15 September 2022
EMA/850880/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revolade

International non-proprietary name: eltrombopag

Procedure No. EMEA/H/C/001110/II/0068

Note

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

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List of abbreviations

AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
ALT	Alanine aminotransferase
ASH	American Society of Hematology
CHMP	Committee for Medicinal Products for Human Use
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical study report
EMA	European Medicines Agency
HCV	Hepatitis C virus
ITP	Immune thrombocytopenia
IVIg	Intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
SAA	Severe aplastic anaemia
SAE	Serious adverse event
TPO-R	Thrombopoietin receptor
TPO-RA	Thrombopoietin receptor agonist

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 20 December 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of indication to include treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) irrespective of time since initial diagnosis, based on an ad-hoc analysis of Study TAPER (CETB115J2411); an ongoing phase II, open-label, prospective, single-arm study in adult ITP patients who are refractory or relapsed after first-line steroids.
As a consequence sections 4.1and 5.1 of the SmPC have been updated.
In addition, the MAH took the opportunity to make some minor amendments in section 4.8 of the SmPC for increased consistency.
An updated RMP version 54.1 has been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0167/2016, P/0070/2019, P/0516/2020 on the agreement of a paediatric investigation plan (PIP).
At the time of submission of the application, the PIP P/0516/2020 was not yet completed as some measures were deferred.
Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0070/2019 on the granting of a (product-specific) waiver.
The PDCO issued an opinion on compliance for the PIP P/0167/2016.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	20 December 2021
Start of procedure	23 January 2022
CHMP Rapporteur's preliminary assessment report circulated on	18 March 2022
PRAC Rapporteur's preliminary assessment report circulated on	24 March 2022
PRAC RMP advice and assessment overview adopted by PRAC on	7 April 2022
Updated CHMP Rapporteur assessment report circulated on	13 April 2022
Request for supplementary information adopted by the CHMP on	22 April 2022
MAH's responses submitted to the CHMP on:	14 July 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	12 August 2022
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	12 August 2022
PRAC RMP advice and assessment overview adopted by PRAC on	1 September 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	8 September 2022
CHMP opinion adopted on	15 September 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Immune (idiopathic) thrombocytopenia (ITP) is an autoimmune disorder characterised by a low circulating platelet count (thrombocytopenia), decreased platelet production and increased platelet destruction. Thrombocytopenia places patients at risks for bruising, mucocutaneous bleeding and more seriously intracranial haemorrhage; although bleeding symptoms may not always be present. Diagnosis of ITP is one of exclusion, when the history, physical examination, complete blood count and examination of peripheral blood smear do not suggest other aetiology for the thrombocytopenia.

In Europe, adult ITP has an incidence of 1.6 to 3.9 cases per 100,000 per year with increasing incidence with older age and equal for the sexes except in the mid-adult years (30-60 years), when the disease is more prevalent in women.

Before 2009, ITP was categorised based on the length of time from initial diagnosis into acute ITP, which lasted for up to 6 months from initial diagnosis, and chronic ITP, which lasted beyond 6 months from initial diagnosis (George *et al* 1996). In 2009, the International Working Group (IWG) released updated guidelines (Rodeghiero *et al* 2009), in which ITP was divided into newly diagnosed ITP (lasting up to 3 months from diagnosis), persistent ITP (lasting between 3 and 12 months from diagnosis) and chronic ITP (lasting more than 12 months from diagnosis). This classification was recently reaffirmed by the American Society of Hematology (ASH) (Neunert *et al* 2019) and a panel of international experts (Provan *et al* 2019).

Newly diagnosed ITP" was defined as all cases at first diagnosis. A new category, "persistent ITP," was introduced which included patients not reaching spontaneous remission or not maintaining complete response off therapy between 3 to 12 months from diagnosis. The IWG noted that the possibility of spontaneous remission is significant during this period and deferral of aggressive therapeutic approaches (such as splenectomy) should therefore be considered. The term "chronic ITP" was reserved for patients with ITP lasting for more than 12 months.

Management

There are several guidelines including different treatment approaches in ITP, with the updated ASH 2019 guideline [Neunert *et al,* 2019] and the updated ICR [Provan *et al,* 2019] being the more relevant ones. Inferences regarding the efficacy of treatments are mainly based on platelet counts as the more reliable surrogate outcome measure. The major goal for treatment of ITP is to provide a platelet count that prevents major bleeding rather than correcting the platelet count to normal levels.

In newly diagnosed ITP (first 3 months), treatment is aimed at rapidly obtaining a safe platelet count (> 30 x 10^9 /L) to prevent or stop haemorrhages and to ensure an acceptable quality of life, avoiding as much as possible treatment-related adverse effects. In both updated guidelines, corticosteroids, unless contraindicated, remain the standard initial treatment of newly diagnosed patients, although they should be used for a limited time (≤ 6 weeks). Use of IV Ig, or IV anti-D where available, may be another appropriate first-line treatment in patients with bleeding, at high risk for bleeding, who require a surgical procedure, or who are unresponsive or contraindicated to prednisone.

Most adult patient relapse upon cessation of steroid treatment. Patients still remaining thrombocytopenic after 3 months from diagnosis or initial treatment (corticosteroids, IVIg, anti-D) are classified in persistent (between 3 to 12 months) or chronic (after at least 12 months).

While the old guidelines did not specifically address patients with persistent ITP (between 3 to 12 months) due to lack of robust efficacy/safety data, the updated guidelines propose different treatment approaches for this refractory population. Usual second-line treatment options are TPO-RA, rituximab and splenectomy, nevertheless, there is no solid evidence that defines the best strategy. Each of these second-line treatments may be effective therapy and therefore the choice of treatment should be individualised based on duration of ITP, frequency of bleeding episodes requiring hospitalisation or rescue medication, comorbidities, age of the patient, medication adherence, medical and social support networks, patient values and preferences, cost and availability.

Available treatment modalities have different mechanisms of action and can be broadly categorised into those that are given only once (or for only 1 course) and are intended to induce a long-term response (rituximab, splenectomy) and those that need continued or chronic administration (low-dose corticosteroids, immunosuppressive agents, TPO-RAs).

TPO-RAs (eltrombopag, romiplostim) have provided excellent responses (>60%) in splenectomised and non-splenectomised patients. Response to continued TPO-RAs persists for up to 6 to 8 years and often

allows other ITP therapy to be reduced or discontinued. Cessation of treatment will lead to the return of thrombocytopenia in most cases, but some patients (10%-30%) may achieve a durable response after TPO-RAs are tapered and withdrawn.

Rituximab shows a response of 60% of patients. Long-term durable responses occur in 20% to 25% of adult patients. Prior to treatment, hepatitis B status should be determined and vaccination against encapsulated gram-positive bacteria should be given.

Splenectomy provides long-term efficacy in approximately 60% of cases. Nonetheless, splenectomy is invasive, irreversible, associated with postoperative complications, and its effectiveness is currently unpredictable, leading many physicians and patients toward postponement and use of alternative approaches. Both guidelines suggest that, if splenectomy is deemed necessary, surgery should be deferred for at least 12 to 24 months from diagnosis (chronic ITP) due to potential for spontaneous remission in the first year.

Fostamatinib represents an option in chronic ITP for adult refractory to the previous treatments. It offers an alternative mechanism for reducing platelet destruction; it may provide response rates of 43% but stable responses of only 18%.

Other medical therapies for patients failing previous therapies, with less robust evidence, are immunosuppressive agents, such as mycophenolate mofetil, cyclosporine A or azathioprine. Danazol and dapsone are "corticosteroid-sparing" agents that may be particularly useful in some patients (e.g. those in whom splenectomy is contraindicated or if other agents are unavailable. Vinca alkaloids are not a chronic therapy option because of neurological toxicity.

2.1.2. About the product

Eltrombopag is an orally bioavailable, thrombopoietin receptor (TPO-R) agonist. Eltrombopag initiates signaling cascades that induce proliferation and differentiation of multipotent bone marrow progenitor cells, which increases the platelet count. Platelet count increase following administration of eltrombopag has been demonstrated in several diseases associated with thrombocytopenia.

Eltrombopag (Revolade) was initially approved in 2010 for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP), who had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Revolade is currently approved for the treatment of:

- patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g., corticosteroids, immunoglobulins),
- thrombocytopenia in adult patients with chronic hepatitis C virus (HCV) infection, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy,
- adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation.

➢ *Previous modifications of the ITP therapeutic indication*

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in adult ITP patients was based on the results of three double-blind, placebo-controlled clinical studies, [**TRA100773A**], [**TRA100773B**], and [**TRA102537/RAISE**], and one open-label study [**TRA108057/REPEAT**]. In all four studies, the study population included adult patients (≥18 years) with ITP that lasted beyond 6

months from initial diagnosis. At that time, ITP was categorised into acute ITP (up to 6 months from initial diagnosis), and chronic ITP (beyond 6 months from initial diagnosis) (George *et al* 1996). Consequently, eltrombopag was initially approved for the treatment of chronic ITP.

In 2009, the International Working Group (IWG) released updated guidelines (Rodeghiero *et al* 2009), in which ITP was divided into newly diagnosed ITP (lasting up to 3 months from diagnosis), persistent ITP (lasting between 3 and 12 months from diagnosis) and chronic ITP (lasting more than 12 months from diagnosis). Taking into account the updated definition of chronic ITP and to remain consistent with the population studied in the registration studies, the ITP indication wording was updated in 2019 to replace the term "chronic" with "lasting 6 months or longer from diagnosis" (*procedure EMEA/H/C/001110/II/0050; approved on 06-Feb-2019*).

- ***Proposed therapeutic indication extension***

In the current variation application, the MAH proposes to modify the ITP indication statement to remove the term "*lasting 6 months or longer from diagnosis*" to allow adult ITP patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) to be treated with eltrombopag after first-line treatment irrespective of time from initial diagnosis. Since only the adult ITP indication is sought to be extended with this submission, the paediatric indication will be separated into an individual statement.

The proposed indication wording is as follows; additions are shown in **bold** text and deletions are marked in strikethrough (~~xxx~~):

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

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

A pre-submission meeting with the CHMP Rapporteur (AEMPS) was held on 22-Sep-2021. The proposed extension of the ITP therapeutic indication and the supportive data package, consisting of clinical trial and real-world data were discussed.

AEMPS stated that due to the limited number of patients from prospective clinical trials (CT), other forms of complementary evidence would be required to support this change. Real-world data (RWD) was considered appropriate as supportive data to CT data. The Agency also recommended to perform pharmacodynamic (PD) modelling to show that the approved doses of eltrombopag increase platelet counts regardless of time from diagnosis.

In addition, the indication extension in paediatric patients was also discussed. The Agency highlighted that the unmet medical need in the paediatric population is less certain than for the adult population due to frequent spontaneous remissions. The Agency stated that the indication extension in paediatrics, based solely on guidelines and limited RWD in children, would be very unlikely, in view of the limited clinical trial data available in children. Guidelines and limited RWD could be considered as supportive to CT data, but cannot replace them. It was also remarked that the use of modelling data could be generally applicable also for children; however, the model would need to be populated by

clinical data generated in children, which are not available to date for children with ITP less than 6 months from diagnosis.

In line with the Agency's feedback, the MAH has provided a pharmacodynamic modelling to complement the prospective clinical trial data and real-world data in adult population. Based on the lack of currently available clinical data in the paediatric population less than 6 months from ITP diagnosis, only the adult indication is sought to be extended with this application.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

The MAH has submitted information for environmental risk assessment (ERA) of eltrombopag olamine in accordance with EMEA/CHMP/SWP/4447/00 Corr 2 guidance to address the following extension of the adult ITP indication: *"Revolade is indicated for the treatment of **adult** patients ~~aged 1 year and above~~ with primary immune thrombocytopenia (ITP) ~~lasting 6 months or longer from diagnosis and~~ who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)."*

This information would not modify the current SmPC.

2.2.2. Ecotoxicity/environmental risk assessment

The MAH has presented an ERA based on the Guidance on "Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr 2)

Phase I: Estimation of exposure

- *Calculation of the Predicted Environmental Concentration (PEC)*

The PEC has been calculated, according to the formula established in the guideline EMEA/CHMP/SWP/4447/00 corr 2, as the sum of all PECs for all eltrombopag indications:

$PEC_{SURFACEWATER}$ = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)
= (75 mg/inhabitant/day * 0.01) / (200 L/inhabitant/day * 10)
= 0.000375 mg/L = 0.375 µg/L for ITP

$PEC_{SURFACEWATER}$ = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)
= (100 mg/inhabitant/day * 0.01) / (200 L/inhabitant/day * 10)
= 0.0005 mg/L = 0.5 µg/L for cHCVaT

$PEC_{SURFACEWATER}$ = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)
= (150 mg/inhabitant/day * 0.01) / (200 L/inhabitant/day * 10)
= 0.00075 mg/L = 0.75 µg/L for SAA

Where:
DOSEai
= 75 mg/patient/day for ITP;
= 100 mg/patient/day for cHCV associated thrombocytopenia

= 150 mg/patient/day for 6 months for SAA
Fpen = 1 % (default)
WASTEWinhab = 200 L/inhabitant/day
DILUTION = 10

Therefore, the overall $PEC_{SURFACEWATER}$ = 0.375 µg/L + 0.5 µg/L + 0.75 µg/L = 1.625 µg/L. In this way, as the action limit of 0.01 µg/L is exceeded, further risk assessment in Phase II- Tier A of the procedure is required.

- *Screening for persistence, bioaccumulation and toxicity.*

The octanol/water partition coefficient (Kow) was estimated to be > 4.1 at pH 5, = 4.52 at pH 7, and = 0.96 at pH 9, using the shake flask method according to the OECD 107 (Report SD2006/0232800/00).

As the estimated log K_{OW} value is clearly above the cu-off of 4.5, a PBT assessment is required.

Phase II-Tier A: Environmental fate and effects analysis

- *Physico-chemical properties and fate*

Biodegradation

The inherent ultimate biodegradability of eltrombopag was assessed under standard test conditions, based upon the OECD guideline 302C Modified MITI Test (II). The primary biodegradation was determined by high performance liquid chromatography (HPLC) analysis. The results from the carbon dioxide evolution data indicated that eltrombopag attained a mean biodegradation of 14% calculated from oxygen consumption values on Day 28. Results from the compound specific analysis showed that there was a loss of parent compound equivalent to 10% primary biodegradation of eltrombopag on Day 28. It can be concluded that eltrombopag is neither readily nor inherently biodegradable in aqueous biodegradation tests.

Adsorption / Desorption

As discussed in the Type II variation for HCV (eCTD sequence 0037), eltrombopag was initially investigated for determination of activated sludge sorption isotherm according to OPPTS 835.1110 (Report SD2006/00091/00). However, no determination of the isotherm was possible in this study due to the instability of the test material in aqueous solution at a concentration and pH relevant to the fate of the test material in the wastewater treatment plant. At the time it was not possible to overcome these technical challenges and, therefore, it was concluded that those physico-chemical characteristics of eltrombopag that contributed to the failure of this study were the same as those which would likely give rise to a Koc value for eltrombopag of greater than 10000 L/kg ostensibly triggering the need for a Phase II Tier B analysis in soil. However, since this submission it was found that it is possible to conduct a soil/sludge adsorption study (OECD 106) with eltrombopag. In this study, the adsorption and desorption of eltrombopag was determined in three soils and two municipal sewage sludges using the batch equilibrium method according to the OECD test guideline no. 106. The following soils/sludges were used: soil I (Speyer 2.3; sandy loam), soil II (Hagenthal; silt loam), soil III (Mechtildshausen; loam), sludge I (Füllinsdorf) and sludge II (Sissach). In order to limit microbial degradation of the test item during the experiment, all soils and both sludge were treated by γ-irradiation before use.

Adsorption kinetics were determined for a soil/sludge-to-solution ratio of 1/100 (1 g soil to 100 mL 0.01 M $CaCl_2$) and a test item concentration of 0.027 µg/mL. For all soils and sludge species, the level of

adsorption (adsorbed fraction of applied) almost reached equilibrium after 48 hours of agitation due to its high adsorption. The fraction of adsorption after 48 hours was 94.1%, 92.7% and 94.6% of the applied radioactivity for soils I to III, respectively, and 95.8% and 95.5% for sludge I and II, respectively. The mass balance, determined for all soils/sludge after 48 hours of adsorption, showed overall mean recoveries of 99.9%, 104.4% and 105.4% for the soils, and 113.3% and 108.8% for both sludges, respectively. The higher recoveries in both sludge species are due to the high amount of non-extractable radioactivity in comparison to the soils, and the small amount of material combusted. The mean K_{OC} adsorption value for the soils were 132,556 mL/g and 8,119 mL/g for the sludge. The adsorption showed to be independent of the cation exchange capacity, organic carbon or clay content of the soils. A slight dependence of the adsorption from the pH could be observed. Desorption kinetics were followed 2, 5, 24 and 48 hours after the 48 hours adsorption period. Very little desorption was observed for all soils/sludge throughout the experiment. The percent of the desorbed radioactivity amounted to 3.5%, 2.6%, 2.5%, 0.9% and 0.9% of adsorbed for soils I, II, III and sludge I and II, respectively after 48 hours of desorption. The mean K_{OC} desorption value for the soils was 302,493 mL/g and 30,492 mL/g for the sludge.

Aerobic Transformation in Aquatic Sediment Systems

The route and rate of degradation of [^{14}C]eltrombopag olamine in two aquatic systems (river and pond) under aerobic conditions were investigated at 20 ºC in the dark. [^{14}C]eltrombopag olamine dissipated from the water phase mainly due to rapid degradation and dissipation into the sediment layer. In the water phase eltrombopag olamine immediately degraded to transformation product M4 with the DT_{50} reached immediately after application. The immediate transformation/degradation of eltrombopag olamine in the water phase was proposed to be driven by abiotic processes, as the dilute biomass associated with "competent" degraders would be too reduced to cause such an abrupt biotic change. The rapid dissipation of [^{14}C]eltrombopag olamine from the aqueous phase led to a subsequent accumulation in the sediment compartment. Between 10 and 20% degradation was observed after 106 days exposure. Eltrombopag olamine is very persistent considering the DT50 values of >1000 d at 12ºC in total system and the DT50 values of 653 and 3244 d at 12ºC in sediment.

The criterion for sediment studies is met if more that 10% of the substance at any time point after or at 14 days is present in sediment. The transformation product M 4 occurs in concentrations of 8.4 and 4.9 % in sediment at study end (day 106) starting with concentrations of 21.2% and 27.4% at day 0. Thus TP M 4 cannot be considered as transient. Eltrombopag was exposed to UV light and measurement of light absorption revealed that this substance does exhibit significant absorption above 290 nm suggesting that degradation via direct photolysis may be a viable environmental depletion mechanism.

- *Aquatic effects studies*

Toxicity data on duckweed (*Lemna minor)*, algae, daphnia and fish were submitted for eltrombopag olamine. Also, the impact of eltrombopag on the respiration rate of activated sludge was assessed The main information of the conducted studies and the study results are summarised in the table below:

Table 1. Data on aquatic effects studies for eltrombopag olamine

Substance	Study / Report	Species	Results	Conclusions

Eltrombopag olamine	Green Algae Growth Inhibition Test (OECD 201)	*Scenedesmus subspicatus*	Eltrombopag olamine significantly adsorbed light at one of the wavelengths required for photosynthesis (460 nm) and that significant inhibition of growth occurred despite the use of the modified test design.	It was considered appropiate to change the test method to a Lemna Growth Inhibition Test (OECD 221).
	Lemna Growth Inhibition Test (OECD 221) / SD2006/03296/00	*Lemna minor*	<u>Average Spedific Growth rate</u>: E_rC_{50} (frond number)=4.1 mg/mL NOEC (frond number)= 0.45 mg/L E_rC_{50} (dry weight)= 7.2 mg/mL NOEC (dry weight)= 0.45 mg/L <u>Yield</u>: E_rC_{50} (frond number)=1.2 mg/mL NOEC (frond number)= 0.45 mg/L E_rC_{50} (dry weight)= 1.2 mg/mL NOEC (dry weight)= 0.45 mg/L	Eltrombopag olamine was considered to be **toxic to *Lemna minor,*** at nominal concentrations as significant effects on growth relative to the control treatment were observed, under the conditions of the test.
	Daphnia Reproduction Test (OECD 211) / 2014N194420_00	*Daphnia magna*	<u>Reproduction</u>: EC_{50} (21 day)> 0.12 mg/L LOEC (21 day)= 0.34 mg/L NOEC (21 day)= 0.12 mg/L <u>Immobility</u>: EC_{50} (21 day)> 0.19 mg/mL LOEC (21 day)= 0.34 mg/L NOEC (21 day)= 0.12 mg/L	Eltrombopag olamine was considered **provided of significant long-term toxicity to aquatic invertebrates.**
	Fish Early Life Stage Toxicity Test (OECD 210) / Report 2014N194417_00	*Danio rerio*	<u>Hatching</u>: LOEC (28 day)= 0.53 mg/L NOEC (28 day)= 0.16 mg/L <u>Larval Survival</u>: LOEC (28 day)= 0.16 mg/L NOEC (28 day)= 0.052 mg/L <u>Length and Weight</u>: LOEC (28 day)= 0.16 mg/L NOEC (28 day)= 0.052 mg/L	Eltrombopag olamine was considered to be **provided of significant long-term toxicity to fish.**
	Activated Sludge Respiratory Inhibition Test (OECD 209) / SD2005/01959/00		EC_{50} >320 mg/L NOEC = 32 mg/L	Eltrombopag olamine was considered **to be not toxic to activated sludge microbial populations.**

- *Calculation of Predicted No-Effect Concentration (PNEC) using assessment factors*

MAH carried out the risk characterisation in Tier A of the environmental risk assessment based on the generated effect data. In order to assess the risk to the aquatic environment, the calculation of PEC/PNEC ratios is required. In compliance with the guideline on environmental risk assessment, the predicted no effect concentration (PNEC) is calculated by applying an assessment factor (AF) to the no observed effect

concentrations (NOEC) values of these studies. A default assessment factor of 10 is applied to calculate the PNEC from the long-term toxicity test and the 10 to calculate anti-microbial effect study.

