment emergent adverse events (TEAEs) (as well as treatment-related, Grade 3/4 TEAEs, and SAEs) from the two Phase 3 studies (Study 310 and Study 311) were generally similar between avatrombopag- and placebo-treated patients, across patients with Child-Pugh class A (49% versus 57%, respectively) and Child-Pugh class B (61% versus 55%) liver disease. This similar incidence of TEAEs, treatment-related, Grade 3/4 TEAEs, and SAEs between the avatrombopag and placebo treatment groups was also the case for liver function across the various MELD score categories: MELD <10 (51% versus 67%, respectively); MELD 10 to 14 (51% versus 43%). While the overall incidence of TEAEs was higher in the avatrombopag versus placebo treatment group in patients with Child-Pugh class C disease (63% versus 43%), none of the TEAEs in these patients were considered to be treatment-related by the investigators. Similarly, in patients with higher MELD scores (>14 to <=24), the overall incidence of TEAEs was higher (70% versus 64%), but there were fewer treatment-related TEAEs in the avatrombopag versus placebo treatment groups (13% versus 23%). The Grade 3/4 TEAEs reported for the five avatrombopag-treated patients (coagulopathy, gastrointestinal haemorrhage, oesophageal varices haemorrhage, pre-existing condition improved, sepsis, hepatic encephalopathy, depression and pneumonia aspiration) were each only reported in individual patients, and there were no unexpected TEAEs or clustering of events to suggest a safety signal. Similarly, the SAEs reported for three avatrombopag-treated patients (gastrointestinal haemorrhage, oesophageal varices haemorrhage, sepsis, hepatic coma, and multiple organ dysfunction) were each only reported in individual patients, and there were no unexpected adverse events or clustering of events that identified a safety signal. Across the clinical development programme, a total of four fatal adverse events were reported in patients with thrombocytopenia and CLD, with three deaths in the combined avatrombopag treatment group and one death in the placebo treatment group. All reported deaths in the avatrombopag group occurred in patients who suffered from Child-Pugh class C liver disease, whereas no deaths in patients with

	Child Pugh class C were reported in the placebo arm. It is possible that the fatal outcomes of hepatic coma and multi-organ failure (acute liver failure, acute kidney injury and respiratory failure) are associated with the natural progression of the underlying disease.
Characterization of the Risk	
Frequency	The incidence of TEAEs in Child-Pugh class C patients especially in the high baseline platelet count group was higher than in the placebo group (66.7 % versus 40% in Studies 310 and 311] and 80.6% versus 54.5% in Studies 202, 204, 310, 311 combined). However, the number of patients treated with avatrombopag was low and a final conclusion cannot be drawn for the safety of avatrombopag in Child Pugh class C patients. There were a total of four TEAEs of death reported during the course of the Phase 2 and Phase 3 studies, three (0.5%) subjects in the total avatrombopag treatment group, and one (0.4%) subject in the total placebo treatment group (ISS Table 20.3.1.4 and Table 20.3.8.4). It is likely that the fatal outcomes of these patients (hepatic coma and multi-organ failure) are associated with the natural progression of the underlying disease.
Severity	May be fatal.
Reversibility	Treatment may be necessary.
Long-term outcomes	May be fatal.
Impact on quality of life	Increased morbidity or mortality.
Risk groups and risk factors	Patients with Child-Pugh class C who receive treatment with avatrombopag; patients with bacterial infections/sepsis, GI bleeding, alcohol intake, drug toxicity, surgery. Hepatocellular carcinoma, or viral hepatitis.
Preventability	Routine medical monitoring of patient.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures and routine pharmacovigilance activities of this risk and its potential consequences are considered appropriate. Further characterization of this risk in the post-marketing setting through PASS study is not expected to change the positive benefit-risk balance.
Public health impact	None identified.

Table 18 Important Potential Risk: Haematological malignancies

Potential mechanisms	TPO-RAs are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production, and can theoretically increase the risk of progression of existing haematological malignancies.
Evidence source(s) and strength of evidence	Given that some haematopoietic cancers express the thrombopoietin (TPO) receptors, it is theorized that administration of TPO-RAs, due to their mechanism of action, may further potentiate the risk of haematological malignancy in ITP patients. However, epidemiologic studies also suggest a possible association between ITP and haematological malignancy (Landgren, 2006; Söderberg, 2006).
Characterization of the Risk	
Frequency	In controlled trials of eltrombopag and romiplostim, the incidence of hematologic malignancy was low and similar in the treatment and placebo groups (Cuker, 2010). Because avatrombopag shares the same mechanism of action as the other TPO receptor agonists, the risk is believed to be similar.
Severity	Variable depending on the type of haematological malignancy.
Reversibility	Depends on type of malignancy. Treatment involves slowing disease progression, managing symptoms, preventing bleeding, and infections.
Long-term outcomes	Variable depending on age, type of malignancy and health status of the patient.
Impact on quality of life	Rarely cause signs or symptoms in the early stages. Complications include anaemia, recurrent infections, bleeding, and increased risk of cancer.
Risk groups and risk factors	Risk groups include patients on long-term treatment with TPO-R agonists, those undergoing multiple procedures who receive repeat dosing with a TPO-R agonist, or patients with myeloproliferative disease or other hematological and nonhematological malignant neoplasms, autoimmune disorders, or endocrine disorders.
Preventability	Routine medical monitoring of the patient.
Impact on the risk benefit balance of the product	Routine risk minimisation measures and routine pharmacovigilance activities of this risk and its potential consequences is considered appropriate. Further characterization of this risk in the post-marketing setting through PASS study is not expected to change the positive benefit-risk balance.
Public health impact	None identified.