$PNEC_{SURFACEWATER}$ = 52 µg/L /10 = 5.2 µg/L (based on lowest NOEC from the most sensitive aquatic species).

$PNEC_{MICROORGANISM}$ = 32000 µg/L /10 = 3200 µg/L (based on NOEC from Activate Sludge Respiration Inhibition study).

$PNEC_{GROUNDWATER}$ **=** 120 µg/L /10 **=** 12 µg/L (based on NOEC from *Daphnia magna* reproduction test)

Calculation of refined $PEC_{SURFACEWATER}$

The $PEC_{SURFACEWATER}$ has been refined using epidemiological data for all registered indications, i.e., cHCVaT, SAA, and ITP (total PEC).

$PEC_{SURFACEWATER}$ = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)
= (75 mg/inhabitant/day * 0.000107) / (200 L/inhabitant/day * 10)
= 0.0401 µg/L for ITP

$PEC_{SURFACEWATER}$ = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)
= (100 mg/inhabitant/day * 0.00174) / (200 L/inhabitant/day * 10)
= 0.087 µg/L for cHCVaT

$PEC_{SURFACEWATER}$ = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)
= (150 mg/inhabitant/day * 0.00000254) / (200 L/inhabitant/day * 10)
= 0.00019 µg/L for SAA

Where:
DOSEai
= 75 mg/patient/day for ITP;
= 100 mg/patient/day for cHCVaT
= 150 mg/patient/day for 6 months for SAA
Fpen
= 10.7 in 100’000 inhabitants; 0.0107 % for ITP
= 174 in 100'000 inhabitants; 0.174 % for cHCVaT
= 0.254 in 100’000 inhabitants; 0.000254 % for SAA
WASTEWinhab = 200 L/inhabitant/day
DILUTION = 10

Therefore, the overall $PEC_{SURFACEWATER}$ = 0.0040 µg/L + 0.87 µg/L + 0.00019 µg/L = 0.091 µg/L.

Calculation of $PEC_{MICROORG}$

Based on the default dilution factor of 10 used between surface water and sewage treatment plants, the $PEC_{MICROORG}$ is ten times higher than the $PEC_{SURFACEWATER}$.

$PEC_{MICROORG}$ = 0.091 µg/L

Calculation of $PEC_{GROUNDWATER}$

According to the guideline, the $PEC_{GROUNDWATER}$ can be assumed to be typically 0.25 times the $PEC_{SURFACEWATER}$. This leads to a $PEC_{GROUNDWATER}$ of 0.023 µg/L, for eltrombopag free acid.

Outcome of Tier A fate and effects analysis

Surface water assessment

Refined $PEC_{SURFACE\ WATER}$ = 0.091 µg/L

$PNEC_{SURFACE\ WATER}$ = 5.2 µg/L

$PEC/PNEC_{SURFACE\ WATER}$ = 0.091 µg/L / 5.2 µg/L = 0.0175

Microorganisms / sewage treatment plant assessment

$PEC_{MICROORG.}$ = 0.91 µg/L

$PNEC_{MICROORG}$ = 3200 µg/L

$PEC/PNEC_{microorg.}$ = 0.091 µg/L / 3200 µg/L = 0.000284

Groundwater assessment

$PEC_{GROUNDWATER}$ = 0.023 µg/L

$PNEC_{GROUNDWATER}$ = 12.0 µg/L

$PEC/PNEC_{GROUNDWATER}$ = 0.023 µg/L / 12.0 µg/L = 0.0019

Table 2. Hazard/risk assessment eltrombopag olamine

Hazard/risk criterion	Data requirement
n-octanol/water coefficient (log Kow) > 3	Fish bioconcentration study conducted in Tier B
Adsorption – Desorption: sludge Koc < 10000	Sorption to sludge below the trigger value for a Tier B terrestrial assessment. No terrestrial assessment required.
$PEC_{SURFACE\ WATER}$ / $PNEC_{SURFACE\ WATER}$ < 1	0.091 µg/L / 5.2 µg/L = 0.0175
$PEC_{MICROORG}$ / $PNEC_{MICROORG}$ < 0.1	0.91 µg/L / 3200 µg/L = 0.000284
$PEC_{GROUNDWATER}$ / $PNEC_{GROUNDWATER}$ < 1	0.023 µg/L / 12.0 µg/L = 0.0019

Phase II-Tier B: Extended environmental fate and effects analysis

- *$PEC_{SURFACEWATER}$ refinement and PEC_{SLUDGE} calculation*

In Tier B the *PEC $_{SURFACEWATER}$* may be refined with information from STP modelling using the SimpleTreat model by incorporating adsorption of substances to sewage sludge in STPs, using the data from the estimation of the adsorption coefficient in sewage sludge from two sewage treatment plants.

First, the $Elocal_{WATER}$ value is calculated according to the EMA guideline formula, where

$Elocal_{WATER}$ = DOSEai * $F_{excreta}$ * F_{pen} * $CAPACITY_{stp}$

ITP: 75 mg/inhabitant/day * 1 * 0.000107 * 10000 inhabitants = 80.25 mg/day

cHCVaT: 100 mg/inhabitant/day * 1 * 0.00174 * 10000 inhabitants = 1740 mg/day

SAA: 150 mg/inhabitant/day * 1 * 0.00000254 * 10000 = 3.81 mg/day

Sum $Elocal_{WATER}$ = 80.25 + 1740 + 3.81 = 1824.06 mg/day

With:

DOSEai

= 75 mg/patient/day for ITP

= 100 mg/patient/day for cHCV associated thrombocytopenia

= 150 mg/patient/day for 6 months for SAA

CAPACITYstp = 10000 inhabitants (R.16 Table R.16-14)

$F_{excreta}$ = 100 %

F_{pen} = 10.7 in 100000 inhabitants; 0.0107 % for ITP

= 174 in 100000 inhabitants; 0.174 % for cHCVaT

= 0.254 in 100000 inhabitants; 0.000254 % for SAA

Applying the outcome of the SimpleTreat calculations the local surface water concentration can be refined as:

$PEC_{SURFACEWATER}$ = ($Elocal_{water}$* $F_{stp\ water}$) / ($WASTEW_{inhab}$ * $CAPACITY_{stp}$ * FACTOR * DILUTION)

= (1824.06 mg/day * 0.4848) / (200 L/inhabitant/day * 10000 inhabitants * 1.0196 * 10) = 0.000043 mg/L = 0.043 µg/L

With:

$Elocal_{water}$ = 1824.06 mg/day

$F_{stp\ water}$ = 48.48 % (from Simpletreat output data)

$WASTEW_{inhab}$ = 200 L/inhabitant/day (R.16 Table R.16-14)

$CAPACITY_{stp}$ = 10000 inhabitants (R.16 Table R.16-14)

FACTOR: 1 + Kpsusp * $SUSP_{water}$ * 10-6= 1 + 1307 L/kg * 15 mg/L * 10-6 = 1.0196

Kp_{susp} = 1307 L/kg (lowest Kd value for soils, as recommended by the draft EMA guidance, 2018, when Kd values do not correlate with organic carbon content)

$SUSP_{water}$ = 15 mg/L (R.16 Table R16-8)

Dilution = 10

While the risk ratio calculated for surface waters in Tier A does not indicate a risk for this environmental compartment and therefore no refinement is required, it can be noted that applying the refined Tier B $PEC_{SURFACEWATER}$ for the calculation of the risk ratio results in a $PEC/PNEC_{SURFACEWATER}$ of 0.0083.

Subsequently, the refined Tier B PECsurface water is used to calculate $PEC_{SEDIMENT}$.

- *Extended effects analysis*

Water sediment effects

The water-sediment study has shown that the level of eltrombopag in sediment at 14 days greater than 10% thereby exceeding the guidance criterion for sediment studies. The toxicity of eltrombopag was evaluated on the sediment-dwelling non-biting midge *Chironomus riparius* by exposure in a static sediment-water test system over a 28-day period in accordance with the requirements of OECD Chemicals Testing Guideline No. 218 Sediment-Water Chironomid Toxicity Test Using Spiked Sediment.

Following a preliminary range-finding test, larvae of *Chironomus riparius* were exposed in groups of 80 (four replicates of 20 larvae per concentration) to formulated sediment spiked with test item over a range of concentrations of 100, 180, 320, 560 and 1000 mg/Kg for a period of 28 days. The numbers of emerged adult midges were recorded daily.

Examination of the numbers of male and female adult midges emerged showed no biological significance between the numbers of male and females. Therefore, it was considered that the test item had no significant effect on the sex ratio of emerged adults.

The toxicity of the test item to the sediment-dwelling larvae of *Chironomus riparius* has been investigated and based on nominal concentrations gave 28-Day EC_{15} and EC_{50} (reduction in emergence) of 350 and 690 mg/Kg respectively. The No Observed Effect Concentration was 560 mg/Kg and the Lowest Observed Effect Concentration was 1000 mg/Kg. The results based on geometric mean measured concentrations gave 28- Day EC_{15} and EC_{50} (reduction in emergence) of 66 and 130 mg/Kg respectively. The No Observed Effect Concentration was 104 mg/Kg and the Lowest Observed Effect Concentration was 185 mg/Kg. The 28-Day EC_{15} and EC_{50} (development rate) values were not determined as only -0.4% reduction in development rate was determined for the 560 mg/Kg test group (the highest concentration where development rate could be calculated). The No Observed Effect Concentration was determined to be 560 mg/Kg (based on nominal concentration and 104 mg/Kg based on estimated geometric mean measured concentrations).

Table 3. Tier B toxicity data for eltrombopag olamine

Development of sediment-dwelling organisms (OECD 218)	EC_{50} (emergence) = 130 mg/kg LOEC (emergence) = 185 mg/kg NOEC (emergence) = 104 mg/kg NOEC (development) = 104 mg/kg

(Report 2016N274772_0)

The $PEC_{SEDIMENT}$ can be calculated following REACH Guidance on information requirements and chemical safety assessment Chapter R16.: Environmental Exposure Estimation (European Chemicals Agency, ECHA, February 2016):

$PEC_{LOCAL\ SED}$ = ($K_{SUSP\text{-}WATER}$ / $RHO_{SUSP)}$ * $PEC_{LOCAL\ WATER}$ * 1000 = (431.6 m^3/m^3 / 1150 kg/m^3) * 0.043 µg/L * 1000 = 16.14 µg/kg (Equation R.16-34)

With:

RHO_{SUSP} = 1150 kg/m^3 (Equation R. 16-1)

$K_{SUSP\text{-}WATER}$ = $Fwater_{SUSP}$ + $Fsolid_{SUSP}$ * (Kp_{SUSP} /1000) * RHO_{SOLID} =

0.9 m_{water}^3/m_{susp}^3 + 0.1 $m_{solid}^3/msusp^3$ * (1723 L/kg_{solid} / 1000) * 2500 kg/m^3 = 431.6 m^3/m^3

(Equation R.16-7)

With:

RHO_{solid} = 2500 kg/m^3 (Equation R. 16.7)

Kp_{susp} = 1723 L/kg (highest K_d value for soils, as recommended by the draft EMA guidance, 2018, when K_d values do not correlate with organic carbon content).

In order to account for the fact that the effect concentration of the sediment toxicity study is expressed as a dry weight concentration, the $PEC_{sediment}$ calculated above, which relates to wet sediment is multiplied with a conversion factor of 4.6, resulting in a dry weight $PEC_{sediment}$ of 74.24 µg/kg.

The $PNEC_{sediment}$, based on the NOEC for the development of the sediment-dwelling larvae of *Chironomus riparius* (Table 5-1) including an assessment factor of 100, is 1040 µg/L.

The risk ratio for sediment therefore calculates as:

$PEC/PNEC_{SEDIMENT}$ = 74.24 µg/kg / 1040 µg/kg = 0.071

This result indicates that eltrombopag does not constitute a risk to sediment compartments.

Bioaccumulation

Table 4. Tier B bioaccumulation data

Bioconcentration in fish (OECD 305)	**Low concentration: 0.0025 mg/L** BCF_{ss} = 14 L/kg BCF_k = 29 L/kg BCF_{ss} lipid-normalised = 336 L/kg **High concentration: 0.025 mg/L** BCFss = 14 L/kg BCF_k = 16 L/kg BCF_{ss} lipid-normalised = 130 L/kg

(Report 2011N113982_01)

The measured octanol water partition coefficient (log Dow, pH 7 = 4.52) of eltrombopag is above 3.0 indicating that eltrombopag could have a tendency to absorb to lipid surfaces and therefore bioaccumulate in the tissues of aquatic organisms.

A study was performed to assess the bioconcentration potential of the test item in rainbow trout (*Oncorhynchus mykiss*). The method followed was that described in the OECD Guideline for the Testing of Chemicals (1996) No 305 "Bioconcentration: Flow- Through Fish Test.

Rainbow trout were exposed, in groups of 52, to an aqueous solution of the test item at concentrations of 0.0025 and 0.025 mg/l for a period of 14 days under dynamic test conditions. Samples of test fish were taken from the solvent control, 0.0025 and 0.025 mg/l test groups on days 5, 7, 10, 12 and 14 and the concentration of test item in the fish tissues determined. After 14 days exposure the remaining fish were subjected to a depuration period of 10 days. Samples of test fish were taken from the solvent control and 0.0025 and 0.025 mg/l test groups on days 3, 5, 7 and 10 of the depuration phase and the concentration of test item determined. The Bioconcentration Factors at steady state (BCFss) for the test item based on total radioactivity in the whole fish after 14 days were calculated to be 14 at concentrations of 0.0025 and 0.025 mg/l (equivalent to 0.0020 and 0.020 mg/l as free base respectively). The Kinetic Bioconcentration Factors (BCFk) were also calculated and were shown to be 29 at a concentration of 0.0025 mg/l and 16 at a concentration of 0.025 mg/l after 14 days.

The uptake and depuration rate constants, k1 and k2, were determined to be 4.4148 and 0.1515 for the 0.0025 mg/l test concentration and 3.0805 and 0.1957 for the 0.025 mg/l test concentration. As the test item had a log K_{ow} of 4.52, following the recommendations of the test guidelines, the Bioconcentration Factors (BCF) values were also calculated as a function of the lipid content. These BCF values were higher than those determined in the whole fish results thereby suggesting that the accumulation of the test item was into the lipid content of the fish. However, as the values were below 2000, the test item would not be classified as bioaccumulative according to the PBT assessment criteria. The Bioconcentration Factors at steady state (BCFss) for the test item as a function of lipid content after 14 days was calculated to be 135 at concentrations of 0.0025 and 0.025 mg/l (equivalent to 0.0020 and 0.020 mg/l as free base respectively). For substances with high lipophilicity (e.g. log Kow >3) the bioconcentration factor should be normalized to 5% lipid content (based on whole body wet weight). The "BCF steady state" recalculated and related to 5% lipid content is 336 and 130 at concentrations of 0.0025 and 0.025 mg/L. The Kinetic Bioconcentration Factors (BCFk) were also calculated and were shown to be 280 at a concentration of 0.0025 mg/l and 136 at a concentration of 0.025 mg/l after 14 days.

The BCFss has been recalculated considering three successive analysis of Cf and normalisation to 5% lipid content as follows:

Low concentration (0.0025 mg/L): BCFss as function of the lipid content (taken from study Report 2011N113982_01): mean value from day 7 – 12 (325, 330, 352) = 336

High concentration (0.025 mg/L): BCFss as function of the lipid content (taken from study Report 2011N113982_01,): mean value from day 7 – 14 (137, 144, 105, 135) = 130

Eltrombopag olamine was shown not to significantly accumulate in fish tissue. At the end of the 10-Day depuration period 88% and 85% of eltrombopag olamine was eliminated from the fish tissues for the 0.0025 and 0.025 mg/l test concentrations respectively. Although this was less than the 90% elimination detailed in the guideline, it was considered that the results of the test were valid given the low BCF values obtained during the study. Based on this information the biological half-life of the test item is considered to be between 3 and 10 days.

Based on the lipid normalised BCFss values of 336 and 130 for the low dose and high dose exposure, respectively, remaining below the criteria for a bioaccumulative substance of a BCF of 2000, eltrombopag is not considered a bioaccumulative substance.

The MAH concludes that, in spite of the fact that no immediate risk was found for eltrombopag and excretion of parent substance by patients is expected to be low, intake of active pharmaceutical ingredients into surface waters should be avoided as far as possible. Therefore, as with all non-readily biodegradable human medicines, patients should be advised not to dispose of unused eltrombopag via domestic sewage.

Table 5. Assessment report providing relevant endpoints of the environmental risk assessment of human pharmaceuticals.

Summary of main study results

Substance (INN/Invented Name): Eltrombopag olamine			
CAS-number : 496775-62-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	92/69/EEC Method A8 (shake-flask method) …	log Dow > 4.1 at pH 5 log Dow = 4.52 at pH 7 log Dow = 0.96 at pH 9	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF (steady-state lipid-normalised) (OECD 305)	336 (low concentration) and 130 (high concentration)	not B
Persistence	DT50 or ready biodegradability	DT at 12°C: 653, 3244 days (sediment) 1043, 3116 days (total system)	vP
Toxicity	NOEC Fish, Early Life Stage Toxicity (OECD 210)	NOEC = 52 µg/L	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.625	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 or …	Koc sludge = 8’534 and 7’703 mL/g	Koc soil = 155’386, 97’529 and 144’754 mL/g Kd sludge = 2’355 and 2’148 mL/g Kd soil = 1’538, 1’307 and 1’723 mL/g
Ready Biodegradability Test	OECD 302 C	Not inherently biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	*Rhine River (sandy loam) Fröschweiher pond, (silt loam) CH, 20°C* DT_{50} water = 2.1/ 1.72 d DT_{50} sediment = 306/ 1520 d DT50, whole system = 489/ 1460 d 53.7/ 42.1% shifting to sediment at day 14 (parent + NER) Transformation product > 10%: M 4 (max. 21.2 and 27.4% day 0; 8.4 and 4.9% at day 106)			Very persistent in aquatic environment
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Lemna, Growth Inhibition Test	OECD 221	NOEC	450	µg/L	*Lemna minor*
Daphnia sp. Reproduction Test	OECD 211	NOEC	120	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	52	µg/L	*Danio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50}	>320000	µg/L	
		NOEC	32000		
Phase IIb Studies					
Bioaccumulation	OECD 305	BCFSS (lipid-normalised)	336 (low concentration) and 130 (high concentration)	L/kg	%lipids: 10% at test start; 8% at end of the test
		BCFkinetic (lipid-normalised)	280/136		Incomplete elimination of 88 and 85% at test end
		CT_{50} =	3- 10 d		
Sediment dwelling organism	OECD 218	NOEC	104	mg/kg	*Chironomus riparius*

2.2.3. Discussion on non-clinical aspects

Phase I. Estimation of exposure

Eltrombopag olamine has a partition coefficient greater than 4.5 (log D_{ow} = 4.52). Therefore, a PBT assessment, including a bioconcentration study in fish has been conducted in Phase II-Tier B of this assessment.

The predicted environmental concentration (PEC) for eltrombopag olamine, considering all indications, is 1.625 µg/L which exceeds the trigger value of 0.01 µg/L as given by EMA guideline, EMA/CHMP/SWP/44609/2010 Rev 1. Therefore, an environmental assessment Phase II –Tier A was performed.

Phase II Tier A. Environmental fate and effects analysis

In chronic toxicity studies, eltrombopag olamine shows a significant toxicity to aquatic organisms, i.e. Lemna (OECD 201), Daphnia magna (OECD 211) and fish (OECD 210) has been observed, being the fish species, Danio rerio (zebra fish), the most sensitive of the aquatic species tested.

The biodegradability of eltrombopag olamine was assessed by the MAH following the OECD guideline 302C Modified MITI Test (II) instead of the Ready Biodegradability test (OECD 301) as advises the guideline on the environmental risk assessment of medical products for human use (EMEA/CHMP/SWP/4447/00). Eltrombopag is not considered biodegradable and the MAH proposed to perform a Tier B assessment.

According to OECD Guidelines for the Testing of Chemiclas No. 308, eltrombopag has been found to quickly dissipate from the water phase into the sediment. The half-life determined in the study on transformation in total water/sediment systems exceeds 120 days, thus being very persistent considering the DT_{50} values of >1000 days at 12ºC in total system and the DT_{50} values of 653 and 3244 days at 12ºC in sediment. Therefore, an assessment for sediment has been presented in Phase II-Tier B of the current environmental risk assessment (OECD 218).

Eltrombopag shows a low potential for adsorption to sludge (K_{oc}<10000), indicate the unlikely affinity to bind to sewage sludge in the SPT, thus a terrestrial assessment in Phase II Tier B is not considered necessary.

Phase II Tier B. Extended environmental fate and effects analysis

The toxicity of eltrombopag to the sediment-dwelling larvae of *Chironomus riparius* (OECD 218) was investigated and revealed no toxicity.

$PEC_{SEDIMENT}$ for eltrombopag and the ratio $PEC_{SEDIMENT}/PNEC_{SEDIMENT}$ were recalculated considering the PEC_{bcf} value calculated as the sum all of each indication PECs, based on prevalence of the diseases for all indications (ITP, cHCVaT and SAA). The result indicates that eltrombopag does not constitute a risk to sediment compartments.

Since eltrombopag has a Log Pow value which is >3 in the environmental pH range, a fish bioaccumulation study (OECD 305) was conducted. In the bioconcentration study in rainbow trout (Oncorhynchus mykiss), eltrombopag olamine was shown not to significantly accumulate in fish tissue. Therefore, eltrombopag cannot be considered bioaccumulative based on the maximum Biocencentration Factors at steady state (BCF_{SS}) of 336 and 130 at a concentration of 0.025 and 0.0025 mg/l respectively, and Kinetic Bioconcentration Factors (BCFk) of 136 and 280 for the low and high dose exposure, respectively, as the BCF remains below the criteria for a bio-accumulative substance.

2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of eltrombopag olamine.

Considering the above data, eltrombopag olamine is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

Rationale for the proposed therapeutic indication extension

The recommended standard-of-care, first-line therapy for newly diagnosed ITP patients who need treatment consists of corticosteroids, unless there is a contraindication or need for more rapid platelet increase. If a faster response is required, especially in case of severe bleeding, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin may be used. Approximately 70-80% of ITP patients initially respond to corticosteroids, but relapses are frequent and long-term remission rates are low (Cuker 2015). Moreover, the majority of patients treated with corticosteroids suffer from significant corticosteroid-related adverse events (AEs).

Updated guidelines (Provan *et al* 2019; Neunert *et al* 2019) recommend the use of thrombopoietin receptor agonists (TPO-RAs) for persistent ITP. Due to the serious side effects of steroid therapy, these guidelines do not recommend a prolonged course of corticosteroids. National guidelines, e.g., the guidelines by the Austrian, German and Swiss medical societies (Matzdorff *et al* 2018), and those published recently by the Spanish ITP group (Lozano *et al* 2021), also recommend earlier use of TPO-RAs in refractory ITP, mainly based on data from observational studies in standard clinical practice.

Considering the high relapse rate and unfavorable safety profile of corticosteroids, treating physicians introduce eltrombopag earlier to shorten the time to achieve optimal platelet counts and to minimise the risk of serious side effects associated with prolonged use of steroids or other therapies such as immunosuppressants and splenectomy.

The revised ITP guidelines and growing real-world evidence for the use of TPO-RAs in patients with newly diagnosed and persistent ITP, indicate a significant unmet need in patients with newly diagnosed and persistent ITP who are refractory to first-line therapies.

In order to support the extension of the Revolade indication for adult ITP, the MAH performed:

1. An update of the established population pharmacokinetic (PK)/pharmacodynamic (PD) model enriched with new clinical trial data (from studies TRA102537, TRA108057 and CETB115J2411) in which the covariate effect of "time since diagnosis" was tested on relevant PD parameters;
2. A subgroup analysis of the completed ITP registration studies ([TRA100773A], [TRA100773B], [TRA102537/RAISE] and [TRA108057/REPEAT] studies);
3. An ad-hoc analysis of an ongoing phase II, open-label, prospective, single-arm study in adult ITP patients who are refractory or relapsed after first-line steroids (Study TAPER, CETB115J2411);
4. A literature review (including Real-World Evidence) on the use of eltrombopag in newly diagnosed and persistent ITP.

GCP

Not applicable as no new clinical trials have been submitted.

2.3.2. Pharmacokinetics

The pharmacokinetics of eltrombopag was described for ITP in the original marketing authorisation application and is essentially unchanged. No additional information is provided in this application.

2.3.3. Pharmacodynamics

The pharmacodynamics of eltrombopag was described for ITP in the original marketing authorisation application and is essentially unchanged. No additional information is provided in this application.

2.3.4. PK/PD modelling

Population PK/PD model

A population pharmacokinetic (PK)/pharmacodynamic (PD) analysis was conducted to confirm that earlier administration of eltrombopag yields similar efficacy (similar percentage of patients reaching the threshold for platelet count of 50 G/L) as when eltrombopag is started at 6 months or later after diagnosis.

The PK model included an absorption compartment (gut), a central (blood) compartment, and a peripheral (tissue) compartment, with absorption lag time, dual sequential first-order absorption and inter-occasional variability on absorption, and with first order elimination. Weight, gender, race (Asian vs. Non-Asian) and the use of corticosteroids were predictors of drug exposure.

The PD model included a precursor production compartment, two transit/maturation compartments and blood was represented by one platelet compartment. Parameters for the PD portion of the model included estimated baseline platelet count (BASE), zero-order production rate of platelet precursors (KIN), first-order maturation rate of platelet precursors (KOUT) and first-order elimination rate of platelets (KP, estimated as KIN/BASE). The model indicates that drug concentration increases the platelet production for responders (through a linear proportionality constant (SLOP)), but not for non-responders (slope equal to 0). In the final model developed by ICON Clinical Research, 81% of the population were considered responders and 19% of the population were considered non-responders. Additional positive factors in platelet production were female and older patients (>50 years of age).

For the purpose of this indication extension, this population PK/PD model was enriched with new clinical trial data ([TRA102537/RAISE], [TRA108057/REPEAT] and CETB115J2411 studies) and updated to test the covariate effect of "time since diagnosis" on relevant parameters and incorporate in the final model if statistically significant.

Simulation-based analysis

Platelet count data from 283 eltrombopag-treated patients - for whom 'time from diagnosis' information' was available - were used in model development, totaling 6157 platelet observations across the 5 studies. In the CETB115J2411 study, 32 patients started eltrombopag treatment 6 or more months from ITP diagnosis, and 72 patients started earlier; in studies TRA100773A and TRA100773B, all 38 patients retained in the modeling dataset started eltrombopag 6 or more months from diagnosis; in the RAISE study, 89 patients started eltrombopag 6 or more months from diagnosis, and 10 patients started earlier, and in the REPEAT study, 37 patients started eltrombopag 6 or more months from diagnosis, and only 5 patients started earlier.

The final platelet model incorporated the effect of time of eltrombopag administration relative to time since diagnosis as a categorical covariate (<6 months since diagnosis vs ≥6 months since diagnosis) on first-order maturation rate of platelet precursors (KOUT), and the effect of gender on platelet production (SLOPE). The estimated effect of time of eltrombopag administration relative to time since diagnosis on KOUT was estimated as 1.12 (close to 1), indicating that platelet dynamics is expected to be similar regardless of the time from ITP diagnosis to start of eltrombopag. Of note, with this final model enriched with data from 3 additional clinical studies, 85.9% of the population were considered

responders and 14.1% of the population were considered non-responders (SLOPE parameter in the model equal 0).

The updated population PK/PD model was subsequently used to simulate platelet count profiles over time for 4 weeks for all the 283 patients by considering a 4-week treatment with 50 mg of eltrombopag once daily and 100 replicates for each of the two following scenarios: one scenario where all the patients started eltrombopag less than six months after ITP diagnosis and a second scenario where all the patients started eltrombopag at least 6 months after ITP diagnosis.

Figure 1 presents the median platelet count over time for the two scenarios described above. This figure indicates that the time difference between treatment start and ITP diagnosis is not expected to result in clinically relevant difference in platelet profile over the simulated 4 weeks.

Table 1 summarises the percentage of patients that reach the threshold of 50 G/L at Weeks 2, 3 and 4 as mean, median, 5^{th} and 95^{th} percentile across all the replicates, stratified by time since diagnosis category (ITP duration ≥6 months, ITP duration <6 months. At each time point (end of Week 2, end of Week 3 and end of Week 4), the median percentage of patients who achieved a platelet count of at least 50 G/L is similar regardless of the time from ITP diagnosis to start of eltrombopag. These median response rates should not be interpreted and compared to observed response rates from the clinical trials because of the following reasons: the simulated scenarios did not consider dose escalation of eltrombopag, the high intra-individual variability which resulted in a wide 90% percentile interval and the high proportion of patients with a severe disease before starting eltrombopag (39% of all 283 patients had baseline platelet count below 15 G/L) who may have needed simulated dose escalation to reach a response.

There is a constant linear proportionality between drug concentration and platelet production in the updated PKPD model. There is also a negligible effect of time of eltrombopag administration relative to time since diagnosis on the maturation rate of platelet precursors (estimated as 1.12, close to 1).

Considering the similar platelet profiles between patients with an ITP duration <6 months and patients with an ITP duration ≥6 months obtained from simulations with a fixed dose of eltrombopag at 50 mg once daily, the platelet count would remain similar if the eltrombopag dosing was based on the dosing algorithm specified in the SmPC.

Figure 1 Simulated median platelet count over time from the updated model for the patients starting eltrombopag less than 6 months or 6 or more months after diagnosis

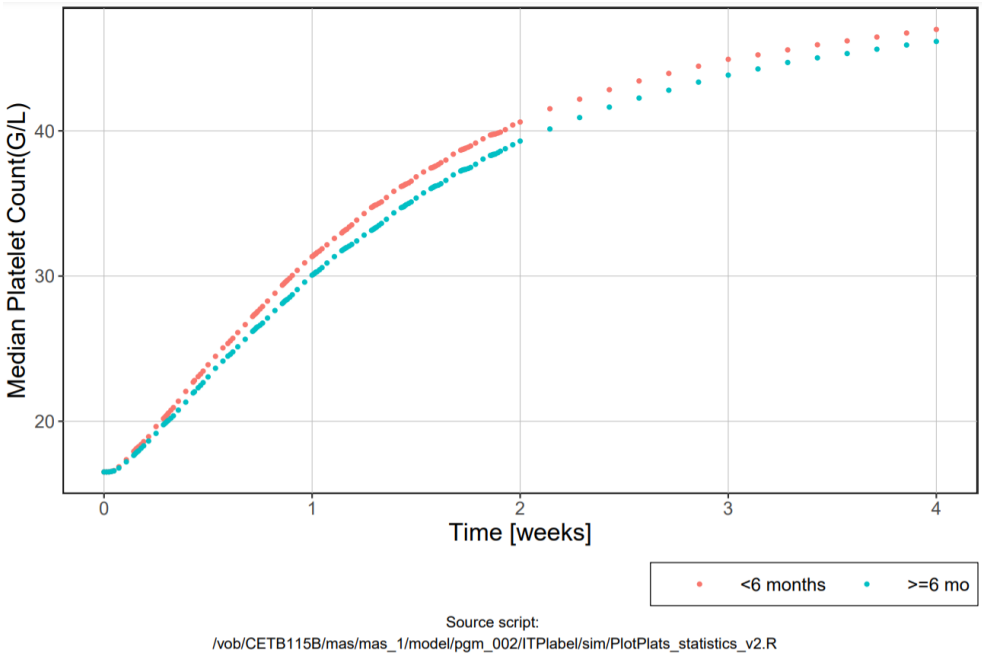


Table 6 Percentage of patients reaching the platelet threshold of 50 G/L stratified by time since diagnosis

Evaluation Timepoint	Time since diagnosis	Mean (%)	Median (%)	Pct_5th	Pct_95th
Week 2	<6 months	39.56	38.09	15.32	63.95
	>=6 months	38.54	37.51	14.41	62.21
Week 3	<6 months	42.5	43.09	17.97	66.86
	>=6 months	41.85	42.35	17.12	66.28
Week 4	<6 months	43.84	44.28	18.02	68.6
	>=6 months	43.32	44.28	18.02	68.02

Source: vob/CETB115B/mas/mas_1/model/pgm_002/ITPlabel/sim/ PlotPlats_statistics.R
Output: vob/CETB115B/mas/mas_1/model/pgm_002/ITPlabel/sim/exports/ PercentageReachingTreshold_AcrossAllRuns.csv

The PKPD modeling and simulations based on the pooled dataset of 5 studies ([TRA100773A], [TRA100773B], [TRA102537/RAISE], [TRA108057/REPEAT], CETB115J2411) demonstrated that the approved doses of eltrombopag increase platelet counts similarly in patients with an ITP duration of less than 6 months at start of eltrompobag and in patients with an ITP duration of at least 6 months at start of eltrombopag.

2.3.1. Discussion on clinical pharmacology

The PK/PD modelling analysis is aimed to evaluate whether the influence of time since diagnosis may provide clinically relevant differences in platelet counts in ITP adult patients receiving eltrombopag. For that purpose, the MAH has used a previously established population PK/PD model in healthy volunteers and ITP patients together with the information from recent clinical trials were the time of diagnosis was recorded to evaluate such covariate effect on PD parameters. Population PK/PD parameters were re-estimated, showing no relevant differences in parameter estimation between the initial and updated PK/PD models, which identified the time since diagnosis effect on kout (12% higher in patients <6 months diagnosed) and gender on platelet production (slope). Then, simulations were conducted over 4 weeks to assess the platelet counts levels. The simulation over 4 weeks between patients with less than 6-month and ≥6-month diagnosis revealed no relevant differences in platelet count levels at 2, 3 and 4 weeks among both groups. The results were comparable in the central tendency statistics (mean and median) and showed comparable variability, which is expected.

The updated PK/PD model was enriched with new clinical trial data ([TRA102537/RAISE], [TRA108057/REPEAT] and CETB115J2411 studies) and used to test the covariate effect of "time since diagnosis" on key PD parameters (as requested in the SA). The number of patients and observations included in the updated PK/PD model seem adequate for the characterization of the PK/PD relationship of eltrombopag in ITP adult patients, although the proportion of patients with time since diagnosis <6-month is unbalanced across the clinical trials included (mean: 30.7%, range: 0-69.2%). This may be problematic due to potential confounding, causing a non-random selection of patients and a likely biased conclusion.

In conclusion, the modelling strategy seems adequate, since a previously developed population PK/PD model has been used and enriched with additional clinical data to predict the categorical effect of time since diagnosis on PD parameters. Although the covariate effect was statistically identified, no clinically relevant changes in platelet count levels were predicted between patients with <6-month and ≥6-month diagnosis across the 4 weeks after the start of treatment. However, the unbalanced proportion of patients with time since diagnosis <6 months could affect the final conclusion obtained. Therefore, the current population PK/PD should be considered of low-impact (descriptive) for supporting the current extension of indication.

2.3.2. Conclusions on clinical pharmacology

The PK/PD properties of using eltrombopag irrespective of the time since diagnosis have been adequately addressed by the MAH. The conclusion that minimal changes are expected in platelet count levels seems adequate, which lack of any clinical relevance, although an unbalanced and non-random selection of patients was observed. Therefore, the claim of using eltrombopag in patients with an ITP duration of less than 6 months and at least of 6 months based on the current population PK/PD model should be considered with caution.

2.4. Clinical efficacy

2.4.1. Main studies

Efficacy data of eltrombopag in adult ITP patients lasting 6 months from diagnosis were described in the original marketing authorisation application and remain unchanged.

In the current variation application, efficacy results from adult ITP broken down by time since diagnosis (newly diagnosed ITP, persistent ITP and chronic ITP) are presented by two ad-hoc analysis.

Subgroup analysis of completed ITP registration studies (*ad-hoc analysis of EXTENDED study)*

- Parent studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in adult ITP patients was based on the results of three double-blind, placebo-controlled clinical studies, **[TRA100773A]**, [**TRA100773B**], [**TRA102537/RAISE**] and one open-label study [**TRA108057/REPEAT**].

In all four studies, the study population included adult patients (≥18 years) diagnosed with chronic ITP, defined at that time as the persistence of thrombocytopenia for at least 6 months and a baseline platelet count of <30 G/L. In these studies, the time from ITP diagnosis was not collected.

After completion of their participation in any of the above studies (parent studies), the patients were offered to continue treatment with eltrombopag in the open-label study [**TRA105325/EXTEND**], until eltrombopag became commercially available. In this study, the date of ITP diagnosis was collected, which allowed derivation of time from ITP diagnosis to the first dose of eltrombopag or matching placebo in the parent study.

Despite the inclusion criteria limiting the enrollment of patients with ITP for at least 6 months, some patients with a time since ITP diagnosis of less than 6 months have been enrolled and treated with eltrombopag or placebo in the parent ITP studies.

- Ad hoc analysis of EXTEND study (efficacy and safety by time since ITP diagnosis)

To support the proposed extension of the adult ITP indication, an ad-hoc analysis of efficacy and safety data by treatment arm (eltrombopag, placebo) and by time since ITP diagnosis (<3 months, 3 to <6 months, 6 to 12 months and >12 months) was conducted in patients who continued treatment in the EXTEND study. Due to the limited number of patients with a time since ITP diagnosis less than 6 months, results from this ad-hoc analysis are presented by pooling the parent ITP studies.

Study populations and definition of the primary efficacy endpoint considered for this ad-hoc analysis are consistent with those presented in the primary clinical study report of each study. The primary efficacy endpoint was the platelet response rate defined as:

- An increase in the platelet count from <30 G/L at baseline to ≥50 G/L after up to 6 weeks of dosing in **TRA100773A** and **TRA100773B** studies,
- A platelet count between 50 and 400 G/L during the 6-month treatment period in TRA102537 study (**RAISE**),
- Achieving a platelet count ≥50 G/L and an increase by at least 2-times the baseline value after up to 42 days of treatment in TRA108057 study (**REPEAT**).

Study participants

Overall, 302/494 (61.1%) (ranging from 43.6% to 74.1%) of patients enrolled in the parent studies were accrued into [**TRA105325/EXTEND**] study.

Among the 302 patients enrolled in the EXTEND study, 3 patients were excluded from this subgroup analysis for the following reasons: one patient due to unknown parent study and 2 patients with an ITP diagnosis date after the exposure to eltrombopag or placebo. Despite the inclusion criteria limiting the enrollment of patients with an ITP diagnosis of at least 6 months, 6.3% (**19/299**) of patients who continued treatment in the EXTEND study started eltrombopag treatment with an ITP diagnosis of less than 6 months (Table 7).

Table 7 Number of adult ITP patients who entered EXTEND, by study and time since diagnosis (intent-to –treat population).

	TRA100773A	TRA100773B	TRA102537 (RAISE)	TRA108057 (REPEAT)	All studies
Patients enrolled, n	117	114	197	66	494
Patients who continued in EXTEND, n (%)	51 (43.6)	61 (53.5)	146 (74.1)	43 (65.2)	302 (61.1)
Patients included in the subgroup analysis, n (%)	51 (43.6)	60 (52.6)	145 (73.6)	43 (65.2)	299 (60.5)[a]
Time since diagnosis, n (%)					
<3 months	0	1 (1.7)	4 (2.8)	2 (4.7)	7 (2.3)
≥ 3 to <6 months	0	1 (1.7)	8 (5.5)	3 (7.0)	12 (4.0)
≥ 6 to ≤12 months	7 (13.7)	9 (15.0)	19 (13.1)	6 (14.0)	41 (13.7)
>12 months	44 (86.3)	49 (81.7)	114 (78.6)	32 (74.4)	239 (79.9)

(a) For one patient it is not know from which parent study they enrolled into EXTEND; For two patients, the ITP diagnosis date was after the exposure to eltrombopag or placebo
* Percentages are based on the number of patients included in this subgroup analysis (N=299)
Source: Tables [Appendix 1 Table 1-11], [Appendix 1 Table 2-11], [Appendix 1Table 3-11] and [Appendix 1 Table 4-11]

Demographics and baseline characteristics

Baseline disease characteristics of the patients who continued in the [EXTEND] study are presented head-to-head by treatment and time since diagnosis (ITP category) in Table 8. These characteristics did not differ substantially from those patients enrolled in the parent studies. Indeed, among all patients enrolled in the parent studies (N=494), 203 patients (41.1%) were receiving ITP medication at randomization, 191 patients (38.7%) had a prior splenectomy, and 208 patients (42.1%) had baseline platelet counts of ≤15 G/L. Among patients included in this subgroup analysis (N=299), 39.1% were receiving ITP medication at randomization, 37.8% had a prior splenectomy, and 38.5% had baseline platelet counts of ≤15 G/L.