SVII.3.2 Presentation of Missing Information

Table 19 Missing Information: Use in Patients with MELD Scores > 24

Evidence source	Patients with a MELD score >24 were excluded from the chronic liver disease pivotal studies because these patients have such a poor prognosis and high mortality rate, e.g., a MELD score of 24 is associated with a 3-month mortality rate of ~20%. Therefore, these patients were not considered ideal patients to enrol in the clinical trials. However, there is no scientific rationale to suggest these patients would not otherwise benefit from and be considered as candidates for avatrombopag prior to a planned procedure, but definitive information is missing.
Population in need of further characterisation	Patients with a MELD score > 24.
Anticipated risk/consequence of the missing information	There is no scientific rationale to suggest the patients would not otherwise benefit from and be considered as candidates for avatrombopag prior to a planned procedure.

Part II Module SVIII – Summary of the Safety Concerns

Table 20 Summary of Safety Concerns

Important identified risks	• Thrombotic/thromboembolic events • Bone marrow fibrosis related to long-term and repeat use
Important potential risks	• Hepatic worsening function in patients with Child-Pugh class C • Haematological malignancies
Missing information	• Use in patients with MELD scores > 24

PART III PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are not believed to be necessary.

III.2 Additional Pharmacovigilance Activities

III.2.1 Chronic liver disease

PASS Summary: Postauthorisation Safety Study (PASS) of Avatrombopag in Patients with Severe Chronic Liver Disease (CLD)

Study short name and title: Postauthorisation Safety Study (PASS) of Avatrombopag in Patients with Severe Chronic Liver Disease (CLD)

Rationale and study objectives: The primary objective is to estimate, among patients with severe CLD and severe thrombocytopenia who are scheduled for an elective invasive procedure, differences between liver function test (LFT) values measured before and after the elective invasive procedure according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion).

The secondary objectives are:

- Describe, among patients with severe CLD and severe thrombocytopenia who are scheduled for an elective invasive procedure, the frequency and severity of specific hepatic clinical outcomes, i.e., ascites and encephalopathy, before and after the procedure (and before and after treatment), according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion).
- Collect, among patients with severe CLD and severe thrombocytopenia treated with avatrombopag who are scheduled for an elective invasive procedure, adverse drug reactions (ADRs) attributed to avatrombopag that are recorded in the patients' medical records.

Study design: This will be a non-interventional, multinational descriptive cohort study conducted through secondary data collected via review of existing medical charts from patients managed in routine clinical practice at clinical sites in countries in Europe.

Study population: The study population will comprise adult patients with documented severe CLD (Child-Pugh C or Model of End-Stage Liver Disease (MELD) score > 24) and severe thrombocytopenia (platelet count $< 50 \times 10^9$/L) initiating treatment with avatrombopag or lusutrombopag or receiving a platelet transfusion in preparation for an elective invasive procedure during the study period.

Milestones:

- Protocol endorsement by EMA: 21 Mar 2024
- Registration in EU PAS Register: No later than 6 months after EMA protocol endorsement and before the start of data collection
- Start of data collection: Estimated 4Q 2024
- End of data collection: Estimated 2Q 2027
- Study progress report: Estimated 2Q 2025
- Final report of study results: Estimated 1Q 2028

III.2.2 Chronic immune thrombocytopenia

PASS Summary: Postauthorisation Safety Study (PASS) of Avatrombopag and Haematological Malignancies in Patients with Primary Immune Thrombocytopenia.

Study short name and title: Postauthorisation Safety Study (PASS) of Avatrombopag and Haematological Malignancies in Patients with Primary Immune Thrombocytopenia.

Rationale and study objectives: There is a theoretical concern that TPO-RAs may stimulate the progression of existing haematologic malignancies such as myelodysplastic syndromes (MDS). The objective is to estimate the incidence rate (IR) of haematological malignancies among patients with primary ITP who initiate avatrombopag. Additionally, the IRs of patients initiating avatrombopag will be put in context with the IR of haematological malignancies estimated among patients with primary ITP who did not receive treatment with avatrombopag.

Study design: This is a non-interventional, population-based, cohort study using secondary data collection. This descriptive study will be conducted in the national health registers in Denmark and Sweden: the DNHR and the SNHR. The study will estimate the IR of haematological malignancies among patients with primary ITP who initiate avatrombopag. To contextualise this IR, the IR of haematological malignancies will also be estimated among patients with ITP who have not received avatrombopag. Finally, a standardised morbidity ratio (SMR) will also be estimated.

Study population: The study population will include adults with a new diagnosis of primary ITP listed on at least 2 separate dates in 2006 or later.

Milestones and Timelines:

- Protocol endorsement by EMA: 25 April 2024
- Registration in the EU PAS Register: No later than 6 months after EMA protocol endorsement and before the start of data collection
- Start of data collection: Q1 2029 (7 years after launch of avatrombopag in the last study country to launch avatrombopag)
- End of data collection: Q3 2029 (7.5 years after launch of avatrombopag in the last study country to launch avatrombopag)
- Final report of study results: Q1 2030 (8 years after launch of avatrombopag in the last study country to launch avatrombopag)

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 21 Table of Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Postauthorisation Safety Study (PASS) of Avatrombopag in Patients with severe Chronic Liver Disease (CLD). Ongoing	Further characterise the safety profile of avatrombopag in relation to changes in liver function measured before and after an elective invasive procedure in patients with Child Pugh class C liver disease patients or patients with MELD scores > 24	Potential risk of hepatic worsening function in patients with Child Pugh class C liver disease. Missing information in patients with MELD scores > 24.	Progress report Final report	Due Q2 2025 Due Q1 2028

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Postauthorisation Safety Study (PASS) of Avatrombopag and Haematological Malignancies in Patients with Primary Immune Thrombocytopaenia Ongoing	The primary objective is to estimate the incidence rate of haematological malignancies among patients with primary ITP who initiate treatment with avatrombopag.	Potential risk of haematological malignancies	Final report	Q1 2030