Table 8: Baseline disease characteristics in ITP registration studies (ITP population restricted to patients who entered EXTEND)

	Eltrombopag treatment group (N=219)			
ITP duration (months):	**<3 m** N=5	**≥3 to <6 m** N=11	**≥6 to ≤12 m** N=30	**>12 m** N=173
Use of ITP medication, n(%)				
Yes	3 (60.0)	7 (63.6)	10 (33.3)	65 (37.6)
No	2 (40.0)	4 (36.4)	20 (66.7)	108 (62.4)

Splenectomy, n(%)				
Yes	1 (20.0)	1 (9.1)	9 (30.0)	73 (42.2)
No	4 (80.0)	10 (90.9)	21 (70.0)	100 (57.8)
Platelet count*, n(%)				
≤15 G/L	1 (20.0)	5 (45.5)	12 (40.0)	62 (35.8)
>15 G/L	4 (80.0)	6 (54.5)	18 (60.0)	111 (64.2)

	Placebo treatment group (N=80)			
ITP duration (months):	**<3 m**	**≥3 to <6 m**	**≥6 to ≤12 m**	**>12 m**
	N=2	N=1	N=11	N=66
Use of ITP medication, n(%)				
Yes	0	1 (100)	5 (45.5)	26 (39.4)
No	2 (100)	0	6 (54.5)	40 (60.6)
Splenectomy, n(%)				
Yes	0	0	2 (18.2)	27 (40.9)
No	2 (100)	1 (100)	9 (81.8)	39 (59.1)
Platelet count, n(%)				
≤15 G/L	1 (50.0)	0	2 (18.2)	32 (48.5)
>15 G/L	1 (50.0)	1 (100)	9 (81.8)	34 (51.5)

* All 43 patients from [TRA108057/REPEAT] were included in the category ">15 G/L" because the protocol-defined platelet count inclusion criteria was ≥20 G/L and ≤50 G/L.

Results

- *Platelet count response rate*

The proportion of responders is presented head-to-head by treatment and time since diagnosis (ITP category) in Table 9 by combining all patients who continued in the EXTEND study. In patients treated with eltrombopag, the proportions of responders after up to 6 weeks of treatment was **80%**, **45.5%**, **66.7%** and **68.2%** in the different ITP categories: newly diagnosed ITP (<3 months), persistent ITP (3 to <6 months and 6 to 12 months), and chronic ITP (>12 months), respectively. For patients with time since ITP diagnosis of 6 months or less, **56.3%** (9/16) randomized to eltrombopag were responders versus **33.3%** (1/3) randomized to placebo. Comparisons to placebo should be considered with caution due to the limited number of patients randomized to placebo within each ITP category.

Table 9 Platelet count response in ITP registration studies (efficacy population restricted to patients who entered EXTEND)

	Eltrombopag treatment group (N=217)*			
Time from diagnosis (months)	**<3 m**	**≥3 to <6 m**	**≥6 to ≤12 m**	**>12 m**
	N=5	N=11	N=30	N=171
Platelet count response at Day 43				
No. Evaluable	5	11	30	170
Responders, n (%)	4 (80.0)	5 (45.5)	20 (66.7)	116 (68.2)
	Placebo treatment group (N=79)			
Time from diagnosis (months)	**<3 m**	**≥3 to <6 m**	**≥6 to ≤12 m**	**>12 m**
	N=2	N=1	N=10	N=66
Platelet count response at Day 43				
No. Evaluable	2	1	9	66
Responders, n (%)	0	1 (100.0)	2 (22.2)	7 (10.6)

* Includes all eltrombopag treatment group irrespective of the dosing group; for [TRA108057/REPEAT] study, only data from cycle 1 was considered.
Population (N=217): eltrombopag-treated patients from the four ITP registration studies included in the respective efficacy population (as defined in the primary clinical study report of each individual study) and enrolled in the EXTEND study.

- *Bleeding rate*

The proportion of patients without bleeding events at baseline and after 6 weeks of treatment (Day 43) is presented head-to-head by treatment and time since diagnosis (ITP category) in Table 10, by combining all patients who continued in the EXTEND study. In patients treated with eltrombopag, the proportion of patients without bleeding events is approximately two-fold higher after 6 weeks of treatment compared to baseline. The proportion of patients without bleeding events increased post baseline to **75%**, **90%**, **63.6%** and **78.6%** for patients with an ITP duration of <3 months (newly diagnosed ITP), 3 to <6 months, 6 to 12 months (persistent ITP) and >12 months (chronic ITP), respectively, compared to a baseline value of **20.0%, 45.5%**, **36.7%** and **31.5%** across the subgroups, respectively. For patients with time since ITP diagnosis of 6 months or less, **85.7%** (12/14) randomized to eltrombopag did not report any post-baseline bleeding events versus **33.3**% (1/3) randomized to placebo. Comparisons to placebo should be considered with caution due to the limited number of patients randomized to placebo within each ITP category.

Table 10: Number (%) of patients without bleeding in ITP registration studies (efficacy population restricted to patients who entered EXTEND)

	Eltrombopag treatment group (N=217)*			
Time from diagnosis (months)	**<3 m**	**≥3 to <6 m**	**≥6 to ≤12 m**	**>12 m**
	N=5	N=11	N=30	N=171
Baseline				
No. Evaluable	5	11	30	168
Without bleeding, n (%)	1 (20.0)	5 (45.5)	11 (36.7)	53 (31.5)
Day 43 (Week 6), n (%)				
No. Evaluable	4	10	22	140
Without bleeding, n (%)	3 (75.0)	9 (90.0)	14 (63.6)	110 (78.6)
	Placebo treatment group (N=79)			
Time from diagnosis (months)	**<3 m**	**≥3 to <6 m**	**≥6 to ≤12 m**	**>12 m**
	N=2	N=1	N=10	N=66
Baseline				
No. Evaluable	2	1	10	63
Without bleeding, n (%)	0	0	5 (50.0)	16 (25.4)
Day 43 (Week 6), n (%)				
No. Evaluable	2	1	8	63
Without bleeding, n (%)	0	1 (100.0)	6 (75.0)	26 (41.3)

* Includes all eltrombopag treatment group irrespective of the dosing group; for [TRA108057/REPEAT] study, only data from cycle 1 was considered.
Source: Tables Appendix 1 Table 1-14], [Appendix 1 Table 2-14], [Appendix 1Table 3-14] and [Appendix 1 Table 4-14]

Ad-hoc analysis of TAPER Study (CETB115J2411 study)

Phase II, Open-label, Prospective, Single-arm, Study to Assess Ability of Eltrombopag to Induce Sustained Remission in Subjects With ITP Who Are Refractory or Relapsed After First-line Steroids (Ad-hoc analysis).

Objectives

Taper Study (CETB115J2411) [*ClinicalTrials.gov*; *NCT03524612*]: will assess the ability of eltrombopag to induce sustained treatment-free remission in ITP subjects who relapsed or failed to respond to an initial treatment with steroids. This study was designed to include patients who failed previous first-line steroid treatments without restrictions to newly diagnosed, persistent or chronic ITP definitions, as previously published data indicated that eltrombopag used for the early stage ITP is as effective and safe as it is in chronic ITP (González-López et al 2017).

The primary analysis of this study, intended to assess the ability of eltrombopag to induce a sustained remission by Month 12, will be performed once all patients have completed 12 months on study or have discontinued early from study. The results of this analysis, once available, will be reported in the primary Clinical Study Report (CSR).

The recruitment was completed on 26-Oct-2020 with 105 patients enrolled of the 101 planned patients. As of 01-Dec-2021, 19 patients are ongoing.

Actual Study Start Date: November 2, 2018 [*ClinicalTrials.gov*; *NCT03524612*]

Estimated Study Completion Date: October 21, 2022 [*ClinicalTrials.gov; NCT03524612]*

Interim Ad-hoc analysis: to support the proposed extension of the adult ITP indication, an ad-hoc analysis of the CETB115J2411 study was conducted using a data cut-off date of 15-Oct-2020.

Study participants

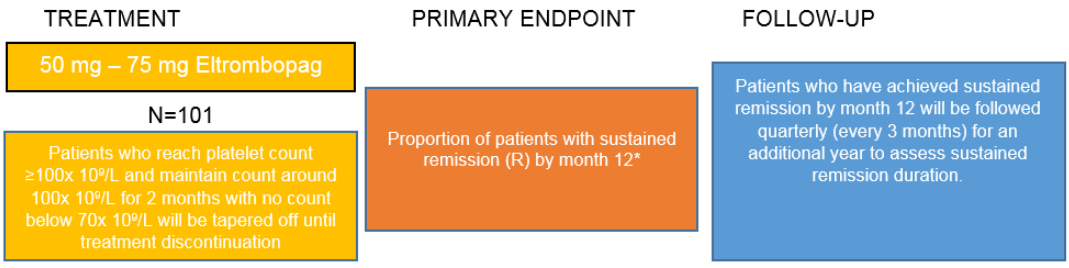
***Study CETB115J2411 (N=105)*:** was designed to include patients who failed previous first-line steroid treatments without restrictions to newly diagnosed, persistent or chronic ITP definitions.

Inclusion Criteria *[ClinicalTrials.gov*:*NCT03524612]*:

- Signed informed consent must be obtained prior to participation in the study
- Subjects ≥ 18 years old
- Subjects with a confirmed diagnosis of primary ITP, who are not responsive or in relapse after a first line of steroid therapy ± intravenous immunoglobulin (IVIG) (used as a rescue therapy)
- Platelet count < 30×10^9/L and assessed as needing treatment (per physician's discretion)

Patients who reach complete response and maintain platelets counts above 70 G/L for two months are eligible to taper-off study drug. The primary endpoint of the study is to determine the proportion of patients with sustained remission off treatment by Month 12 (Figure 2).

Figure 2 TAPER (CETB115J2411) study design



*Sustained remission is defined as patients who:
Reach platelet count ≥100x 10⁹/L (complete response [CR]) and then maintain platelet counts around 100x 10⁹/L for 2 months (with no counts below 70x 10⁹/L) AND then taper off the drug until treatment discontinuation while, maintaining platelet count ≥30x 10⁹/L in the absence of bleeding (no bleeding AEs) or use of any rescue medication until month 12

Population:

- Patients with ITP, ≥18 years of age
- Relapsed or failed to respond after first line steroid treatment
- Platelet count < 30x 10⁹/L and need for treatment

Ad-hoc analysis: included only patients with at least 6 months of data or patients who discontinued the study prior to Month 6. Newly enrolled ongoing patients who have not completed 6 months on study at the time of the data cutoff date were not included in these analyses.

Patients included in the ad-hoc analyses were categorised by time since diagnosis, as follows:

- Group A: Time since ITP diagnosis <3 months (newly diagnosed ITP)
- Group B: Time since ITP diagnosis 3 to <6 months (persistent ITP)
- Group C: Time since ITP diagnosis 6 to ≤12 months (persistent ITP)
- Group D: Time since ITP diagnosis >12 months (chronic ITP)

Full Analysis Set (FAS): all patients who received at least one dose of eltrombopag.

Safety Set: included all patients who received at least one dose of eltrombopag.

Treatment

Drug: eltrombopag

Eltrombopag is for oral use and comes in 12.5, 25, 50 and 75 mg tablets; prescribed dose is taken once daily *[ClinicalTrials.gov:NCT03524612]*.

Sample size (ad-hoc analysis)

For the ad-hoc analysis, 82/105 (78.1%) patients from study CETB115J2411 were eligible for. All 82 patients had at least one dose of eltrombopag. Approximately one quarter of patients (24.4%) discontinued treatment; the main reason for discontinuation was due to physician decision (13.4%). The majority (61.0%) of patients are still on treatment and 14.6% of patients have tapered-off eltrombopag as per protocol (Table 11).

Outcomes/endpoints (ad-hoc analysis)

Efficacy endpoints are presented by time since ITP diagnosis (called "ITP categories") using the FAS.

Response rate was defined as the proportion of patients with a platelet count of ≥50 G/L at least once by Week 9 Day 1 (~Day 57) without rescue therapy (consistent with the response rate definitions used in the pivotal registration studies for the ITP indication).

Partial response (PR) and complete response (CR) by Week 9 Day 1 were also presented using the following definition: proportion of patients with a platelet count ≥30 G/L (PR) or ≥100 G/L (CR) at least once by Week 9 Day 1 (~Day 57) without rescue therapy.

In response derivations, '*without rescue therapy'* is any platelet count assessment at least 14 days (≥14 days) after rescue therapy. It is noted that rescue therapy is allowed within the first 14 days per CETB115J2411 protocol.

The following supportive efficacy endpoints were summarized to assess the effect of eltrombopag on the durability of the response, the time to response and the occurrence of bleeding events:

- R50_2BL: proportion of patients who achieved a platelet count ≥50 G/L and 2× baseline at Week 7 Day 1 (~Day 43) without rescue therapy

- R50_4out6: proportion of patients with a platelet count of ≥50 G/L by Week 9 Day 1 (~Day 57) on at least 4 out of 6 consecutive scheduled platelet assessments without rescue therapy

- R50_6out8: proportion of patients with a platelet count of ≥50 G/L within first 6 months of dosing on at least 6 out of 8 consecutive scheduled platelet assessments without rescue therapy

-PR_6M: proportion of patients with a platelet count ≥30 G/L at least once within first 6 months without rescue therapy

-Median platelet count over time

-Time to first response threshold, ≥30 G/L, ≥50 G/L and ≥100 G/L

-WHO and ITP bleeding scales results by visit

Other descriptive analyses were provided on:

-Disposition and demographics

-Transfusions over time

-Rescue therapy over time

-Eltrombopag exposure

-Adverse events

-Deaths

Randomisation

N/A (Single Arm Study)

Blinding (masking)

None (Open Label Study)

Statistical methods

Since this clinical trial aims to have patients come off drug after achieving complete response (platelet count ≥100 G/L) and maintaining it for 2 months, efficacy analysis was focused on the first two months (~57 days) of the trial, to assess the effect of eltrombopag while on treatment. The safety analyses are presented until Month 6.

Data: Only data up to and including Month 6 (Study day 183 – Week 27 Day 1) was used. Data after Month 6 was not used in these analyses.

The results from this ad-hoc analysis (*data cutoff date of 15-Oct-2020*) presented will only be used to support the proposed extension of the adult ITP indication.

The limits imposed for the population and data analysed (restricted to up to 6 months from start of eltrombopag), as well as for the planned analyses (efficacy endpoints assessed while on treatment) allow to have an optimal independency between this ad-hoc analysis assessing the effect of eltrombopag while on treatment and the planned primary analysis assessing the ability of eltrombopag to maintain a response after treatment discontinuation.

Safety results from this ad-hoc analysis are presented using the Safety Set which included all patients who received at least one dose of eltrombopag.

Only descriptive analyses were performed:

- Frequencies and percentages for categorical data;
- Continuous variables are summarized by number of patients, mean, standard deviation, minimum, 25th-quantile, median, 75th-quantile and maximum unless otherwise indicated;
- Kaplan-Meier curves for time to event analyses;
- Graphs were provided where applicable.

Results

Included population

For the ad-hoc analysis, 82/105 (78.1%) patients from study CETB115J2411 were eligible. All 82 patients had at least one dose of eltrombopag. Approximately one quarter of patients (24.4%) discontinued treatment; the main reason for discontinuation was due to physician decision (13.4%). The majority (61.0%) of patients is still on treatment and 14.6% of patients have tapered-off eltrombopag as per protocol (Table 11).

Treatment discontinuations were reported for 34.2% of the patients with newly diagnosed ITP, 11.1% in patients with persistent ITP lasting 3 to <6 months from diagnosis, 12.5% in patients with persistent ITP lasting 6 to ≤12 months from diagnosis, and 30.0% in patients with chronic. Study discontinuations were reported with 31.6%, 11.1%, 12.5% and 20.0%, respectively.

Table 11 Patient disposition by ITP duration within first 6 months of treatment (Full analysis set)

Table 1-1 (Page 1 of 2)
Patient disposition by ITP duration within first 6 months
(Full analysis set)

	Group A N=38 n(%)	Group B N=18 n(%)	Group C N=16 n(%)	Group D N=10 n(%)	All Patients N=82 n(%)
Patients treated					
Treated	38 (100)	18 (100)	16 (100)	10 (100)	82 (100)
Ongoing treatment*	17 (44.7)	13 (72.2)	14 (87.5)	6 (60.0)	50 (61.0)
Completed treatment	8 (21.1)	3 (16.7)	0	1 (10.0)	12 (14.6)
Discontinued from treatment	13 (34.2)	2 (11.1)	2 (12.5)	3 (30.0)	20 (24.4)
Reason for treatment discontinuation					
Physician Decision	8 (21.1)	2 (11.1)	0	1 (10.0)	11 (13.4)
Lack of Efficacy	8 (21.1)	1 (5.6)	0	1 (10.0)	10 (12.2)
New therapy for study indication	0	1 (5.6)	0	0	1 (1.2)
Adverse Event	1 (2.6)	0	1 (6.3)	1 (10.0)	3 (3.7)
Death	1 (2.6)	0	0	1 (10.0)	2 (2.4)
Subject Decision	1 (2.6)	0	1 (6.3)	0	2 (2.4)
New therapy for study indication	0	0	1 (6.3)	0	1 (1.2)
Personal Reasons	1 (2.6)	0	0	0	1 (1.2)
Protocol Deviation	1 (2.6)	0	0	0	1 (1.2)
New Therapy For Study Indication	1 (2.6)	0	0	0	1 (1.2)
Discontinued from study	12 (31.6)	2 (11.1)	2 (12.5)	2 (20.0)	18 (22.0)
Reason for study discontinuation					
Physician Decision	8 (21.1)	1 (5.6)	0	2 (20.0)	11 (13.4)
Lack of Efficacy	7 (18.4)	0	0	1 (10.0)	8 (9.8)
Adverse Event	1 (2.6)	0	0	0	1 (1.2)
As Per Protocol	0	0	0	1 (10.0)	1 (1.2)
New therapy for study indication	0	1 (5.6)	0	0	1 (1.2)
Death	1 (2.6)	1 (5.6)	0	0	2 (2.4)
New Therapy For Study Indication	2 (5.3)	0	0	0	2 (2.4)
Adverse Event	0	0	1 (6.3)	0	1 (1.2)
Subject Decision	0	0	1 (6.3)	0	1 (1.2)
Withdraw Consent	0	0	1 (6.3)	0	1 (1.2)
Guardian Decision	1 (2.6)	0	0	0	1 (1.2)
Adverse Event	1 (2.6)	0	0	0	1 (1.2)

* Ongoing at the time of data cut-off date 15OCT2020

Demographics and baseline characteristics

The majority of patients were female (58.5%), median (min-max) age was 49 years (18-88 years).

The median (min-max) age was 54.0 years (20-87), 45.0 (22-88), 49.0 (21-88) and 50.0 (18-74) across all ITP categories respectively. Females were the majority in all categories except for chronic ITP (52.6%, 66.7%, 81.3% and 30.0%, respectively) (Table 12).

Table 12 Demographics and baseline characteristics by ITP duration (Full analysis set)

Time from diagnosis Demographic variable	<3 months N=38	3 to <6 months N=18	6 to ≤12 months N=16	>12 months N=10	All Patients N=82
Age (years)					
Mean	49.9	44.8	50.1	46.1	48.3
Median	54.0	45.0	49.0	50.0	49.0
Min-Max	20-87	22-88	21-88	18-74	18-88
Age category -n (%)					
18 - <45 years	17 (44.7)	9 (50.0)	7 (43.8)	4 (40.0)	37 (45.1)
45 - <65 years	10 (26.3)	5 (27.8)	4 (25.0)	4 (40.0)	23 (28.0)

Time from diagnosis Demographic variable	<3 months N=38	3 to <6 months N=18	6 to ≤12 months N=16	>12 months N=10	All Patients N=82
65 - <75 years	8 (21.1)	3 (16.7)	3 (18.8)	2 (20.0)	16 (19.5)
75 - <85 years	2 (5.3)	0	1 (6.3)	0	3 (3.7)
≥85 years	1 (2.6)	1 (5.6)	1 (6.3)	0	3 (3.7)
Sex -n (%)					
Female	20 (52.6)	12 (66.7)	13 (81.3)	3 (30.0)	48 (58.5)
Male	18 (47.4)	6 (33.3)	3 (18.8)	7 (70.0)	34 (41.5)
Race -n (%)					
White	37 (97.4)	16 (88.9)	14 (87.5)	10 (100)	77 (93.9)
American Indian or Alaska Native	0	1 (5.6)	2 (12.5)	0	3 (3.7)
Asian	0	1 (5.6)	0	0	1 (1.2)
Black or African American	1 (2.6)	0	0	0	1 (1.2)
Ethnicity – n (%)					
Not Hispanic or Latino	25 (65.8)	9 (50.0)	10 (62.5)	9 (90.0)	53 (64.6)
Hispanic or Latino	10 (26.3)	8 (44.4)	6 (37.5)	0	24 (29.3)
Not reported	1 (2.6)	1 (5.6)	0	1 (10.0)	3 (3.7)
Unknown	2 (5.3)	0	0	0	2 (2.4)
Time since initial diagnosis (days)					
Mean	34.5	129.9	271.5	2130.0	357.2
Median	27.0	124.0	278.0	1628.0	106.0
Min-Max	7-88	94-175	184-364	403-5008	7-5008
Platelet count at baseline (G/L)					
Mean	25.4	31.6	31.1	24.4	27.8
Median	13.5	17.5	22.7	25.0	19.0
Min-Max	1-149	7-144	1-106	7-40	1-149

Time since initial diagnosis is the difference in days between the date of initial diagnosis and the first dose date.