PART IV PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

Table 22 Postauthorisation efficacy studies

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Table 23 Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Thrombotic/Thromboembolic Events	Routine risk communication: • SmPC sections 4.4 and 4.8 • Package Leaflet (PL) section 2 and 4
Bone Marrow Fibrosis Related to Long-Term and Repeat Use	No risk minimisation measures specific to bone marrow fibrosis. Routine risk communication for long-term and repeat use: • SmPC sections 4.2, 4.4, and 4.8 • Package Leaflet (PL) section 2 and 4
Hepatic worsening function in patients with Child-Pugh class C	Routine risk communication: • SmPC sections 4.2 and 4.4 • Package Leaflet (PL) section 2
Haematological malignancies	Routine risk communication: • SmPC section 4.4 • Package Leaflet (PL) section 2
Use in patients with MELD scores > 24	Routine risk communication: • SmPC sections 4.2, 4.4, 5.1 and 5.2 • Package Leaflet (PL) section 2

SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

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

V.3 Summary of Risk Minimisation Measures

Table 24 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Thrombotic/Thromboembolic Events	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • Package Leaflet (PL) section 2 and 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities
Bone Marrow Fibrosis Related to Long-Term and Repeat Use	No routine risk minimisation measures specific to bone marrow fibrosis. Routine risk communication for long-term and repeat use: • SmPC sections 4.2, 4.4, and 4.8 • Package Leaflet (PL) section 2 and 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities
Hepatic worsening function in patients with Child-Pugh class C	Routine risk communication: • SmPC sections 4.2 and 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: PASS study
Haematologic malignancies	Routine risk communication: • SmPC section 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: PASS study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with MELD scores > 24	Routine risk communication: • SmPC sections 4.2, 4.4, 5.1 and 5.2 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: PASS study

PL = Package Leaflet, SmPC = Summary of Product Characteristics.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN FOR DOPTELET®

This is a summary of the risk management plan (RMP) for Doptelet 20 mg film coated tablets. The RMP details important risks of Doptelet, how these risks can be minimised and how more information will be obtained about Doptelet's risks and uncertainties (missing information).

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

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

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

I The Medicine and What it is Used for

Doptelet is authorised for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure. Doptelet is also authorised for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). It contains avatrombopag as the active substance and it is given by oral administration.

Further information about the evaluation of Doptelet's benefits can be found in the EPAR for Doptelet, including in its plain-language summary, available on the European Medicines Agency (EMA) website under the medicine's webpage: https://www.ema.eurpa.eu/en/medicines/human/EPAR/doptelet.

II Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

Measures to minimise 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 minimise its risks.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report (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 Doptelet is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Doptelet are risks that need special risk management activities to further investigate or minimise 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 Doptelet. 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).

Table 25 List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	• Blood clots and complications related to blood clots (Thrombotic/thromboembolic events) • Bone Marrow Fibrosis Related to Long-Term and Repeat Use
Important potential risks	• Hepatic worsening function in patients with Child-Pugh class C • Haematological malignancies
Missing information	• Use in patients with MELD scores > 24

II.B Summary of Important Risks

Table 26 Summary of Important Identified and Potential Risks

Important Identified Risks	
Thrombotic / Thromboembolic Events	
Evidence for linking the risk to the medicine	As a class, TPO receptor agonists stimulate the production of endogenous platelets, and thus may increase the risk of occurrence of thrombotic / thromboembolic events. In addition, patients with chronic liver disease (CLD) and immune thrombocytopenia (ITP) are also known to be at increased risk for occurrence of these events. In the clinical development program, 7.0% (9/128) of patients with chronic ITP who were treated with avatrombopag experienced a thromboembolic event. With the exception of cerebrovascular accident which was reported in 1.6% (2/128) patients, there was no clustering of a specific thromboembolic event type, the time to onset varied from greater than 26 weeks to less than 4 weeks after beginning treatment, there was no relationship to drug dose, and the events typically occurred at a platelet count below the upper limit of normal (450,000/μL). In patients with CLD, 0.4% (1/274) experienced a thromboembolic event.
Risk factor and risk groups	Avatrombopag was not studied in patients with prior thromboembolic events. Patients with chronic liver disease or chronic immune thrombocytopenia are at increased risk for thrombotic / thromboembolic events as a comorbidity. Additional risk factors include a history of deep vein thrombosis, pulmonary embolism, superficial vein thrombosis, stroke/other neurological disorders associated with paralysis, immobilization >3 days, increasing age, pregnancy and puerperium (<8 weeks from delivery), cancer, cancer therapy, contraceptives, obesity, smoking, acute myocardial infarction and heart failure, fractures, oestrogen intake, surgery/trauma, or genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency).
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • Package Leaflet (PL) section 2 and 4 Additional risk minimisation measures: None

Bone Marrow Fibrosis Related to Long-Term and Repeat Use	
Evidence for linking the risk to the medicine	With long-term use, thrombopoietin receptor agonists (TPO-RAs) may increase the risk of development or progression of reticulin fibres/fibrosis within the bone marrow. The clinical importance of this observation is unknown. The pathophysiology remains incompletely understood, however increased bone marrow reticulin is believed to be a result of TPO receptor stimulation, leading to an increased number of megakaryocytes in the bone marrow, which may subsequently release cytokines. Cytokines appear to be necessary for fibrosis to occur. Avatrombopag, a TPO-RA, requires chronic dosing for use in patients with ITP and may pose a risk for the development of or progression of reticulin fibres/fibrosis within the bone marrow. In the clinical development programme, 1 of 128 (<1%) ITP patients was treated initially with eltrombopag for 56 days, followed by avatrombopag treatment for 161 days. Thirty-one days after avatrombopag therapy was discontinued, a bone marrow biopsy showed a bone marrow reticulin fibrosis of 2+ with focal areas of 3+. This patient also had a pre-treatment elevated bone marrow reticulin fibrosis (1+). For patients with CLD who undergo multiple procedures, avatrombopag may also be prescribed before each procedure is performed, but experience with repeat use is limited.
Risk factors and risk groups	No specific risk factor has been identified in clinical trials. Risk groups include patients on long-term treatment with TPO-R agonists, those undergoing multiple procedures, or patients with myeloproliferative disease or other hematologic and nonhematologic malignant neoplasms, autoimmune disorders, or endocrine disorders.
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.4, and 4.8 • Package Leaflet (PL) section 2 and 4 Additional risk minimisation measures: None
Important Potential Risks	
Hepatic worsening function in patients with Child-Pugh Class C	
Evidence for linking the risk to the medicine	Across the clinical development programme, a total of four fatal adverse events were reported, with three deaths occurring in the avatrombopag treatment group and one death in the placebo treatment group. All reported deaths in the avatrombopag group occurred in patients who had Child-Pugh class C liver disease, whereas no deaths in patients with Child-Pugh class C were reported in the placebo arm. It is possible that the fatal outcomes of hepatic coma and multi-organ failure (acute liver failure, acute kidney injury and respiratory failure) are associated with the natural progression of the underlying disease.
Risk factors and risk groups	Patients with Child-Pugh class C who receive treatment with avatrombopag; patients with bacterial infections/sepsis, GI bleeding, alcohol intake, drug toxicity, surgery. Hepatocellular carcinoma, or viral hepatitis.

Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2 and 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS study: Postauthorisation Safety Study of Avatrombopag in Patients with Severe Chronic Liver Disease See section II.C of this summary for an overview of the post-authorisation development plan.
Haematological malignancies	
Evidence for linking the risk to the medicine	Given that some haematopoietic cancers express the thrombopoietin (TPO) receptors, it is theorized that administration of TPO-RAs, due to their mechanism of action, may further potentiate the risk of haematological malignancy in ITP patients. However, epidemiologic studies also suggest a possible association between ITP and haematological malignancy (Landgren, 2006; Söderberg, 2006).
Risk factors and risk groups	Risk groups include patients on long-term treatment with TPO-R agonists, those undergoing multiple procedures who receive repeat dosing with a TPO-R agonist, or patients with myeloproliferative disease or other hematologic and nonhematologic malignant neoplasms, autoimmune disorders, or endocrine disorders.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS: Postauthorisation Safety Study of Avatrombopag and Haematological Malignancies in Patients with Primary Immune Thrombocytopenia. See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information	
Use in Patients with MELD Scores > 24	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.4, 5.1 and 5.2 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS study: Hepatic safety of avatrombopag in patients with Child Pugh class C liver disease or MELD scores > 24 See section II.C of this summary for an overview of the post-authorisation development plan.

PL = Package Leaflet, SmPC = Summary of Product Characteristics.

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are currently no studies which are conditions of the marketing authorisation or specific obligations of Doptelet®.

II.C.2 Other Studies in Post-authorisation Development Plan

II.C.2.1 Chronic liver disease

Study short name: Postauthorisation Safety Study (PASS) of Avatrombopag in Patients with Severe Chronic Liver Disease (CLD)

Purpose of the study: The primary objective is to estimate, among patients with severe CLD and severe thrombocytopenia who are scheduled for an elective invasive procedure, differences between liver function test (LFT) values measured before and after the elective invasive procedure according to the treatment received (i.e., avatrombopag, lusutrombopag, or platelet transfusion).

II.C.2.2 Primary chronic immune thrombocytopenia

Study short name: Postauthorisation Safety Study (PASS) of Avatrombopag and Haematological Malignancies in Patients with Primary Immune Thrombocytopenia

Purpose of the study: There is a theoretical concern that TPO-RAs may stimulate the progression of existing haematologic malignancies such as myelodysplastic syndromes (MDS). The objective is to estimate the incidence rate (IR) of haematological malignancies among patients with primary ITP who initiate avatrombopag. Additionally, the IRs of patients initiating avatrombopag will be put in context with the IR of haematological malignancies estimated among patients with primary ITP who did not receive treatment with avatrombopag.

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Annex 1 EudraVigilance Interface

Annex 2 Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme

The following Post-Approval Safety Studies (PASS) are included in the Pharmacovigilance Plan. No studies have been completed.

Table 27 Planned and Ongoing Studies

Study Status	Summary of Objectives	Safety Concerns Addressed	Protocol Link Milestones
Postauthorisation Safety Study (PASS) of Avatrombopag in Patients with severe Chronic Liver Disease (CLD). Ongoing	Further characterise the safety profile of avatrombopag in relation to changes in liver function measured before and after an elective invasive procedure in patients with Child Pugh class C liver disease patients or patients with MELD scores > 24	Potential risk of hepatic worsening function in patients with Child Pugh class C liver disease. Missing information in patients with MELD scores > 24.	Progress report: Q2 2025 Final report: Q1 2028
Postauthorisation Safety Study (PASS) of Avatrombopag and Haematological Malignancies in Patients with Primary Immune Thrombocytopaenia Ongoing	The primary objective is to estimate the incidence rate of haematological malignancies among patients with primary ITP who initiate treatment with avatrombopag.	Potential risk of haematological malignancies	Final report: Q1 2030

Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

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Part C Previously Agreed Protocols for Ongoing Studies and Final Protocols Not Reviewed by the Competent Authority.....63

Part A Requested Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review with This Updated Version of the RMP

Not applicable.

Part B Requested Amendments of Previously Approved Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review with This Updated Version of the RMP

Not applicable.

Part C Previously Agreed Protocols for Ongoing Studies and Final Protocols Not Reviewed by the Competent Authority

Not applicable.

Annex 4 Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV

None

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

Not applicable.