Treatment exposure

The median (25-75th percentile) duration of exposure to study treatment was 6.01 months (5.91-6.05) with a median exposure of 6.01 months in all ITP categories (Table 13).

The median (25-75th percentile) actual dose intensity was 51.3 mg/day (10.7-67.9) for patients with newly diagnosed ITP, 46.6 (25.7-67.6) in persistent ITP (3 to <6 months), 63.9 (32.4-73.0) in persistent ITP (6 to ≤12 months), and 56.3 (22.6-69.5) in chronic ITP.

Table 13 Duration of exposure to eltrombopag by time from ITP diagnosis within first 6 months of treatment (Safety set)

Time from diagnosis	<3 months N=38	3 to <6 months N=18	6 to ≤12 months N=16	>12 months N=10	All Patients N=82
Total number of patients receiving eltrombopag – n (%)	38 (100)	18 (100)	16 (100)	10 (100)	82 (100)
Duration of exposure (months)					
Mean (SD)	4.80 (1.990)	5.56 (1.378)	5.69 (0.902)	5.1 (2.022)	5.18 (1.722)
Median	6.01	6.01	6.01	6.01	6.01
Q1-Q3	3.06-6.05	6.01-6.05	5.95-6.02	5.98-6.01	5.91-6.05
Min-Max	0.5-6.2	1.4-6.1	3.2-6.2	0.3-6.1	0.3-6.2
Duration of exposure categories (months) – n (%)					
<1	4 (10.5)	0	0	1 (10.0)	5 (6.1)
1 – <2	2 (5.3)	1 (5.6)	0	0	3 (3.7)
2 – <3	3 (7.9)	1 (5.6)	0	1 (10.0)	5 (6.1)
3 – <4	1 (2.6)	0	2 (12.5)	0	3 (3.7)
4 – <5	2 (5.3)	0	0	0	2 (2.4)
5 – <6	6 (15.8)	2 (11.1)	4 (25.0)	1 (10.0)	13 (15.9)
≥6	20 (52.6)	14 (77.8)	10 (62.5)	7 (70.0)	51 (62.2)

Efficacy results

- *Platelet count response rate*

By week 9, platelet response defined as at least once platelet count ≥ 50 G/L was achieved in 84.3% to 94.4% of patients in all categories/subgroups by time since ITP diagnosis. Response rates were higher when a platelet response was defined as a platelet count > 30 G/L, ranging between 88.2% to 100% for subgroups by time since ITP diagnosis (Table 14).

Table 14: Patient hematologic response by ITP duration (Full analysis set)

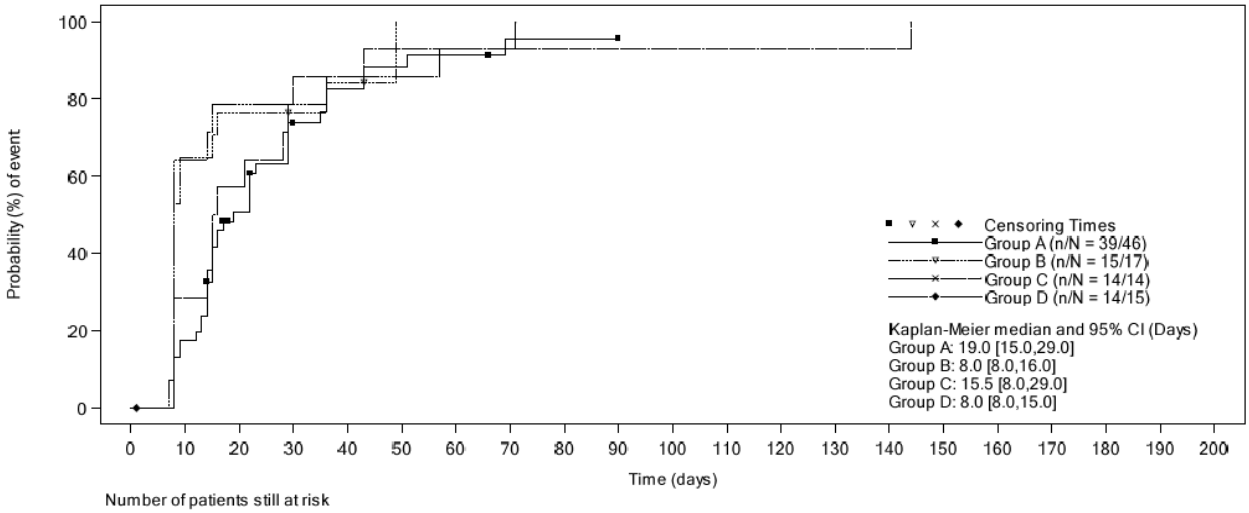
	<3 months N=51 n(%) 95% CI	3 to <6 months N=21 n(%) 95% CI	6 to <=12 months N=18 n(%) 95% CI	>12 months N=15 n(%) 95% CI	All Patients N=105 n(%) 95% CI
Response by Week 9					
R50: platelet count ≥50 G/L at least once by Week 9 Day 1 (~Day 57)	43 (84.3) (71.4, 93.0)	19 (90.5) (69.6, 98.8)	17 (94.4) (72.7, 99.9)	13 (86.7) (59.5, 98.3)	92 (87.6) (79.8, 93.2)
PR: platelet count ≥30 G/L at least once by Week 9 Day 1 (~Day 57)	45 (88.2) (76.1, 95.6)	19 (90.5) (69.6, 98.8)	18 (100.0) (81.5, 100.0)	13 (86.7) (59.5, 98.3)	95 (90.5) (83.2, 95.3)
CR: platelet count ≥100 G/L at least once by Week 9 Day 1 (~Day 57)	38 (74.5) (60.4, 85.7)	16 (76.2) (52.8, 91.8)	13 (72.2) (46.5, 90.3)	13 (86.7) (59.5, 98.3)	80 (76.2) (66.9, 84.0)
Supportive efficacy endpoints					
R50_2BL: platelet count ≥50 G/L and 2x baseline at Week 7 Day 1 (~Day 43)	35 (68.6) (54.1, 80.9)	15 (71.4) (47.8, 88.7)	9 (50.0) (26.0, 74.0)	9 (60.0) (32.3, 83.7)	68 (64.8) (54.8, 73.8)
R50_4out6: platelet count ≥50 G/L by Week 9 Day 1 (~Day 57) on at least 4 out of 6 consecutive scheduled platelet assessments	35 (68.6) (54.1, 80.9)	16 (76.2) (52.8, 91.8)	12 (66.7) (41.0, 86.7)	11 (73.3) (44.9, 92.2)	74 (70.5) (60.8, 79.0)
R50_6out8: platelet count ≥50 G/L on at least 6 out of 8 consecutive scheduled platelet assessments	36 (70.6) (56.2, 82.5)	17 (81.0) (58.1, 94.6)	13 (72.2) (46.5, 90.3)	12 (80.0) (51.9, 95.7)	78 (74.3) (64.8, 82.3)
PR_6M: platelet count ≥30 G/L at least once within first 6 months	46 (90.2) (78.6, 96.7)	19 (90.5) (69.6, 98.8)	18 (100.0) (81.5, 100.0)	14 (93.3) (68.1, 99.8)	97 (92.4) (85.5, 96.7)

95% confidence interval (CI) based on Clopper and Pearson exact method;

Source: [Appendix 2 Table 2-1]

The median time to first response ⩾50 G/L at any time within the first 6 months from start of eltrombopag was comparable across all ITP categories (from 8 to 19 days) (Figure 3). For complete response it ranged from 15 to 29 days across all ITP categories.

Figure 3: Kaplan-Meier plot of time to first response – platelet count ≥50 G/L by Month 6 (Full analysis set)



Number of patients still at risk

Time (days)	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200
Group A	46	38	20	9	6	4	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Group B	17	6	4	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Group C	14	10	6	2	2	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
Group D	15	5	3	3	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0

Log-rank test p-value (between Groups A, B, C and D) = 0.336
Patients who have a baseline platelet count ≥50 G/L are excluded from analysis.
Group A: newly diagnosed ITP (time since ITP diagnosis <3 months), Group B: persistent ITP (time since ITP diagnosis 3 to <6 months), Group C: persistent ITP (time since ITP diagnosis 6 to ≤12 months), Group D: chronic ITP (time since ITP diagnosis >12 months).

The median (25-75th percentile) increase in platelets from Baseline to Week 9 Day 1 was 97.5 G/L (35.0, 163.0). The median platelet count increased from Baseline to Week 9 Day 1 ranged from 43.5 to 107.0 across ITP categories.

Table 15 Time to first response – platelet count ≥50 G/L by Month 6 (Full analysis set)

Time from diagnosis	**<3 months** N=38	**3 to <6 months** N=18	**6 to ≤12 months** N=16
Patients excluded from analysis*	5 (13.2)	4 (22.2)	4 (25.0)
No. of events – n (%)	27 (71.1)	13 (72.2)	12 (75.0)
No. censored – n (%)	6 (15.8)	1 (5.6)	0
Time to response (days) – Percentiles (95% CI) [1]:			
25%	14.0 (8.0, 15.0)	8.0 (NE, NE)	11.0 (8.0, 15.0)
Median	17.0 (14.0, 22.0)	8.5 (8.0, 16.0)	18.0 (8.0, 30.0)
75%	36.0 (22.0, 69.0)	16.0 (8.0, NE)	29.5 (15.0, NE)
% Event probability estimates (days) (95% CI) [2]:			
<7	0 (NE, NE)	0 (NE, NE)	0 (NE, NE)
≥14	33.3 (17.9, 49.5)	64.3 (32.5, 84.1)	33.3 (9.4, 60.0)
≥28	67.0 (46.4, 81.2)	78.6 (43.2, 93.3)	66.7 (30.7, 87.0)
≥42	79.4 (57.3, 90.9)	85.7 (46.7, 96.9)	83.3 (40.4, 96.4)
≥56	87.6 (64.2, 96.1)	NE	91.7 (32.6, 99.3)

	>12 months N=10	**All Patients** N=82
Patients excluded from analysis*	0	13 (15.9)
No. of events – n (%)	9 (90.0)	61 (74.4)
No. censored - n (%)	1 (10.0)	8 (9.8)
Time to response (days) - Percentiles (95% CI) [1]:		
25%	8.0 (7.0, 8.0)	8.0 (8.0, 9.0)
Median	8.0 (7.0, 36.0)	15.0 (14.0, 21.0)
75%	22.0 (8.0, NE)	30.0 (22.0, 43.0)
% Event probability estimates (days) (95% CI) [2]:		
<7	0 (NE, NE)	0 (NE, NE)
≥14	55.6 (18.3, 81.6)	42.6 (30.7, 54.1)
≥28	77.8 (28.6, 95.1)	70.8 (57.8, 80.4)
≥42	88.9 (21.7, 99.1)	82.8 (70.4, 90.4)
≥56	88.9 (21.7, 99.1)	90.2 (78.1, 95.8)

*Patients who have a baseline platelet count ≥50 G/L are excluded from analysis.
Time to first hematologic response (days) = Date of first response/censoring – start date of first dose + 1.
Censoring rule: Patients are censored at last contact date (earliest date of: last platelet assessment, death or cutoff date) if no response within first 6 months.
Median time to first reported event (relapse) is derived using Kaplan-Meier method and 95% CI according to Brookmeyer & Crowley (1982). CI: Confidence interval; NE: Non-estimable. Source: [Appendix 2 Table 2-5]

Platelet count changes over time have been submitted as part of this application. The median (25-75th percentile) increase in platelets from Baseline to Week 9 Day 1 was 84.5 G/L (36.5, 165.6). The median platelet count increases from Baseline to Week 9 Day 1 ranged from 40 to 107 across ITP categories.

- **Rescue therapy**

The proportion of patients who required rescue therapy excluding the first 14 days within first 6 months were slightly higher in patients with newly diagnosed or chronic ITP (23.5% and 20.0%, respectively) compared to patients with persistent ITP (0% and 5.6%).

Table 16: Summary of rescue therapy counts by time point and time from ITP diagnosis within first 6 months of treatment (Full analysis set)

Time from diagnosis	<3 months N=51 n (%)	3 to <6 months N=21 n (%)	6 to ≤12 months N=18 n (%)	>12 months N=15 n (%)	All patients N=105 n (%)
Any rescue therapy given by time point					
≤ Day 14	16 (31.4)	2 (9.5)	4 (22.2)	3 (20.0)	25 (23.8)
Day 15 to Month ≤3	10 (19.6)	0	0	3 (20.0)	13 (12.4)

Month >3 to ≤6	4 (7.8)	0	1 (5.6)	0	5 (4.8)
Month ≤6	21 (41.2)	2 (9.5)	4 (22.2)	3 (20.0)	30 (28.6)

n: number of patients with rescue therapy received by the time point.

Rescue therapies starting on or after the start of study treatment but not more than 30 days after end of treatment or starting prior to and continuing after the start of study treatment are summarized.

Only 6 (5.7%) patients had platelet transfusions in the first 6 months of treatment, including 5 patients with newly diagnosed ITP and 1 patient with persistent ITP. Five patients had these transfusions within the first 3 months and one patient after 3 months.

- **Bleeding**

When assessed with the WHO Bleeding Scale, the proportion of patients without bleeding increased during eltrombopag treatment in all ITP categories**.**

Table 17: Number (%) of patients without bleeding over time by WHO Bleeding Scale

Time from diagnosis	<3 months N=51	3 to <6 months N=21	6 to ≤12 months N=18	>12 months N=15	All Patients N=105
Baseline, N	51	21	18	15	105
n (%)	19 (37.3)	12 (57.1)	9 (50.0)	11 (73.3)	51 (48.6)
Week 2, N	49	21	18	14	102
n (%)	32 (65.3)	13 (61.9)	14 (77.8)	12 (85.7)	71 (69.6)
Week 4, N	46	21	17	14	98
n (%)	41 (89.1)	20 (95.2)	15 (88.2)	13 (92.9)	89 (90.8)
Week 9, N	42	17	18	13	90
n (%)	37 (88.1)	17 (100)	16 (88.9)	12 (92.3)	82 (91.1)
Week 27, N	30	17	14	10	71
n (%)	29 (96.7)	16 (94.1)	14 (100)	9 (90.0)	68 (95.8)

Source: [Appendix 2 Table 3-1]

The severity of bleeding also decreased in all ITP categories, which was reflected by a rapidly decreasing proportion of patients with grade 2 bleeding events. For example, in newly diagnosed ITP, 5 patients (9.8%) had grade 2 bleeding at baseline, and none or only a single patient starting from Week 4.

When assessed with the ITP bleeding scale, skin bleeding detected by physical examination was the most frequent bleeding at baseline across all the categories of ITP. The proportion of patients with skin bleeding decreased during eltrombopag treatment when compared to baseline in all ITP categories. The remaining types of bleeding were less frequent at baseline, and included epistaxis, oral, gastrointestinal, urinary, and gynecological bleeding. The proportion of patients with these bleedings also decreased during eltrombopag treatment across all ITP categories.

Table 18 Number (%) of patients with skin bleeding by physical examination over time by ITP Bleeding Scale

Time from diagnosis	<3 months N=38	3 to <6 months N=18	6 to ≤12 months N=16	>12 months N=10	All Patients N=82
Baseline, N	38	18	16	10	82
Grade 1, n (%)	17 (44.7)	10 (55.6)	8 (50.0)	2 (20.0)	37 (45.1)
Grade 2, n (%)	7 (18.4)	1 (5.6)	1 (6.3)	1 (10.0)	10 (12.2)
Week 4, N	33	18	15	9	75
Grade 1, n (%)	6 (18.2)	1 (5.6)	2 (13.3)	0	9 (12.0)
Grade 2, n (%)	0	0	0	0	0
Week 9, N	31	15	16	8	70
Grade 1, n (%)	2 (6.5)	1 (6.7)	1 (6.3)	1 (12.5)	5 (7.1)
Grade 2, n (%)	2 (6.5)	0	0	0	2 (2.9)
Week 27, N	22	14	13	8	57
Grade 1, n (%)	1 (4.5)	2 (14.3)	0	1 (12.5)	4 (7.0)
Grade 2, n (%)	0	0	1 (7.7)	0	1 (1.8)

Source: [Appendix 2 Table 3-2]

4.4.3. Effectiveness data (Real-World Evidence)

A literature review was conducted using search terms for eltrombopag and newly diagnosed or persistent ITP. The identified 27 studies were published from 2014 till 2021. Out of the 27 identified publications, 7 (3 prospective and 4 retrospective studies) were classified as the most relevant in terms of study design, data completeness, and the size of study population. The remaining publications were excluded from the analysis because of the type of publication, a small sample size, small numbers of patients with newly diagnosed or persistent ITP, small numbers of patients receiving eltrombopag as a single agent, or lack of efficacy data by ITP category.

The MAH claims that, overall, these studies have demonstrated that eltrombopag is effective and safe in patients with newly diagnosed and persistent ITP once lack of response to first-line therapies has been confirmed, which may happen already within the first 3 months from diagnosis. Moreover, the effectiveness (Table 19 and Table 20) and safety profile of eltrombopag was shown to be similar to that seen in patients with chronic ITP.

Table 19 Real-world evidence from prospective studies

First author Publication year	Tripathi 2014	Tran 2017	Lucchini 2021
No. of patients	25	39	51
Age category	Adults; Adolescents (≥15y)	Adults	Adults
ITP category (n)	ND (25)	ND (NA)	ND (22)
		P (NA)	P (29)
Response (CR), %	**76 (NA)**	**67 (44)**	**67 (35)**

ND = newly diagnosed ITP; P = persistent ITP; C = chronic ITP; CR = complete response, NA = not available

Table 20 Real-world evidence from retrospective studies

First author Publication year	González-López 2017	Rivolti 2019	Iino 2020	Moulis 2021
No of patients	220	28	77 (64 treated with eltrombopag)	156
Age category (n)	Adults	Adults	Adults	Adults
ITP category (n)	ND (30)	ND (6)	ND (50)	ND/P (95)
	P (30)	P (4)	P (5)	
	C (160)	C (18)	C (22)	
Response (CR), %	**90 (76)**	**79 (68)**	**79 (60)**	**81 (73)***

ND = newly diagnosed ITP; P = persistent ITP; C = chronic ITP; CR = complete response.

*Assessed in 48 patients with a platelet count below 30 G/L at eltrombopag initiation

A briefly summary of efficacy results these most relevant studies is displayed below:

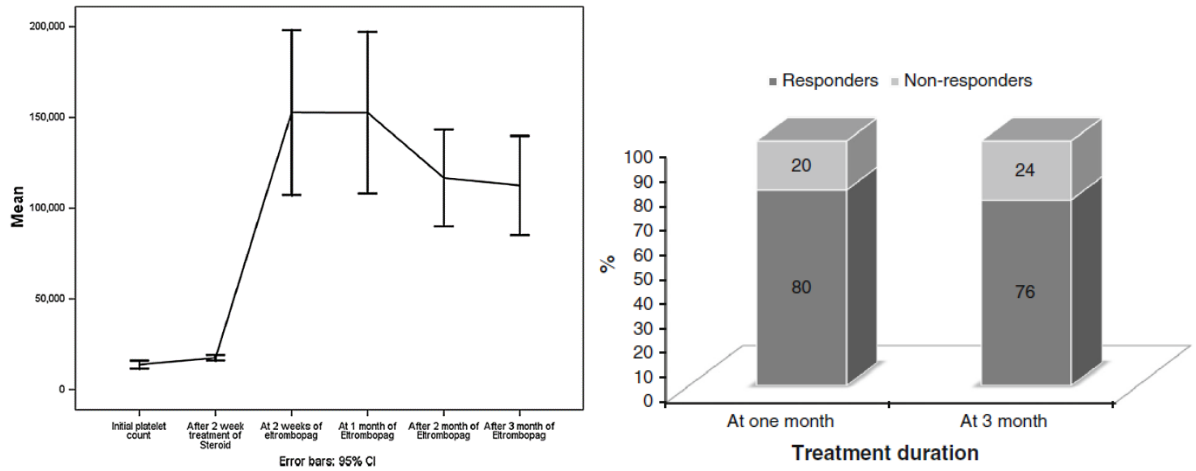
Prospective studies

Tripathi et al 2014

The goal of this study was to assess response to eltrombopag in 25 adult and adolescent patients (median age 27 years, range 15-55 years) with newly diagnosed ITP who were refractory to corticosteroids.

None of the patients responded to prednisolone at a dose of 2 mg/kg/day for 2 weeks. These patients were given 50 mg/day of eltrombopag, and prednisolone was gradually tapered and discontinued within 2 weeks. After 2 weeks of eltrombopag treatment, the mean platelet count increased from 17.5 G/L to 152 G/L. After one month of eltrombopag treatment, 80% of patients achieved a response (platelet count >50 G/L). Response was maintained at Month 3 in 76% of patients.