Annex 7 Other Supporting Data (Including Referenced Material)

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Annex 8 Summary of Changes to the Risk Management Plan Over Time

Table 28 Summary of Changes to the Risk Management Plan

Version	Approval Date Procedure	Change
1.0	Not applicable.	Not applicable.
1.1	Not applicable	1. Updated Part II, Module SV to add information on post-authorisation experience. 2. Updated Part II, Modules SVII.1.2, SVII.3.1, SVII3.2, SVIII to add information regarding the 'potential risks' of avatrombopag use in Child-Pugh class C patients, bone marrow fibrosis with long-term (off-label) and repeat use, and recurrence of thrombocytopenia with or without bleeding upon cessation of therapy (long-term use). 3. Updated Part II, Modules SVII.1.2, SVII3.2, and SVIII to add 'missing information' regarding the use of avatrombopag in splenectomy patients, patients receiving interferon products, patients undergoing highly invasive procedures, patients with MELD scores > 24. 4. Updated Part V, sections V.1 and V.3 to add information on the 'potential risks' and 'missing information' as listed in Part II, immediately above. 5. Updated Part VI, sections II.A and II.B to add information on the 'potential risks' and 'missing information' as listed in Part II, immediately above.
1.2	Not applicable	1. Updated Part I, Table 1, section on 'Brief description of the product' to be consistent with SmPC. 2. Updated Part II, subpart SIV.1, Table 10 to include information on subjects with MELD scores > 24. 3. Updated Part II, subpart SIV.2 to include information on patients with Child-Pugh class C. 4. Updated Part II, subpart SVII.1.1 to add anaemia and myalgia to the list of risks. 5. Updated Part II, subpart SVII.1.2, Table 14 to clarify the wording regarding hepatic worsening function in patients with Child-Pugh class C, to combine the potential risks of off-label use / repeat use, and bone marrow fibrosis, and to delete the potential risk of drug-drug interactions. 6. Updated Part II, subpart SVII.3.1, to delete information regarding drug-drug interactions, and to update Tables 15 and 16 with information on additional pharmacovigilance activities, and to combine the potential risks of off-label / repeat use and bone marrow fibrosis (long term use) into a single potential risk in Table 17. 7. Updated Part II, subpart SVIII, Table 23 to delete drug-drug interactions as a potential risk, reword the potential risk regarding Child-Pugh class C patients, and combine the potential risks of

Version	Approval Date Procedure	Change
		off-label / repeat use and bone marrow fibrosis (long term use) into a single potential risk. 8. Updated Part II, subpart III.1 to include references to the follow-up questionnaires on Child-Pugh class C, MELD scores > 24, or deaths. 9. Updated Part III.2 with information regarding a postmarketing surveillance study of thromboembolic- and hepatic-related adverse events and deaths. 10. Updated Part III.3, Table 24, Category 3 with information on the postmarketing surveillance study of thromboembolic- and hepatic-related adverse events and deaths. 11. Updated Part V, Table 25 to delete information regarding drug-drug interactions, reword the safety concern regarding Child-Pugh class C patients, and to combine the potential risks of off-label / repeat use and bone marrow fibrosis (long term use) into a single potential risk. Routine risk minimisation measures were also revised to align with the updated SmPC. 12. Updated Part V, Table 26 to include additional information on pharmacovigilance activities for thrombotic/thromboembolic events, hepatic worsening function in patients with Child-Pugh class C, and patients with MELD scores > 24. Risk Minimization Measures were also updated to align with the updated SmPC. 13. Updated Part VI, subpart II.A, Table 27 to delete drug-drug interactions as a potential risk, reword the potential risk regarding Child-Pugh class C patients, and combine the potential risks of off-label / repeat use and bone marrow fibrosis (long term use) into a single potential risk. 14. Updated Part VI, subpart II.B, Table 28 to include additional pharmacovigilance activities for patients with thrombotic/thromboembolic events, hepatic worsening function in patients with Child-Pugh class C, and patients with MELD scores > 24. Risk minimisation measures were also updated to align with the revised SmPC. 15. Populated Part VI, subpart II.C.2 with information on the planned postmarketing surveillance study of thromboembolic- and hepatic-related adverse events and death. 16. Added information regarding the planned postmarketing surveillance study of thromboembolic- and hepatic-related adverse events and deaths to Table 29 in Annex 2. 17. Included questionnaires designed to collect detailed safety information in patients with Child-Pugh class C, Meld score > 24, and death in Annex 4.

Version	Approval Date Procedure	Change
1.3	Not applicable	1. Corrected some spelling inconsistencies throughout the document (i.e. British vs American English). 2. Section III.2 (Additional Pharmacovigilance Activities) has been updated to address the new PASS proposal. 3. Section III.3 (Summary Table of Additional Pharmacovigilance Activities), has been updated to address the Applicant's new PASS proposal, and to include 'Hepatic worsening function in patients with Child-Pugh class C and 'Use in patients with MELD scores > 24 as safety concerns to be addressed in the PASS. 4. The Applicant has removed references to SmPC section 4.1 and the Package Leaflet (PL) from the list of risk minimisation measures for the safety concern of 'Bone marrow fibrosis related to long-term (off-label) and repeat use' in RMP Part V.I. Table 25, Part V.III. Table 26, and Part VI.II.B Table 28. 5. Part VI (Summary of the Risk Management Plan), Section 1 has been revised to reflect the anticipated final approved indication and to remove the tablet strength. Section II.B, Table 28 has been revised for conciseness. Section II.C.2 has been revised to reflect the Applicant's new PASS proposal. 6. Annex 2, Table 29 has been updated to reflect the Applicant's new PASS proposal. 7. Annex 4 has been updated to incorporate revised questionnaires to incorporate requested changes in sections on Medical History, Adverse Event Information, and Laboratory information. 8. Tables 16, 17, 18 and 28 have been revised to include more detail of the risk groups and risk factors.
2.0	Procedure #: EMEA/H/C/0004722/0000 Date: 26 April 2019	1. RMP approved under the MAA 2. Date on cover page updated. 3. On page 2, the fields 'Risk Management Plan version number', 'Date for final sign-off', and 'Rationale for submitting an updated RMP' have been updated. 4. On page 4, the fields for 'Details of currently approved RMP', 'Version number', 'Approved with procedure', and 'Date of approval (Opinion date)' have been updated. 5. In Table 1, the fields for 'Indication(s) in the EEA', 'Dosage in the EEA', and 'Pharmaceutical form(s) and strengths' were updated from 'proposed' to 'current.' 6. In Part VI, 'Summary of the Risk Management Plan', under the subsection of 'Risk factors and risk groups' for the important potential risk: 'Bone Marrow Fibrosis Related to Long-term (Off-Label) and Repeat Use', the paragraph which read, 'As avatrombopag has also been investigated, but not approved for use in patients with ITP, it may pose a risk for long-term off-label use in patients intolerant or resistant to other, authorised treatment options.' Has been deleted.

Version	Approval Date Procedure	Change
2.1		The following have been updated within the RMP as part of the Type II variation procedure for the extension of indication to include 'treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments': 1. ITP added as a new proposed indication 2. Addition of the epidemiology of adult patients with ITP (**Part II: Module SI**; with supporting reference added to **Annex 7**) 3. Exclusion criteria in pivotal studies for the ITP indication and limitations to detect adverse reactions in the clinical trial development programme updated (**Part II: SIV)** 4. Post-authorisation experience information updated (**Part II: Module SV)** 5. Addition of the Important Identified Risk of potentially clinically important interactions between DOPTELET and dual moderate or strong CYP3A4/5 and CYP2C9 inhibitors and inducers (**Part II: Module SVII** and **Module SVIII**; and reflected in the updates to **Part V** and **Part VI**) 6. Updates to information on the important identified and potential risks of thrombotic/thromboembolic events and recurrence (rebound) of thrombocytopenia to include information about these risks in patients with ITP (**Part II: Module SVII**) 7. Update to the important potential risk of bone marrow fibrosis related to long-term and repeat use to reflect the chronic use of avatrombopag in patients with ITP (**Part II: Module SVII**) 8. **Annex 2** updated to reflect the submission of the PASS feasibility study to the EMA on 19 September 2019

Version	Approval Date Procedure	Change
2.2		1. Updated the proposed ITP indication to read "Treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobins) in **Table 1** 2. Provided additional information regarding the proposed dosing instructions for the ITP indication (**Table 1**) 3. Additional guidance provided on the limitations to detect adverse reactions in the clinical trial development programme (**Part II SIV.2**) 4. Reclassified the important potential risk of thrombotic/ thromboembolic events to an important identified risk (**Part II SVII 1.2 (Table 15), SVII.2, SVIII, Part VI IIA**) 5. Removed 'potentially clinically important interactions with dual moderate or strong CYP3A4/5 and CYP2C9 inhibitors' from the proposed revised list of safety concerns and other sections and included it in section **SVII 1.1 (Table 14)** on "Risks not considered important for inclusion in the list of safety concerns in the RMP 6. Added the 'uncommon' adverse reaction terms to the list of risks for the ITP indication **SVII 1.1 (Table 14)** 7. Sections **Part III.2 and 3, Part VI C.2, Annex 2** have been updated to reflect the proposal to conduct a feasibility study regarding a PASS to gather additional safety information on avatrombopag in patients with ITP

2.3		1. Revisions to **Table 1**, section on "dosage in the EEA" were incorporated for the chronic immune thrombocytopenia indication. 2. Updated **Part II SV1** to note Doptelet has been approved in China for the chronic liver disease indication. 3. In **Part II, SVII.1.2** elevated the risk of "Bone marrow fibrosis related to long-term and repeat use" to an "Important identified risk" from an "Important potential risk." 4. In **Part II, SVII.1.2** added "Haematological malignancies" as an "Important potential risk." 5. In **Part II, SVII.1.2** removed "Recurrence (rebound) of thrombocytopenia with or without bleeding upon cessation of therapy (long-term use)" as an "Important potential risk." 6. In **Part II, SVII.2** described the addition of the new safety concern of "Haematological malignancies" as an "Important potential risk", the elevation of "bone marrow fibrosis" to an "Important identified risk" from an "Important potential risk", and the removal of "Recurrence (rebound) of thrombocytopenia with or without bleeding upon cessation of therapy (long-term use) as an "Important potential risk." 7. In **Part II, SVII.3.1** elevated the risk of "Bone marrow fibrosis related to long-term and repeat use" to an "Important identified risk" from an "Important potential risk." (**Table 17**) 8. In **Part II, SVII.3.1** removed "Recurrence (rebound) of thrombocytopenia with or without bleeding upon cessation of therapy (long-term use)" as an "Important potential risk." (former **Table 19**) 9. In **Part II, SVII.3.1** added "Haematological malignancies" as an "Important potential risk." 10. In **Part II SVIII** updated the summary of safety concerns (**Table 24**) to reflect the addition of the new safety concern of "Haematological malignancies" as an "Important potential risk", the elevation of "bone marrow fibrosis" to an "Important identified risk" from an "Important potential risk", and the removal of "Recurrence (rebound) of thrombocytopenia with or without bleeding upon cessation of therapy (long-term use) as an "Important potential risk." 11. In **Part IV and Annex V**, added plans for an outline of a post-authorisation efficacy study. 12. In **Part V.1**, updated **Table 27** to include "Haematological malignancies", and removed the safety concern of "Recurrence (rebound) of thrombocytopenia with or without bleeding upon cessation of therapy (long-term use) as an "Important potential risk." 13. In **Part V.3**, updated **Table 28** updated the summary of risk minimisation measures regarding routine risk minimisation measures for "Bone marrow fibrosis related to long-term and repeat use", "Haematological malignancies", and removed the safety concern of "Recurrence (rebound) of thrombocytopenia with or without bleeding upon cessation of therapy (long-term use) as an "Important potential risk." 14. In **Part VI II.A, Table 28** updated the list of important risks and missing information to reflect the addition of the new safety concern of "Haematological malignancies" as an "Important