Figure 4 Platelet count and response rates within 3 months of eltrombopag treatment



Source: *Tripathi et al 2014*

Five patients who did not respond to eltrombopag 50 mg and one patient who lost response subsequently were offered other options along with splenectomy.

Bleeding episodes and severity decreased significantly in all those who achieved response (76 %). Bleeding symptoms were assessed by the WHO scale.

Tran et al 2017

The aim of this study was to assess efficacy and safety of eltrombopag in patients with newly diagnosed and persistent ITP within 6 months of diagnosis. Thirty-nine adult ITP patients (median age 52 years) who were refractory to prior therapy were enrolled and treated with eltrombopag for 12 weeks. The median (Q1, Q3) time from diagnosis was 2.2 months (1.1, 5.4 months). Prior therapies included corticosteroids (95% of patients), IVIg (58% of patients), and immunosuppression (28% of patients). The starting dose of eltrombopag ranged from 50 mg to 75 mg/day, depending on the baseline platelet count. The median dose at Week 12 was 50 mg/day. Thirty-six (92.3%) patients completed 12 weeks of treatment, while 3 (7.7%) patients discontinued earlier (2 patients required a new ITP therapy and 1 patient developed thrombocytosis).

At Week 12, 67% of patients achieved overall response, including 44% with complete response (platelet count >100 G/L), 15% with partial response (platelet count >50 G/L) and 8% with minor response (platelet count ≥30 G/L) with ≥50% reduction in the dose intensity of concomitant ITP therapy compared to screening.

At Week 26, overall response was achieved by 54% of patients, including 28% with complete response, 21% with partial response and 5% with minor response.

Lucchini et al 2021

This prospective, multi-center phase 2 trial evaluated eltrombopag in 51 adult patients with primary ITP (22 with newly diagnosed ITP and 29 with persistent ITP) who were refractory to or relapsed after first-line therapy. The study was divided into period of treatment (PT) from Week 1 to Week 24, period of tapering and discontinuation (PTD) from Week 25 up to Week 32, and period of observation (PO) of 24 weeks starting from eltrombopag discontinuation.

At Week 24, 34 (66.7%) patients (14 with newly diagnosed ITP and 20 with persistent ITP) achieved a response (platelet count ≥30 G/L and at least a two-fold increase from baseline), including 18 (35%) patients (6 newly diagnosed and 12 persistent) with complete response (platelet count ≥100 G/L). No significant difference in platelet response was seen between newly diagnosed ITP and persistent ITP.

Five bleeding events were reported: one grade 3 retinal hemorrhage at Week 1; two grade 2 epistaxis: one at Week 14 and one at Week 28; one grade 1 menorrhagia at Week 38; one grade 1 mucosal bleeding at Week 10. For the last three events, patients were off treatment.

Retrospective studies

González-López et al 2017

This was a retrospective study of 220 adult patients with ITP, including 30 patients with newly diagnosed ITP (up to 3 months from diagnosis), 30 patients with persistent ITP (more than 3 months to up to 12 months from diagnosis), and 160 patients with chronic ITP (more than 12 months from diagnosis.

Response was defined as a platelet count of ≥30 G/L and at least two-fold increase in the baseline platelet count. Complete response (CR) was defined as a platelet count of ≥100 G/L. The definition of response required simultaneous resolution of bleeding symptoms and absence of rescue or concomitant treatments during previous 8 weeks.

Groups were homogenous with regards to age, baseline platelet count and number of previous therapies. For parameters likely to increase over time such as proportion of splenectomized patients, proportion of prior rituximab and duration of ITP, a gradual increase was observed from newly diagnosed to chronic ITP patients.

Of the 220 patients enrolled, 180 (90%) achieved a response; among them 167 (75.9%) achieved a CR after a 15-month follow-up. The rates of response were the highest in newly diagnosed ITP (93.3% of responses with 86.7% of CR) and slightly lower in persistent ITP (83.3% of responses with 80.0% of CR) and chronic ITP (79.4% of responses with 73.1% of CR.

	Newly diagnosed ITP n (%) N=30	**Persistent ITP** n (%) N=30	**Chronic ITP** n (%) N=160
Overall response	28 (93.3)	25 (83.3)	127 (79.4)
Complete response	26 (86.7)	24 (80.0)	117 (73.1)
Partial response	2 (6.7)	1 (3.3)	10 (6.3)

Rivolti et al 2019

The goal of this retrospective study was to assess the efficacy and safety of TPO-RAs in newly diagnosed, persistent and chronic ITP. Out of 28 adult patients (median aged 61 years), 6 patients had newly diagnosed ITP, 4 had persistent ITP and 18 had chronic ITP. Twenty-one patients received eltrombopag, and 7 patients received eltrombopag and romiplostim sequentially (5 patients switched from eltrombopag to romiplostim and 2 patients switched from romiplostim to eltrombopag). Median duration of treatment was 8 months (range: 1-76) for eltrombopag and 4 months (range: 1-21) for romiplostim.

The overall response rate was 78.5% for eltrombopag (3 responses, 19 complete responses) and 43% for romiplostim (1 response, 2 complete responses). All patients with newly diagnosed ITP and persistent ITP responded to treatment, compared to 72% of patients with chronic ITP.

Moulis et al 2021

This retrospective real-world evidence analysis was designed to assess the use, efficacy and safety of eltrombopag in adult ITP patients treated with eltrombopag within 6 months of ITP diagnosis. It was based on data from the French CARMEN registry that included 799 ITP patients. One-hundred fifty-six (19.5%) patients were treated with eltrombopag, out of whom 95 (60.9%) patients were treated during

the first 6 months of ITP (newly diagnosed and persistent ITP). The mean age was 60.5 years; 52.6% were men; 34.7% had ≥1 comorbidity of the Charlson Comorbidity Index (CCI); 58.9% had at ≥1 cardiovascular risk factor (not including age and sex).

At ITP diagnosis, the median platelet count was 7 G/L and 80% patients had bleeding. Therapy prior to eltrombopag included corticosteroids in 95.8% of patients, IVIg in 69.5% of patients, dapsone in 11.6%, hydroxychloroquine in 6.3%, rituximab in 5 (5.3%), romiplostiin 5 (5.3%), vinblastine in 5 (5.3%), danazol in 2 (2.1%); no patient was splenectomized. Median time from ITP onset to eltrombopag was 1.6 months with 74 (77.9%) of patients having newly diagnosed ITP (up to 3 months from ITP diagnosis).

Eltrombopag was used as second-line and third-line agent in 41 (43.2%) and 32 (33.7%) patients, respectively. Among the 95 patients, 48 had a platelet count <30 G/L at eltrombopag initiation; among them, 39 (81.3%) achieved overall response (platelet count ≥30 G/L) and 35 (72.9%) complete response (platelet count ≥100 G/L). Concomitant treatment was withdrawn in 58% of cases.

Iino et al 2020

This observational retrospective analysis was conducted using data from real-world clinical practice. Seventy-seven adult ITP patients (median age 69, range 17-92 years) were treated with TPO-RAs, out of whom 64 patients received eltrombopag (median dose 25 mg, range 12.5-50 mg) and 13 patients received romiplostim. Most of the patients had newly diagnosed ITP 50 (65%), 5 (6%) of patient had persistent ITP and 22 (29%) of patients had chronic ITP.

Overall response, which included complete response (platelet count ≥100 G/L) and response (platelet count 30 to 100 G/L), was achieved in 79.2% of patients (46 patients with complete response, 15 patients with response). Out of 32 patients who discontinued TPO-RAs because of complete response, 27 (84%) patients had newly diagnosed ITP. Most of the patients (n=30; (94%)), who discontinued TPO-RAs after achieving complete response had received eltrombopag with median dose of 25 mg (range 12.5-50 mg). Two-year treatment-free remission (TFR) rate was 66.4% in patients with newly diagnosed ITP who achieved CR. Of note, 18 (94%) of patients who maintained remission at 2 years were treated with eltrombopag.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

To support the efficacy of eltrombopag in patients with ITP ≤ 6 months, no new complete clinical trials have been submitted. Instead, two ad-hoc analyses of subgroups from: 1) ITP registration studies; 2) Interim analysis of ongoing phase II TAPER study (CETB115J2411), have been provided. Eltrombopag efficacy was explored among different patient subgroups by time from ITP diagnosis.

In addition, real world evidence of the already use of eltrombopag in patients with less than 6 months from ITP diagnosis in clinical practice has been provided.

A **subgroup analysis of the completed ITP registration studies** ([TRA100773A], [TRA100773B], [TRA102537/RAISE] and [TRA108057/REPEAT] studies) was performed. Due to the fact that these studies did not collect patient data of time from diagnosis, it is acceptable that data are analysed through the open label study TRA105325/EXTEND, which included patients from the parent studies that continued treatment until eltrombopag became commercially available and where time from diagnosis was collected. Nonetheless, as an open study, its robustness decreases.

The conduct of the ad-hoc subgroup analysis of the TAPER study is considered adequate due to the similarity of the study populations (adult patients who failed first-line therapy with baseline platelet

counts <30 G/L) and of the primary efficacy endpoint definition (platelet count ≥50 G/L) with the ones explored in parent studies. Nineteen of the 299 patients included in the ad-hoc analysis had < 6 months from ITP diagnosis. The study protocol, the SAP and in-depth details of the ad-hoc statistical analysis have been requested during the evaluation of the application. The submitted analysis seems to be in line with the SAP provided. Demographics and baseline characteristics from EXTEND study are similar to the ones from parent studies: a greater percentage of subjects were female and the study population was predominantly white with a median age around 50 years. The majority of patients with less than 6 months from diagnosis was no splenectomised, which concurs with the recommended approach of deferring splenectomy to more advanced stages of the disease.

Efficacy data and additional analyses

The ad-hoc analysis of the TAPER study included 5 adult patients with newly diagnosed ITP [<3 months from diagnosis] and 41 patients with persistent ITP [3 months to < 12 months from diagnosis] who were treated with eltrombopag. In total, **16** patients had <6 months from ITP diagnosis and were treated with eltrombopag.

Platelet count responses achieved showed that eltrombopag raises platelet counts irrespective of time from diagnosis in a relevant proportion of patients. The proportions of responders after up to 6 weeks of treatment was **80%** (4/5) (newly diagnosed ITP), **45.5%** (5/11) (persistent ITP; 3 to <6 months), **66.7%** (20/30) (persistent ITP; 6 to 12 months) and **68.2%** (116/171) (chronic ITP). If a comparison is made, **56.3%** (9/16) randomized to eltrombopag were responders versus **33.3%** (1/3) randomized to placebo in the subgroup of patients with less than 6 months form diagnosis

It is already known that the degree of bleeding in ITP is largely dependent on the degree of thrombocytopenia and therefore while platelet counts increase with eltrombopag treatment, bleeding rates decrease. The results of this analysis showed that this trend can also be confirmed in the subgroup of patients with less than 6 months from diagnosis. At week 6, the proportion of patients without bleeding events increased post baseline to **75%** (3/4) (newly diagnosed ITP), **90%** (9/10) (persistent ITP; 3 to <6 months)**, 63.6%** (14/22) (persistent ITP; 6 to 12 months) and **78.6%** (110/140) (>12 months), compared to a baseline value of **20.0%** (1/5)**, 45.5%** (5/11), **36.7%** (11/30) and **31.5%** (53/168) across the subgroups, respective. If a comparison is made, **85.7%** [12/14] randomized to eltrombopag did not report any post-baseline bleeding events *versus* **33.3**% [1/3] randomized to placebo.

Although favourable effects were observed both for platelet response and bleeding reduction, the very small sample size included in this ad-hoc analysis cannot be ignored, especially with regards to newly diagnosed ITP (only 5 patients with <3 months from ITP diagnosis). This specially apply to the comparison made with the placebo group, where only 3 patients had less than 6 months from diagnosis, which implies that these results have to be interpreted with caution. Moreover, it should be kept in mind that it is a subgroup analysis not previously pre-specified, also limiting the reliability on the results.

Data regarding reduction in ITP therapy or need for rescue treatment broken down by subgroups in EXTEND study have been provided at the CHMP request. However, due to the small sample size of the study regarding subgroups, no conclusion can be drawn in this respect.

The previous limited sample derived from parent studies increases with the submitted **ad-hoc interim analysis of the ongoing phase II TAPER study** (**CETB115J2411).**

While the primary aim of the study is to assess the ability of eltrombopag of inducing a sustained remission by Month 12 in patients who relapsed or failed to respond to an initial treatment with steroids (N=105); the initial submitted ad-hoc analysis (*cut-off date 15-Oct-2022*; **n=82**) presents

data of platelet counts and bleeding rates up to and including month 6, with the aim of assessing eltrombopag efficacy irrespective of time from diagnosis.

Initial cut- off date (15-Oct-2020) of TAPER Study (n=82) was not recent. As it was stated in the documentation that 105 patients were enrolled in the mentioned study, therefore 23 additional patients had been enrolled since the cut-off date, which was a significant body of additional data. Consequently, the MAH was requested to submit an updated report, which could be useful to reinforce the evidence submitted through clinical trials.

From the initial submitted data (*cut-off date 15-Oct-2022)*, specifically**, 56 patients** were treated with eltrombopag with <6 months from diagnosis (**n=38**: newly diagnosed ITP; **n= 18**; 3 to <6 months). One quarter of the patients discontinued from treatment (24,4%) being the main reason physician decision (13,4%). Although not included in the clinical overview provided by the MAH, 12.2% of this physician decisions were due to lack of efficacy, with the greatest percentage of observed in the subgroup of newly diagnosed (21.1% (8/38), 5.6% (1/18), 0%, 10% (1/10). The same trend was observed regarding study discontinuation. The MAH was requested to compare these rates with pivotal trials and discuss its clinical relevance also taking into account reported deaths and literature.

Patients' demographics and baseline characteristics are similar to the ones explored in parent studies with a great proportion of females, white race and a median age round to 50 years. The general great percentage of women throughout all categories (except chronic ITP) agrees with the known characteristics of the disease where women prevalence is higher in the mid-adult years, ensuring this the external validity of the study. Platelet count at baseline were $<30\times10^9$/L, in line with inclusion criteria of parent studies and the median exposure was 6.01 months in all ITP categories.

In this analysis, platelet count responses (≥50 G/L at least once) increased in a relevant proportion of patients (ranged from **80.0%** to **94.4%** by Week 9 across all ITP categories), supporting the results observed in the subgroups analysis from parent studies. Similar rates were observed for platelet threshold of ≥30 G/L; (ranged from **80.0%** to **100%**) and for the threshold of ≥100 G/L (ranged from **73.7%** to **80.0%**). The median time to first response ≥50 G/L was comparable across all ITP categories (from 8 to 17 days) and a slightly more time was observed for complete response (ranged from 22 to 29 days), which was not unexpected. Results from supportive efficacy endpoints, which reflect more sustained or durable responses, also showed favorable results for eltrombopag treatment (response rates ≥50 G/L on at least 6 out of 8 consecutive assessments in the first 6 months on study showed durable responses with rates ranging from **68.8%** to **83.3%** across the ITP categories).

Regarding the use of rescue therapy, overall, about one quarter needed it in the first 6 months, mainly during the first 14 days (allowed per protocol) with prednisone being the main one used. The proportion of patients who required rescue therapy was slightly higher in patients with newly diagnosed or chronic ITP (26.3% and 20.0%, respectively) if compared to patients with persistent ITP (0% and 6.3%). These percentages are within expected for TPO-AR in ITP, as a similar percentage was also reported with romiplostim (≈45%).

With respect to bleeding events, results were also in line with those from ad-hoc analysis from parent studies; the proportion of patients without bleeding increased during eltrombopag treatment in all ITP categories at Week 4: newly diagnosed ITP [patients without bleeding increased from 39.5% (15/38) at baseline to **84.8%** (28/33)], 3 to <6 months [from 61.1% (11/18) to **94.4%** (17/18)], 6 to ≤12 months [from 50.0% (8/16) to **86.7%** (13/15)] and >12 months [from 70.0% (7/10) to **100%** (9/9).

In response to the clarifications requested, the MAH has acknowledged that the initial cut-off used for the TAPER ad-hoc analysis (*15-Oct-2020*), was outdated. In this regard, the MAH has clarified that, nowadays, the study is still ongoing with 4 patients and therefore, an updated interim report with a more recent updated cut-off has been provided (*22-Oct-2021*; n=105). Of them, 51 patients fall in the

category of newly diagnosed ITP (< 3 months) and 21 belong to the category of persistent ITP (3 to <6 months).

It should be pointed out that the MAH asserts that both time-points used in the analyses were prespecified in the study protocol, being the second one (*22-Oct-2021),* prespecified for the primary analysis of the study, which reduces the risk of bias of favouring the results by selecting the time point through observation.

In terms of efficacy, results from such updated analysis do not differ from those observed in the previous analysis in terms of rase in platelet counts and decrease in bleeding rates.

On the other hand, the need of rescue therapy is continued to be seen in approximately one quarter of the patients (23.8%) in the first 14 days (allowed per protocol) in the updated analysis. The proportion of patients who required rescue therapy excluding the first 14 days within first 6 months were slightly higher in patients with newly diagnosed or chronic ITP (23.5% and 20.0%, respectively) compared to patients with persistent ITP (0% and 5.6%). Nonetheless, these percentages show similarity with the 18% of the patients who required rescue treatment in RAISE study, which served as basis for initial authorisation.

In addition, after being required to, the MAH has provided median platelet count over time with interquartile range by time since diagnosis, which show the achievement of counts over 50 G/L after 3 week of treatment maintained through the 27 weeks period, irrespective of time from diagnosis.

On the other hand, updated analysis of TAPER study (N=105) continues to show a slight increase (of approx. 10 %.) in the rate of treatment discontinuation and of study discontinuation due to lack of efficacy in the subgroup of patients with newly diagnosed ITP (< 3 months). When compared this rate with data from register studies, such increase is continued to be observed, as only a 1.4% (7/494) of the patients included in such studies discontinued treatment due to lack of efficacy (only 1 patient was included in the ad-hoc analysis of EXTEND study and treated with eltrombopag).

The MAH has discussed this issue and argues that the observed increase in study J2411 (TAPER) might be due to an excessively early treatment discontinuation by the investigators, given the primary aim of the study (need to ensure an appropriate response to taper and maintain response) and given the uncertainty regarding the bleeding profile of these patients at the initial stages of the disease, which would lead investigators to be more cautious. These arguments can be agreed.

Related to this, if the reported deaths for haemorrhage are taken into account (which could be considered as lack of efficacy), it is acknowledged that sample size and design of TAPER study precludes to reach any conclusion about the association with the risk of haemorrhage and the ITP chronological stage of the disease. However, there seems to be a consistency between the reported deaths rates in the study and the ones reported in literature.

Consequently, although events suggesting lack of efficacy from study J2411 (TAPER study) cannot be viewed as conclusive, weighting them up with the overall high response rates and the decrease in the rates of bleeding observed in the study, they can be viewed as not concerning.

In conclusion, favorable effects were also observed for eltrombopag in this ad-hoc analysis; however, limitations of a non-controlled study (single-arm) should be kept in mind as they hind the assessment of causality of the treatment effect and therefore, results should be interpreted with caution. Nonetheless, additional clarifications were requested regarding the two ad-hoc analysis performed:

Patients with ITP may respond to one TPO-RA but not to another (*Al-Samkari et al. Br J Haematol 2022*). Limited data are available describing outcomes in non-responder patients following prior treatment with eltrombopag. The MAH was requested to provide more details on those patients who do

not have an adequate response to eltrombopag, including switching outcomes to other agents (e.g. other available TPO-RAs) that may reduce platelet count fluctuations and/or achieve a platelet response. In this regard, it remains uncertain if such patients responded to another treatment or benefited from switching between TPO-ARs as the MAH has not provided clinical details from the patients who did not have an adequate response to eltrombopag in TAPER study, arguing that that was not the aim of the carried out study.

In the EXTEND study and in TAPER study (CETB115J2411), the number of patients, included in each treatment group compared with prior ITP medication lines, was unclear. The MAH was requested to clarify whether eltrombopag efficacy and/or safety were different in heavily pre-treated ITP population in function of severity of underlying ITP. In this regard, the MAH has clarified that in ongoing TAPER study, all enrolled patients had only received steroid courses and therefore, were not heavily pre-treated. In this respect, it is considered that, given the recommendations provided in current guidelines, it is expected that in clinical practice, patients with < 6 months form diagnosis mostly match these characteristics of not being heavily pre-treated. On the other hand, in register studies, eltrombopag has previously demonstrated its response in patients irrespective of the use of concomitant ITP medication at randomization/enrolment or splenectomy status, as it is stated in the current SmPC. Given that pivotal trials mostly included patients with chronic ITP, it is understandable that patients were more heavily pre-treated in those studies. Although an extensive clarification whether numerical differences in response rates and/or certain AEs are known with the long-term eltrombopag use in patients who had previously received rituximab or splenectomy has not been provided, this issues is not considered essential within the current procedure since patients with less than 6 months form diagnosis are expected no to be heavily pre-treated.