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		potential risk", the elevation of "bone marrow fibrosis" to an "Important identified risk" from an "Important potential risk", and the removal of "Recurrence (rebound of thrombocytopenia with or without bleeding upon cessation of therapy (long-term use) as an "Important potential risk." 15. In **Part VI II.B, Table 30** updated the summary of important identified and potential risks to reflect the addition of the new safety concern of "Haematological malignancies" as an "Important potential risk", elevated the existing risk of "bone marrow fibrosis" to an "Important identified risk" from an "Important potential risk", and removed "Recurrence (rebound) of thrombocytopenia with or without bleeding upon cessation of therapy (long-term use) as an "Important potential risk."
2.4		1. On cover page, updated the EU address to reflect the Marketing Authorisation Holder transfer from Dova Pharmaceuticals to Sobi AB based on Commission Decision of 09 Oct 2020. 2. Revisions were incorporated into the 'Evidence source(s) and strength of evidence' section for the Important Identified Risk of 'Thrombotic/Thromboembolic Events' (**Table 16, Part II SVII.3.1)**. 3. Revisions were incorporated into the 'Evidence source(s) and strength of evidence' section for the Important Identified Risk of "Bone marrow fibrosis related to long-term and repeat use' (**Table 17, Part II SVII.3.1)**. 4. With regards to the public summary section of the RMP, revisions were incorporated to the 'Evidence for linking the risks to the medicine' in section **II.B** regarding the safety concerns 'Thrombotic/thromboembolic events' and 'Bone marrow fibrosis related to long-term and repeat use'. 5. Updated **Part IV**, **Table 26**, by adding due dates for the various milestones. 6. **Annex II, Table 31**, updated the section on "Safety Concerns Addressed" for the ITP PASS to be in line with **Section III.3, Table 25.** 7. **Annex II, Table 31**, updated to now include information on the PAES as found in **Part IV**, and added information regarding the ITP PAES.

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2.5		1. **Part I**, **Table 1**, revised the section on "Posology" to make it consistent with the current proposed version of the SmPC 2. **Part SV.1.** revised to reflect updated exposure information. 3. **Part III.3**, **Table 25**, **Category 3,** updated the "Milestones" and "Due Dates" columns by deleting the submission of the ITP PASS study protocol within 3 months of approval of the Type II Variation for the ITP indication. 4. **Part IV**, **Table 26**, deleted information pertaining to a PAES study. 5. **Annex 2**, **Table 31**, deleted information pertaining to a PAES study, and for the ITP PASS, deleted the submission of the ITP PASS study protocol within 3 months of approval of the Type II Variation for the ITP indication.
2.6		1. **Part III.2.1.**, **III.3, Table 25,** and **Annex 2** updated to state the submission date of the final CLD PASS report will be entered as soon as the feasibility study report is agreed by EMA. 2. **Part III.2.2.**, **III.3, Table 25,** and **Annex 2** updated to state the submission date of the final ITP PASS report will be entered as soon as the feasibility study report is agreed by EMA.
2.7		1. **Part III.3, Table 25, Category 3** and **Annex II, Table 31** updated to reinsert that the results of the ITP PASS feasibility will be submitted within 3 months of approval of the Type II Variation for the ITP indication 2. **Part III.3, Table 25, Category 3** and **Annex 2**, **Table 31** updated to remove completed activities

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3.0	Submitted as part of procedure EMEA/H/C/004722/R/0018, but rejected by EMA	General 1. RMP updated as a part of the 5-Year Renewal application for Doptelet. 2. **Part I, Table 1** - updated as previously approved information regarding indications for use and dosage appeared as 'Proposed' rather than 'Current'. 3. **Part II, Module SI** – updated information and corrections made to epidemiology information for the target populations. 4. **Part II, Module SIII** – section updated to reflect current clinical trial exposure. 5. **Part II, Module SV** – updated exposure information provided in Table 12 and Table 13. 6. **Part II, Module SVII, Table 14 & SVII.2** – hypersensitivity reactions added to Table 14. Rationale for this update is provided in SVII.2. Pharmacovigilance Plan 1. **Part III.2** - Additional pharmacovigilance activities updated to reflect current status and projected milestones of the planned ITP PASS and CLD PASS studies. 2. **Part III.2.2** - Added study details of an MAH voluntarily initiated non-interventional study which is ongoing in the EU. 3. **Part III.3** - Table 26 updated to reflect current status of the Category 3 ITP PASS and CLD PASS studies. Annexes **Annex 2** – updated to reflect current status of the planned ITP PASS and CLD PASS studies **Annex 4** – updated questionnaires to add additional ethnicity fields; replaced Dova Pharmaceuticals logo with Sobi logo.

4.0		1. Revision to **Table 1**, sections on "Indication(s) in the EEA" and "Dosage in the EEA" were incorporated for the chronic immune thrombocytopenia (ITP) indication and posology approved by the EMA. 2. Revision to **Table 1**, section regarding "Is/will the product be subject to additional monitoring in the European Union (EU)? – removing the Black triangle. 3. In **Part II, SIII** – Clinical Trial Exposure – Data reformatted to align with RMP template EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2. Data shown as pooled versus per individual trial. Exposure data updated with DLP May 2025. 4. In **Part II, SV.1** - Post-authorization Exposure, Section was abbreviated for relevance and clarity according to EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2. 5. In **Part II, SV.1.2, Table 11 and 12**, Exposure data was updated through DLP May 2025. 6. In **Part II, SVII, Table 14**, removed the missing information as current minimization measures are in place through the description of the risk in the SPC section 4.4 (special warnings and precautions) and the monitoring of these components through routine pharmacovigilance activities. 7. In **Part II, SVII.2**, history of the reclassification of Thrombotic/thromboembolic events as an important identified risk, history of the reclassification of Bone marrow fibrosis related to long-term and repeat use as an important identified risk, history of Haematological malignancies as a new important potential risk, and history of Recurrence (rebound) of Thrombocytopenia With or Without Bleeding Upon Cessation of Therapy (Long-Term Use) removed from the list of important potential risks were deleted as these reclassifications have already occurred as of RMP version 2.7. 8. In **Part II, SVII.2.1**, included the proposal to remove missing information - Use in splenectomy patients with chronic liver disease, Use in patients receiving interferon products and Safety in patients undergoing invasive procedures. Removal of the missing information is proposed as current minimization measures put in place through the description of the risk in the SPC section 4.4 (special warnings and precautions) and the monitoring of these components through routine pharmacovigilance activities. 9. In **Part II, SVII.3.1, Table 15**, section regarding "Impact on the risk benefit-balance of the product" removed the reference to the utilization of the Thrombotic/Thromboembolic event questionnaire to collect follow-up information in addition to routine pharmacovigilance activities.

		10. In **Part II, SVII.3.1, Table 17**, section regarding "Impact on the risk benefit-balance of the product" removed the reference to the utilization of the Hepatic-related event questionnaire to collect follow-up information in addition to routine pharmacovigilance activities and added a reference to the CLD PASS which is not expected to change the benefit-risk balance. 11. In **Part II, SVII.3.1, Table 18**, section regarding "Impact on the risk benefit-balance of the product" added a reference to the CLD PASS which is not expected to change the benefit-risk balance. 12. In **Part II, SVII.3.2**, Use in Splenectomy Patients with Chronic Liver Disease, Use in Patients Receiving Interferon Products, and Safety in Patients Undergoing Highly Invasive Procedures was removed as missing information. 13. In **Part II, SVIII, Table 20**, section regarding "Missing information," Use in Splenectomy Patients with Chronic Liver Disease, Use in Patients Receiving Interferon Products, and Safety in Patients Undergoing Highly Invasive Procedures was removed as missing information. 14. In **Part III, specifically section III.1**, the reference to the utilization of targeted questionnaires for reports of Thrombotic/Thromboembolic events, Hepatic-related events, and reports of death was removed. 15. In **Part III, specifically sections III.2.1 and III.2.2**, updated information on the CLD PASS and the ITP PASS. 16. In **Part III, specifically section III.3, Table 21, Category 3**, updated information on the CLD PASS and the ITP PASS. 17. In **Part V, Section V.1, Table 23**, removed Safety concerns including 'Use in Splenectomy Patients with Chronic Liver Disease', 'Use in Patients Receiving Interferon Products', and 'Safety in Patients Undergoing Highly Invasive Procedures' in addition to the Routine risk minimisation activities for these safety concerns. 18. In **Part V, Section V.3, Table 24**, for the Safety Concern Thrombotic/Thromboembolic Events, reference to the use of the Thrombotic/Thromboembolic events questionnaire and the ITP PASS was removed as additional pharmacovigilance activities. 19. In **Part V, Section V.3, Table 24**, for the Safety Concern Bone Marrow Fibrosis Related to Long-Term and Repeat Use, the ITP PASS was removed as additional pharmacovigilance activities. 20. In **Part V, Section V.3, Table 24**, for the Safety Concern Hepatic worsening function in patients with Child-Pugh class C, reference to the use of the Hepatic-related events questionnaire was removed as additional pharmacovigilance activities.

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		21. In **Part V, Section V.3, Table 24**, Safety concerns including 'Use in Splenectomy Patients with Chronic Liver Disease', 'Use in Patients Receiving Interferon Products', and 'Safety in Patients Undergoing Highly Invasive Procedures' were removed. 22. In **Part V, Section V.3, Table 24**, for the Safety Concern Use in patients with MELD scores > 24, reference to the use of the Hepatic-related events questionnaire was removed as additional pharmacovigilance activities. 23. In **Part VI, Section II.A, Table 25**, Missing information including 'Use in Splenectomy Patients with Chronic Liver Disease', 'Use in Patients Receiving Interferon Products', and 'Safety in Patients Undergoing Highly Invasive Procedures' were removed. 24. In **Part VI, Section II.B, Table 26**, for the Important Identified Risk 'Thrombotic/Thromboembolic Events', section regarding Additional pharmacovigilance activities was removed since there are no additional pharmacovigilance activities. 25. In **Part VI, Section II.B, Table 26**, for the Important Identified Risk 'Bone Marrow Fibrosis Related to Long-Term and Repeat Use, section regarding Additional pharmacovigilance activities was removed since there are no additional pharmacovigilance activities. 26. In **Part VI, Section II.B, Table 26**, all references to the following Missing Information were removed: 'Use in Splenectomy Patients with Chronic Liver Disease', 'Use in Patients Receiving Interferon Products', and 'Safety in Patients Undergoing Highly Invasive Procedures'. 27. In **Part VI, Sections II.C.2.1 and II.C.2.2,** information regarding the CLD PASS and ITP PASS were updated. 28. **Annex 2, Table 27**, information regarding the CLD PASS and ITP PASS were updated. Particularly the Summary of Objectives and the Milestones. 29. **Annex 4**, reference to the utilization of targeted questionnaires for reports of Thrombotic/Thromboembolic events, Hepatic-related events, and reports of death was removed. This Annex is now Not applicable. 30. **Annex 8, Table 28**, Version 3.0, (submitted as part of procedure EMEA/H/C/004722/R/0018 but rejected by EMA) was added including a summary of changes made at that time.
4.1		1. Minor rewording update in SVII.2.1 2. Corrected formatting and hyperlinking errors

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4.2		1. Update of relevant milestones related to CLD PASS study