Moreover, regarding TAPER study design, clarifications related to the threshold of a platelet count of 70 $x10^9$/L (at least), or preferably, $100x10^9$/L, and the aim to discontinue treatment with eltrombopag below a thrombocyte count of 50 $x10^9$/L have been provided as requested. It seems that the tapering approach followed in TAPER study differs from other published approaches. Nonetheless, it is acknowledged that there is no currently consensus regarding optimal approaches to tapering and discontinuation of TPO-RA therapy. Nevertheless, these issues are not relevant to the current procedure.

Effectiveness data through literature review from recent real-world evidence (period time from 2014-till 2021) were also provided. The evidence submitted show that eltrombopag is frequently used-off label during clinical practice in patients with < 6 months once lack of response to fist-line has been confirmed, which is not unexpected according to current guidelines (Neunert *et al,* 2019; Provan *et al,* 2019).

Results from 7 published studies (3 prospective and 4 retrospective), rated by the company as the most relevant found, were provided. Five of them (*Tripathi et al 2014; Lucchini et al 2021; González-López et al 2017; Rivolti et al 2019; Iino et al 2020*) specify the number of patients included differentiated by ITP categories (in total 133 patients had newly diagnosed ITP and 68 patients persistent ITP). In contrast, the remaining two studies (*Tran et al 2017; Moulis et al 2021*) do not distinguish between the number of patients included in each category (in total 134 patients within 6 months of ITP diagnosis).

All of the above studies included adult patients (except from *Tripathi et al 2014* study which also included adolescents > 15 years) who were refractory or relapsed to first line-therapy and with a general median platelet count at presentation < 30 x 10^9/L. Overall, the most common administered dose of eltrombopag was 50 mg/day. Therefore, although it is not feasible to carry out a strict comparison, it could be assumed that characteristics of these observational studies do not differ greatly from the ones of clinical trials.

First of all, it must be taken into account that robust evidence that can be drawn from routine clinical

settings is limited, and therefore, interpretation of data must be done with caution. Single arms studies, small sample sizes, potential selection bias in retrospective studies or concomitant treatment used as rescue therapy influencing response rates, are aspects, among other, that should be kept in mind when data are interpreted.

Nonetheless, results show the achievement of clinically relevant platelet responses in a considerable proportion of patients with < 6 months from diagnosis [ranged: 67%-90%] suggesting that eltrombopag effect is the same regardless of time since diagnosis. The majority of the publications also report a decrease in bleeding rates and some of them also report a decrease in the use of rescue medication or concomitant ITP therapy. Since these results are in line with those achieved in the clinical trial ad-hoc analyses, they can be considered as supportive.

In summary, the above presented efficacy data showed that adult patients achieved relevant platelet response counts when treated with eltrombopag irrespective of time for ITP diagnosis and this translates into a reduction in the rate of bleeding, which is the goal in ITP therapy. No relevant differences have been observed in patients with less than 6 months from diagnosis when compared with those with >6 months. Nonetheless, these results come from ad-hoc analysis and have not been yet confirmed specifically by a controlled trial in patients with less than 6 months from diagnosis.

Within this procedure, additional data is provided by the EXTEND open-label extension study, which recruited patients from the parent studies. However, its limited sample size (19 patients with less than 6 months from ITP diagnosis of which only 16 were treated with eltrombopag) precludes from reaching an accurate conclusion based solely on this study. Interim updated ad-hoc analysis (*cut-off date 21-Oct-2021*) from the ongoing phase II TAPER study (CETB115J2411) reinforces such evidence providing additional 72 patients with less than 6 months from diagnosis.

If the two analyses are weighted together, it could be expected a similar efficacy of eltrombopag regardless of time since ITP diagnosis.

Even so, it is considered that evidence submitted through clinical trials (the one which provides the greatest robustness) is limited. On the other hand, it is also acknowledged that ITP is a disease with a low incidence (1.6 to 3.9 cases per 100,000 per year). In these cases, it is considered that supportive data from clinical practice bring added value to complement and confirm the efficacy seen in trials.

In this regard, effectiveness data provided from real world evidence concurs with efficacy data observed form clinical trials as well as confirms the expected off-label used of eltrombopag in daily practice.

2.4.3. Conclusions on the clinical efficacy

Two ad-hoc analyses in which eltrombopag efficacy was explored among different patient subgroups by time from ITP diagnosis have been provided. Real world evidence of the clinical use of eltrombopag in patients with ITP < 6 months from diagnosis has been also provided.

The subgroup analysis from the pivotal ITP registration studies [TRA100773A], [TRA100773B], [TRA102537/RAISE] and [TRA108057/REPEAT], included 5 adult patients with newly diagnosed ITP and 41 patients with persistent ITP treated with eltrombopag (specifically 16 patients with < 6 months from diagnosis). The updated interim ad-hoc analysis of data from the ongoing TAPER study (CETB115J2411 study) included 51 adult patients with newly diagnosed ITP and 39 adult patients with persistent ITP (specifically 72 patients with < 6 months from diagnosis treated with eltrombopag).

The above presented efficacy data show favorable effects for eltrombopag, with relevant increases in platelet count correlated with decreases of bleeding events, irrespective of time from diagnosis. No relevant differences are observed when compared with the subgroup of patients with < 6 months from

diagnosis with those with > 6 months. Nonetheless, these results come from ad-hoc analyses with limited sample size and have not yet been confirmed specifically by a controlled trial in patients with less than 6 months from diagnosis.

Support with data from real world evidence is considered relevant when a high off- label use in clinical practice is expected, such as in the case of TPO-AR. Data provided (n=335 patients with newly and persistent ITP) show that eltrombopag seems to be also effective when it is started in earlier stages of the disease and confirm that there is an already off-label use of eltrombopag in patients with less than 6 months from diagnosis when response failure to first line therapy is confirmed, which is not unexpected according to what it is stablished in current guidelines (Neunert *et al,* 2019; Provan *et al*, 2019). Although it must be taken into account that robust evidence that can be drawn from routine clinical settings is limited, and that, consequently, interpretation of data should be done with caution, results show the achievement of clinically relevant platelet responses in a considerable proportion of patients with newly and persistent ITP (ranged from 67%-to 90%), in line with what has been observed in ad-hoc analysis from clinical trials.

To conclude, although it is considered that a greater effort could have been done by the MAH to generate a more robust evidence, especially in a context of 10 years post-marketing period, the evidence provided is sufficient to conclude that eltrombopag effect is similar irrespective of time from ITP diagnosis.

2.5. Clinical safety

Introduction

The safety of eltrombopag in ITP lasting more than 6 months from diagnosis was described in the original marketing authorisation application and remains unchanged.

According to the SmPC, up to now, the most important known serious adverse reactions in adults were thrombotic/thromboembolic events and hepatotoxicity (generally mild but requiring monitoring of transaminase levels before and after starting treatment) and potential unfavourable effects of bone marrow fibrosis and malignancies that cannot be ruled out with the available data. The most common adverse reactions occurring in at least 10% of patients included nausea, diarrhoea, increased alanine aminotransferase and back pain.

As the basis of this application, the company also provides safety results from two ad-hoc analyses presented by time since diagnosis: 1) ITP registration studies (extension study EXTEND); 2) Interim analysis of ongoing phase II study **CETB115J2411** (*cut-off date of 15-Oct-2020*).
Additional safety data can be extracted from submitted real world evidence of the use of eltrombopag in clinical practice.

Safety data from completed clinical studies in adult ITP patients (EXTEND study)

Three hundred and two patients received at least one dose of eltrombopag and were included in the safety population of **EXTEND study**, of which 19 were patients with ITP less than 6 months from diagnosis (**16** treated with eltrombopag; **5** patients with <3 months since ITP diagnosis and **11** patients with 3 to <6 months since ITP diagnosis).

Adverse events were reported by ≥74% of patients on eltrombopag, with similar frequencies reported across the ITP categories. The proportion of patients who reported at least one adverse event was 80% (4/5), 81.8% (9/11), 76.7% (23/30) and 74% (128/173) for patients with an ITP duration of <3 months (newly diagnosed ITP), 3 to <6 months, 6 to 12 months (persistent ITP), and >12 months (chronic ITP),

respectively. The company should provide a summarize table of the reported frequencies across the ITP categories where the mentioned percentages are reflected/justified.

The most frequent adverse events for the subset of patients included in these analyses were provided in the application [Appendix 1 Table 1-16], [Appendix 1 Table 2-16], [Appendix 1 Table 3-16] and [Appendix 1 Table 4-16] for [TRA100773A], [TRA100773B], [TRA102537/RAISE] and [TRA108057/REPEAT], respectively. The company also provided summarised tables of adverse events by time since ITP diagnosis in the EXTEND study, in line with the summary safety tables provided for study CETB115J2411.

Study CETB115J2411 (TAPER)

On the other hand, 82 patients were included in the safety population of the **ad-hoc analysis of study CETB115J2411** (*cut-off 15 October 2020*); of which **56** had less than 6 months from diagnosis; **38** with <3 months since ITP diagnosis and **18** with 3 to <6 months since ITP diagnosis).

Safety results from this ad-hoc analysis are presented using the Safety Set which included all patients who received at least one dose of eltrombopag. Only descriptive analyses were performed. The safety analyses are presented until Month 6.

Patient exposure

The median (25-75th percentile) duration of exposure to study treatment was 6.01 months (5.91-6.05) with a median exposure of 6.01 months in all ITP categories (Table 21).
The median (25-75th percentile) actual dose intensity was 51.3 mg/day (10.7-67.9) for patients with newly diagnosed ITP, 46.6 (25.7-67.6) in persistent ITP (3 to <6 months), 63.9 (32.4-73.0) in persistent ITP (6 to ≤12 months), and 56.3 (22.6-69.5) in chronic ITP.

Table 21 Duration of exposure to eltrombopag by time from ITP diagnosis within first 6 months of treatment (Safety set)

Time from diagnosis	<3 months N=38	3 to <6 months N=18	6 to ≤12 months N=16	>12 months N=10	All Patients N=82
Total number of patients receiving eltrombopag – n (%)	38 (100)	18 (100)	16 (100)	10 (100)	82 (100)
Duration of exposure (months)					
Mean (SD)	4.80 (1.990)	5.56 (1.378)	5.69 (0.902)	5.1 (2.022)	5.18 (1.722)
Median	6.01	6.01	6.01	6.01	6.01
Q1-Q3	3.06-6.05	6.01-6.05	5.95-6.02	5.98-6.01	5.91-6.05
Min-Max	0.5-6.2	1.4-6.1	3.2-6.2	0.3-6.1	0.3-6.2
Duration of exposure categories (months) – n (%)					
<1	4 (10.5)	0	0	1 (10.0)	5 (6.1)
1 – <2	2 (5.3)	1 (5.6)	0	0	3 (3.7)
2 – <3	3 (7.9)	1 (5.6)	0	1 (10.0)	5 (6.1)
3 – <4	1 (2.6)	0	2 (12.5)	0	3 (3.7)

Time from diagnosis	<3 months N=38	3 to <6 months N=18	6 to ≤12 months N=16	>12 months N=10	All Patients N=82
4 – <5	2 (5.3)	0	0	0	2 (2.4)
5 – <6	6 (15.8)	2 (11.1)	4 (25.0)	1 (10.0)	13 (15.9)
≥6	20 (52.6)	14 (77.8)	10 (62.5)	7 (70.0)	51 (62.2)

Source: [Appendix 2 Table 6-1]

Adverse events

The majority of patients (84.1%, range 70.0% - 94.4 across ITP categories) had at least one adverse event (AE) (Table 22). The percentage of patients with treatment-related AEs ranged from 18.8% to 50.0% across ITP categories.

Fifteen patients (18.3%, range 0 - 22.2% across ITP categories) had at least one serious adverse event (SAE). The percentage of patients with treatment-related SAEs was also comparable across ITP categories (3.7%, range 0 -12.5%).

The overall rate of adverse events leading to discontinuation and dose adjustment/interruption was also comparable in all ITP categories.

Table 22 Overview of adverse events by ITP duration within first 6 months of treatment (Safety set)

	<3 months N=38		3 to <6 months N=18		6 to ≤12 months N=16	
Category	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Adverse events	31 (81.6)	12 (31.6)	17 (94.4)	7 (38.9)	14 (87.5)	4 (25.0)
Treatment-related	8 (21.1)	1 (2.6)	7 (38.9)	0	3 (18.8)	2 (12.5)
SAEs	8 (21.1)	7 (18.4)	4 (22.2)	4 (22.2)	3 (18.8)	3 (18.8)
Treatment-related	1 (2.6)	0	0	0	2 (12.5)	2 (12.5)
Fatal SAEs	1 (2.6)	1 (2.6)	1 (5.6)	1 (5.6)	0	0
Treatment-related	0	0	0	0	0	0
AEs leading to discontinuation	2 (5.3)	2 (5.3)	0	0	1 (6.3)	1 (6.3)
Treatment-related	0	0	0	0	1 (6.3)	1 (6.3)
AEs leading to dose adjustment/interruption	8 (21.1)	4 (10.5)	3 (16.7)	1 (5.6)	2 (12.5)	1 (6.3)
Treatment-related	3 (7.9)	1 (2.6)	2 (11.1)	0	2 (12.5)	1 (6.3)
AEs requiring additional therapy	28 (73.7)	7 (18.4)	14 (77.8)	2 (11.1)	7 (43.8)	3 (18.8)
Treatment-related	4 (10.5)	0	4 (22.2)	0	2 (12.5)	2 (12.5)

	>12 months N=10		All Patients N=82	
Category	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Adverse events	7 (70.0)	1 (10.0)	69 (84.1)	24 (29.3)
Treatment-related	5 (50.0)	1 (10.0)	23 (28.0)	4 (4.9)

SAEs	0	0	15 (18.3)	14 (17.1)
Treatment-related	0	0	3 (3.7)	2 (2.4)
Fatal SAEs	0	0	2 (2.4)	2 (2.4)
Treatment-related	0	0	0	0
AEs leading to discontinuation	1 (10.0)	0	4 (4.9)	3 (3.7)
Treatment-related	0	0	1 (1.2)	1 (1.2)
AEs leading to dose adjustment/interruption	2 (20.0)	1 (10.0)	15 (18.3)	7 (8.5)
Treatment-related	2 (20.0)	1 (10.0)	9 (11.0)	3 (3.7)
AEs requiring additional therapy	4 (40.0)	1 (10.0)	53 (64.6)	13 (15.9)
Treatment-related	1 (10.0)	1 (10.0)	11 (13.4)	3 (3.7)

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.
Source: [Appendix 2 Table 7-1]

The most common adverse events (>10% in all patients) were headache (18.4% vs. 22.2% vs. 12.5% vs. 10.0%), and thrombocytopenia (21.1% vs. 16.7% vs. 12.5% vs 0%) in newly diagnosed to chronic ITP, respectively. The uncoded term for one patient with newly diagnosed ITP was Basal Cell Carcinoma. AEs suspected to be related to study treatment are available in [Table 23].

Table 23 Adverse events suspected to be related to study treatment by system organ class and preferred term by ITP duration within first 6 months (Safety set)

Table 7-4 (Page 1 of 6)
Adverse events suspected to be related to study treatment by system organ class and preferred term by ITP duration within first 6 months
(Safety set)

	Group A N=38		Group B N=18		Group C N=16	
Primary system organ class Preferred term	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Number of patients with at least one event	8 (21.1)	1 (2.6)	7 (38.9)	0	3 (18.8)	2 (12.5)
Cardiac disorders	1 (2.6)	0	0	0	0	0
Tachycardia	1 (2.6)	0	0	0	0	0
Eye disorders	0	0	1 (5.6)	0	0	0
Conjunctival haemorrhage	0	0	1 (5.6)	0	0	0
Gastrointestinal disorders	4 (10.5)	0	2 (11.1)	0	0	0
Diarrhoea	0	0	2 (11.1)	0	0	0
Nausea	2 (5.3)	0	1 (5.6)	0	0	0
Abdominal pain	1 (2.6)	0	1 (5.6)	0	0	0
Abdominal pain upper	1 (2.6)	0	0	0	0	0
Stomatitis	1 (2.6)	0	0	0	0	0
General disorders and administration site conditions	1 (2.6)	0	0	0	0	0
Fatigue	1 (2.6)	0	0	0	0	0
Hepatobiliary disorders	1 (2.6)	0	1 (5.6)	0	0	0
Cholestasis	0	0	1 (5.6)	0	0	0
Hyperbilirubinaemia	1 (2.6)	0	0	0	0	0

Primary system organ class Preferred term	Group D N=10 All grades n (%)	Group D N=10 Grade >=3 n (%)	All Patients N=82 All grades n (%)	All Patients N=82 Grade >=3 n (%)
Number of patients with at least one event	5 (50.0)	1 (10.0)	23 (28.0)	4 (4.9)
Cardiac disorders	0	0	1 (1.2)	0
Tachycardia	0	0	1 (1.2)	0
Eye disorders	0	0	1 (1.2)	0
Conjunctival haemorrhage	0	0	1 (1.2)	0
Gastrointestinal disorders	1 (10.0)	0	7 (8.5)	0
Diarrhoea	1 (10.0)	0	3 (3.7)	0
Nausea	0	0	3 (3.7)	0
Abdominal pain	0	0	2 (2.4)	0
Abdominal pain upper	0	0	1 (1.2)	0
Stomatitis	0	0	1 (1.2)	0
General disorders and administration site conditions	0	0	1 (1.2)	0
Fatigue	0	0	1 (1.2)	0
Hepatobiliary disorders	0	0	2 (2.4)	0
Cholestasis	0	0	1 (1.2)	0
Hyperbilirubinaemia	0	0	1 (1.2)	0

Primary system organ class Preferred term	Group A N=38 All grades n (%)	Group A N=38 Grade >=3 n (%)	Group B N=18 All grades n (%)	Group B N=18 Grade >=3 n (%)	Group C N=16 All grades n (%)	Group C N=16 Grade >=3 n (%)
Immune system disorders	0	0	1 (5.6)	0	0	0
Hypersensitivity	0	0	1 (5.6)	0	0	0
Infections and infestations	0	0	0	0	1 (6.3)	1 (6.3)
Diarrhoea infectious	0	0	0	0	1 (6.3)	1 (6.3)
Injury, poisoning and procedural complications	1 (2.6)	0	0	0	0	0
Intentional product misuse	1 (2.6)	0	0	0	0	0
Investigations	3 (7.9)	1 (2.6)	4 (22.2)	0	2 (12.5)	0
Blood alkaline phosphatase increased	1 (2.6)	0	2 (11.1)	0	1 (6.3)	0
Alanine aminotransferase increased	1 (2.6)	0	1 (5.6)	0	1 (6.3)	0
Aspartate aminotransferase increased	1 (2.6)	0	0	0	0	0
Blood alkaline phosphatase	0	0	0	0	1 (6.3)	0
Blood bilirubin increased	1 (2.6)	1 (2.6)	0	0	0	0
Blood lactate dehydrogenase increased	1 (2.6)	0	0	0	0	0
Blood uric acid increased	0	0	1 (5.6)	0	0	0
Gamma-glutamyltransferase abnormal	0	0	0	0	1 (6.3)	0
Transaminases increased	0	0	1 (5.6)	0	0	0
Nervous system disorders	3 (7.9)	0	2 (11.1)	0	0	0
Headache	3 (7.9)	0	2 (11.1)	0	0	0
Dizziness	0	0	1 (5.6)	0	0	0

Primary system organ class Preferred term	Group D N=10 All grades n (%)	Group D N=10 Grade >=3 n (%)	All Patients N=82 All grades n (%)	All Patients N=82 Grade >=3 n (%)
Immune system disorders	0	0	1 (1.2)	0
Hypersensitivity	0	0	1 (1.2)	0
Infections and infestations	0	0	1 (1.2)	1 (1.2)
Diarrhoea infectious	0	0	1 (1.2)	1 (1.2)
Injury, poisoning and procedural complications	0	0	1 (1.2)	0
Intentional product misuse	0	0	1 (1.2)	0
Investigations	1 (10.0)	0	10 (12.2)	1 (1.2)
Blood alkaline phosphatase increased	1 (10.0)	0	5 (6.1)	0
Alanine aminotransferase increased	0	0	3 (3.7)	0
Aspartate aminotransferase increased	0	0	1 (1.2)	0
Blood alkaline phosphatase	0	0	1 (1.2)	0
Blood bilirubin increased	0	0	1 (1.2)	1 (1.2)
Blood lactate dehydrogenase increased	0	0	1 (1.2)	0
Blood uric acid increased	0	0	1 (1.2)	0
Gamma-glutamyltransferase abnormal	0	0	1 (1.2)	0
Transaminases increased	0	0	1 (1.2)	0
Nervous system disorders	0	0	5 (6.1)	0
Headache	0	0	5 (6.1)	0
Dizziness	0	0	1 (1.2)	0

Primary system organ class Preferred term	Group A N=38 All grades n (%)	Group A N=38 Grade >=3 n (%)	Group B N=18 All grades n (%)	Group B N=18 Grade >=3 n (%)	Group C N=16 All grades n (%)	Group C N=16 Grade >=3 n (%)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (6.3)	1 (6.3)
Pulmonary embolism	0	0	0	0	1 (6.3)	1 (6.3)
Skin and subcutaneous tissue disorders	2 (5.3)	0	0	0	0	0
Rash	1 (2.6)	0	0	0	0	0
Dermatitis allergic	0	0	0	0	0	0
Rash maculo-papular	1 (2.6)	0	0	0	0	0
Vascular disorders	0	0	0	0	1 (6.3)	1 (6.3)
Deep vein thrombosis	0	0	0	0	1 (6.3)	1 (6.3)
Hypotension	0	0	0	0	0	0

Primary system organ class Preferred term	Group D N=10 All grades n (%)	Group D N=10 Grade >=3 n (%)	All Patients N=82 All grades n (%)	All Patients N=82 Grade >=3 n (%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.2)	1 (1.2)
Pulmonary embolism	0	0	1 (1.2)	1 (1.2)
Skin and subcutaneous tissue disorders	2 (20.0)	1 (10.0)	4 (4.9)	1 (1.2)
Rash	1 (10.0)	0	2 (2.4)	0
Dermatitis allergic	1 (10.0)	1 (10.0)	1 (1.2)	1 (1.2)
Rash maculo-papular	0	0	1 (1.2)	0
Vascular disorders	1 (10.0)	0	2 (2.4)	1 (1.2)
Deep vein thrombosis	0	0	1 (1.2)	1 (1.2)
Hypotension	1 (10.0)	0	1 (1.2)	0

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.

Serious adverse event/deaths/other significant events

A total of two patients died by the cut-off date in Groups A (patients with newly diagnosed ITP) and B (patients with 3 to <6 months from ITP diagnosis), respectively. These on-treatment deaths were caused by central nervous system haemorrhage and intracranial haemorrhage. These deaths were not considered related to eltrombopag by the investigator.

Although not submitted within the documentation of this application, deaths narratives were provided at the moment of the pre-submission meeting:

- *Patient*

An elderly patient who first relapsed 3 months after diagnosis after receiving first line steroid therapy.

At the time of study-entry, the patient's medical history reported ongoing benign prostatic hyperplasia, diabetes as well as hypercholesterolemia. The past medical history included prior conditions of myocardial infarction and stent placement, for which the patient received ecopirin, PLANOR and clopidogrel but all treatments were discontinued prior to study start.

The patient received the first dose of eltrombopag 50 mg QD on 13-Feb-2020 (Study Day 1) with a platelet count of 1 x 109/L. On 20-Feb-2020 (Study Day 8), the patient had a platelet count of 0 G/L and experienced a SAE Grade 4 Upper GI bleed and was treated with IVIG and pantoprazole. The upper GI bleed resolved on 23-Feb-2020 (Study Day 11).

The patient remained on eltrombopag 50 mg for 14 days before being increased, as per protocol, to a dose of 75 mg QD on 27-Feb-2020 (Study Day 15) when the platelets were reported as 22 G/L. The 75 mg QD dose was maintained for 7 days before being reduced, as per protocol, to 50 mg QD on 05-Mar-2020 (Study Day 22) when the platelets reached 304 G/L.

After 7 days at a dose of 50 mg QD, the eltrombopag treatment was interrupted, as per protocol, on 12-Mar-2020 (Study Day 29) when the platelets reached 1139 G/L. After a treatment interruption of 15

days, eltrombopag treatment was restarted on 27-Mar-2020 (Study Day 44) at 50 mg QD when the platelets dropped to 79 G/L.

The patient had been on 50 mg QD for 4 days when he was hospitalized on 30-Mar-2020 (Study Day 47) due to low platelet count (8 G/L) for which he received methylprednisolone on 31- Mar-2020 (Study Day 48) for three days and IVIG on 02-Apr-2020 (Study Day 50).

The platelets further dropped three days later to 1 G/L and the eltrombopag dose was increased to 75 mg QD on 03-Apr-2020 (Study Day 51). On 06-Apr-2020 (Study Day 54) the patient experienced central nervous system (CNS) bleeding and died that same day.

In total, the patient received eltrombopag for 39 days. The fatal event was reported to be due to CNS bleeding and low platelet count. Both events were assessed as not suspected to be related to eltrombopag by the investigator.

- *Patient:*

An young adult patient initially diagnosed on 01-Jun-2019, who first relapsed on 19-Aug-2019 following first-line steroid treatment. The medical history reported a prior condition of menorrhagia.

At screening the patient had a platelet count of 27 G/L and she received the first dose of eltrombopag 50 mg QD on 16-Sep-2019 (Study Day 1). The dose of 50 mg QD was maintained for 14 days until the platelet count dropped to 8 G/L on 30-Sep-2019 (Study Day 15) and the eltrombopag dose was then increased, as per protocol, to 75 mg QD.

The patient remained on 75 mg QD for 44 days and continued experiencing Grade 4 thrombocytopenia with platelet counts remaining below 8 G/L throughout.

The patient's physician decided to discontinue the treatment on 12-Nov-2019 (Study Day 58) due to lack of response and a platelet count of 2 G/L at the End of Treatment visit on 13-Nov- 2019. The patient also experienced Grade 2 menorrhagia on 13-Nov-2019 (Study Day 59/ End of treatment day). In total, the patient received eltrombopag for 58 days.

During the 30-day safety follow-up period, the patient experienced fatal intracranial hemorrhage 8 days after the last dose of eltrombopag. The fatal event was reported to be due to intracranial hemorrhage and was assessed as not suspected to be related to eltrombopag by the investigator.

MAH conclusion

The MAH concludes that eltrombopag is well tolerated in ITP patients and has a well-established safety profile based on the safety data that supported the regulatory approval in adult and paediatric immune thrombocytopenia (ITP), HCV-associated thrombocytopenia, severe aplastic anemia (SAA), as well as on the extensive post-marketing data since the initial approval in the EU in 2010. The cumulative post-marketing exposure to eltrombopag was calculated as 372,128 patient-years.

The two ad-hoc analyses presented by time since diagnosis also demonstrated that the safety profile of eltrombopag was comparable across all ITP categories. The majority of the AEs were in accordance with the known safety profile of eltrombopag and their incidence rates were comparable across the ITP categories.

Safety data from Real World Evidence

The MAH has provided Real World Evidence of the eltrombopag safety through literature review.

Results from 7 published studies (3 prospective and 4 retrospective), rated by the company as the most relevant found, were provided (*Tripathi et al 2014; Lucchini et al 2021; González-López et al 2017;*

Rivolti et al 2019; Iino et al 2020; Tran et al 2017; Moulis et al 2021). For more details of such studies, refer to previous Efficacy section: ***'Effectiveness data from Real World Evidence'***.

Summary of the main safety results from those studies are displayed below:

Prospective studies

Tripathi et al 2014

The goal of this study was to assess response to eltrombopag in 25 adult and adolescent patients (median age 27 years, range 15-55 years) with newly diagnosed ITP who were refractory to corticosteroids.

None of the patients responded to prednisolone at a dose of 2 mg/kg/day for 2 weeks. These patients were given 50 mg/day of eltrombopag, and prednisolone was gradually tapered and discontinued within 2 weeks.

Six (24%) patients had mild headache on eltrombopag treatment but did not necessitate any treatment. Three (12%) patients had mild increases in Alanine Aminotransferase (ALT) levels.

Tran et al 2017

The aim of this study was to assess efficacy and safety of eltrombopag in patients with newly diagnosed and persistent ITP within 6 months of diagnosis. Thirty-nine adult ITP patients (median age 52 years) who were refractory to prior therapy were enrolled and treated with eltrombopag for 12 weeks. The median (Q1, Q3) time from diagnosis was 2.2 months (1.1, 5.4 months). Prior therapies included corticosteroids (95% of patients), IVIg (58% of patients), and immunosuppression (28% of patients). The starting dose of eltrombopag ranged from 50 mg to 75 mg/day, depending on the baseline platelet count. The median dose at Week 12 was 50 mg/day. Thirty-six (92.3%) patients completed 12 weeks of treatment, while 3 (7.7%) patients discontinued earlier (2 patients required a new ITP therapy and 1 patient developed thrombocytosis).

Two patients had SAEs of venous thromboembolism (deep vein thrombosis at a platelet count 97 G/L; pulmonary embolism at a platelet count of 240 G/L). There were no other AEs or deaths.

In conclusion, the study showed that eltrombopag was generally well tolerated and in patients with newly diagnosed and persistent ITP within 6 months from diagnosis.

Lucchini et al 2021

This prospective, multi-center phase 2 trial evaluated eltrombopag in 51 adult patients with primary ITP (22 with newly diagnosed ITP and 29 with persistent ITP) who were refractory to or relapsed after first-line therapy. The study was divided into period of treatment (PT) from Week 1 to Week 24, period of tapering and discontinuation (PTD) from Week 25 up to Week 32, and period of observation (PO) of 24 weeks starting from eltrombopag discontinuation.

Twenty-three patients (45%) reported a total of 51 AEs and 16 SAEs. Five AEs were considered treatment-related: deep vein thrombosis (n=1), nausea (n=2), hypertransaminasemia (n=1) and diarrhea (n=1). Eltrombopag was interrupted because of toxicity in three patients (6%): hypertransaminasemia, deep vein thrombosis and acute myeloid leukemia.

There were 3 cases of thrombosis (6%). The first was a posterior tibial DVT developed nearly two months after treatment was started, while patient was receiving 75 mg/day of eltrombopag and platelet count was 20 G/L. Two patients experienced acute myocardial infarction: one patient was receiving 75 mg/day and the other was receiving 25 mg/day of eltrombopag; the event occurred four months after starting treatment in both cases and platelet count was 95 and 209 G/L, respectively. Both patients died because

of this thrombotic complication. Among these three thrombotic events, only the DVT was considered by the investigators related to eltrombopag.

Five bleeding events were reported: one grade 3 retinal hemorrhage at Week 1; two grade 2 epistaxis: one at Week 14 and one at Week 28; one grade 1 menorrhagia at Week 38; one grade 1 mucosal bleeding at Week 10. For the last three events, patients were off treatment.

- **Retrospective studies**

González-López et al 2017

This was a retrospective study of 220 adult patients with ITP, including 30 patients with newly diagnosed ITP (up to 3 months from diagnosis), 30 patients with persistent ITP (more than 3 months to up to 12 months from diagnosis), and 160 patients with chronic ITP (more than 12 months from diagnosis.

After 15 months of follow-up, 70 (31.8%) patients reported AEs during eltrombopag treatment, most of them were mild to moderate with 15 patients reporting grade 3–4 AEs. There were no significant differences in the proportion of patients with AEs among the ITP categories.

Three grade 3-4-events occurred in newly diagnosed ITP: one brain haemorrhage in a patient with no response to eltrombopag, one sudden death in a patient with a background of cardiac arrhythmia, and one bilateral pneumonia in al chronic obstructive pulmonary disease patient. All these three patients died. Two persistent ITP cases suffered serious adverse events, one massive stroke with ITP in CR in a carotid stenosis who died 3 days later and one haemorrhage in a non-responding patient who survived. Ten serious adverse events were recorded in chronic ITP group. Eight of them died because of them; three secondary neoplasms, three sever upper respiratory tract infections, one sudden death in a patient with a background of acute myocardial infarct and on stroke in a patient who suffered from atrial fibrillation. The remaining two patients recovered from the brain haemorrhages.

Most common adverse effects were headache and hepatobiliary laboratory abnormalities (HBLAs). One persistent ITP had a venous thrombosis and on chronic ITP had a grade II myelofibrosis but after cessation of eltrombopag.

Rivolti et al 2019

The goal of this retrospective study was to assess the efficacy and safety of TPO-RAs in newly diagnosed, persistent and chronic ITP. Out of 28 adult patients (median aged 61 years), 6 patients had newly diagnosed ITP, 4 had persistent ITP and 18 had chronic ITP. Twenty-one patients received eltrombopag, and 7 patients received eltrombopag and romiplostim sequentially (5 patients switched from eltrombopag to romiplostim and 2 patients switched from romiplostim to eltrombopag). Median duration of treatment was 8 months (range: 1-76) for eltrombopag and 4 months (range: 1-21) for romiplostim.

Six (21%) patients experienced Grade 3-4 AEs: 1 pulmonary embolism, 1 acute myocardial infarction, 1 deep vein thrombosis, and 2 headaches. Four patients died of other causes, the details of which were not provided in the publication.

Moulis et al 2021

This retrospective real-world evidence analysis was designed to assess the use, efficacy and safety of eltrombopag in adult ITP patients treated with eltrombopag within 6 months of ITP diagnosis. It was based on data from the French CARMEN registry that included 799 ITP patients. One-hundred fifty-six (19.5%) patients were treated with eltrombopag, out of whom 95 (60.9%) patients were treated during the first 6 months of ITP (newly diagnosed and persistent ITP). The mean age was 60.5 years; 52.6% were men; 34.7% had ≥1 comorbidity of the Charlson Comorbidity Index (CCI); 58.9% had at ≥1 cardiovascular risk factor (not including age and sex).

Overall, 17 ADRs were reported in 16 (16.8%) patients; thrombocytosis (n=5), venous thrombosis (n=6: 4 pulmonary embolism, 1 deep vein thrombosis, 1 superficial vein thrombosis), rash (n=3), hepatitis, gastrointestinal discomfort, and diarrhea (n=1 each).

Iino et al 2020

This observational retrospective analysis was conducted using data from real-world clinical practice. Seventy-seven adult ITP patients (median age 69, range 17-92 years) were treated with TPO-RAs, out of whom 64 patients received eltrombopag (median dose 25 mg, range 12.5-50 mg) and 13 patients received romiplostim. Most of the patients had newly diagnosed ITP 50 (65%), 5 (6%) of patient had persistent ITP and 22 (29%) of patients had chronic ITP.

AEs were reported in 38 (49%) patients during treatment with TPO-RAs, and in 12 (38%) patients during the treatment-free period. Frequent adverse events (two patients each) were insomnia, nausea, skin rash, oral candidiasis, oral submucosal hemorrhage, liver transaminase elevation, and hyperglycemia; however, these adverse events were not serious. Serious adverse events were observed during the TPO-RA treatment period, and they included single cases of cerebellar infarction after 5 months on eltrombopag, subarachnoid hemorrhage, and worsening of abdominal aortic aneurysm after 1.2 years on eltrombopag. There were no fatal AEs in the study.

2.5.1. Discussion on clinical safety

To support the safety of eltrombopag in patients with ITP ≤ 6 months from diagnosis no new completed clinical trials have been submitted. The MAH also rely on data derived from from two ad-hoc analyses presented by time since diagnosis: 1) ITP registration studies (extension study EXTEND) in which 19/302 patients had <6 months since ITP diagnosis (16 treated with eltrombopag); 2) Interim analysis of ongoing phase II TAPER study (CETB115J2411 study) (updated *cut-off date of 21-Oct-2021*) in which 72 patients had <6 months since ITP diagnosis and were treated with eltrombopag. Supportive safety data from the real-world evidence have been also provided.
The safety population of both analyses included patients who had received at least one dose of eltrombopag.

The **EXTEND study** was intended to assess eltrombopag long-term safety and tolerability. The overall safety results from **EXTEND study** were previously already submitted. Within this procedure, the MAH breaks down the results by subgroups of time from diagnosis (ad-hoc analysis). Although very limited sample size, data from 16 included eltrombopag treated patients with less than 6 months from diagnosis do not seem to reveal any specific pattern or safety concern when compared with patients with >6 months. The MAH has provided summarised tables of adverse events by time since diagnosis as requested. The type of adverse events more commonly reported in patients with less 6 months from ITP diagnosis (fatigue, constipation, headache and nasopharyngitis) are already known and manageable in clinical practice.

In the initial **ad-hoc analysis of TAPER study (CETB115J2411 study)** (*cut-off date: 15-Oct-2020*)**,** the included patients (N=82, of which 56 patients had < 6 months from diagnosis) had a comparable duration of exposure to eltrombopag with a median exposure of 6.01 months for all the subgroups. 62.2% (51/82) of the patients had received >=6 months of eltrombopag treatment.

Analysis of adverse events in the ad-hoc analysis showed similar rates between all the ITP subgroups [81.6% (31/38) (<3 months) ,94.4% (17/18) (3 to <6 months); 87.5% (14/16) (6 to ≤12 months) and 70% (7/10) (>12 months)]. With regards to treatment-related adverse events no increase was seen in patients with less than 6 months from diagnosis [21,1% (8/38) (<3 months), 38.9% (7/18) (3 to <6

months); 18.8% (3/16) (6 to ≤12 months) and 50.0% (5/10) (>12 months)]. Treatment-related SAEs was also comparable across ITP categories [2.6% (1/38)(<3 months), 0 % (3 to <6 months); 12.5% (2/16) (6 to ≤12 months) 0% (>12 months)]; as well as treatment-related adverse events leading to discontinuation [0% (<3 months); 0% (3 to <6 months); 6.3% (1/16) (6 to ≤12 months); 0% (>12 months) or treatment-related adverse events leading to dose adjustment/interruption [7.9% (3/38)(<3 months); 11.1% (2/18) (3 to <6 months); 12,5% (2/16) (6 to ≤12 months); 20% (2/10) (>12 months). No relevant differences were neither observed in treatment-related adverse events requiring additional therapy [10.5% (4/38) (<3 months); 22.2% (4/18) (3 to <6 months); 12.5% (2/16) (6 to ≤12 months);10% (1/10) (>12 months)].

The reported adverse events concur with the already known ones for eltrombopag. The most common adverse events (>10% in all patients) were headache (18.4% vs. 22.2% vs. 12.5% vs. 10.0%), and thrombocytopenia (21.1% vs. 16.7% vs. 12.5% vs 0%) in newly diagnosed to chronic ITP, respectively. With less frequency, other common reported adverse events were hepatobiliary laboratory abnormalities, nauseas, diarrhoea, asthenia, epistaxis and petechiae.
In the updated ad-hoc analysis (*cut-off date: 21-Oct-2021*), the inclusion of 23 additional patients (N=105, of which 72 had ITP< 6 months), do not significantly modify the previously observed safety results. Incidence of TEAE (29.4% [15/51], 47.6% [10/21], 33.3% [6/18], 46.7% [7/15]) and treatment-related SAEs (3.9% [2/51], 0%, 16.7% [3/18], 0%) continue without differing greatly across ITP categories in newly diagnosed to chronic ITP, respectively. The overall rate of treatment-related adverse events leading to discontinuation and of dose adjustment/interruption were also comparable in all ITP categories. The most commonly reported adverse events (>10% in all patients) continued to be headache (17.6% vs. 38.1% vs. 11.1% vs. 20.0%), and thrombocytopenia (21.6% vs. 23.8% vs. 11.1% vs 0%) in newly diagnosed to chronic ITP, respectively.

Safety data from Real World Evidence: the MAH has carried out a literature review and has provided reference to 7 recent observational studies (3 prospective and 4 retrospectives studies) which explored the safety of eltrombopag in patients with less than 6 months from diagnosis when used in routine clinical settings. Although with limited robustness, the safety profile of eltrombopag observed in patients less than 6 months from diagnosis (n≈ 335 patients with newly and persistent ITP) seems similar when compared to patients with a longer time from diagnosis, and the type of reported adverse events are overall in line with the already known safety profile of eltrombopag. Frequently reported non-serious AES were headache and hepatobiliary laboratory abnormalities.
More frequently reported SAEs were related to thrombosis complications and hemorrhages events.

Initially, two deaths in patients with <6 months from diagnosis were reported in TAPER study (on-treatment deaths due to central nervous system haemorrhage and intracranial haemorrhage), one with newly diagnosed ITP and other in the subgroup of 3 to < 6 months from ITP diagnosis.

Despite the investigator did not consider the two deaths related to eltrombopag, they could be considered as lack of efficacy. Since haemorrhages events due to lack of efficacy are also described in the submitted literature and 12,2% (10/82) of the patients discontinued treatment due to lack of efficacy in TAPER study [(21,1% (8/38) in ITP < 3 months and 5,6% (1/18) in ITP < 6 months)], the MAH was requested to discuss death events and its relation with the lack of efficacy rates observed in TAPER study (1º cut-off date) and compared them with data from pivotal studies and literature. Moreover, a common adverse event reported in TAPER study was thrombocytopenia (21.1% vs. 16.7% vs. 12.5% vs 0%) in newly diagnosed to chronic ITP, which could also be attributed to lack of efficacy. The MAH was requested to discuss its relation with lack of efficacy rates and an adequate response was provided.

Regarding thrombocytopenia events, although a higher rate is continued to be observed in early phases of the disease in the updated analysis [(21.6% (11/51) vs. 23.8% (5/21) vs. 11.1% (2/18) vs. 0%

respectively], it is acknowledged that, of these events, the most relevant ones (Grade 3), were similarly distributed across ITP categories. Moreover, the MAH points out that, in addition to a likely reporting bias, the majority of thrombocytopenia events occurred during the first 14 days after starting eltrombopag with similar probability of happening across ITP categories. In this regard, it is admitted that this two-week period may be considered as the most likely period for observing isolated low platelet counts because of the likelihood that a full treatment effect has not been yet obtained, specially taking in to account the overall high response rates achieved by week 9 (84.3% (ITP duration <3 months), 90.5% (ITP duration 3 to <6 months).

On the other hand, in the updated analysis two additional deaths were also reported (1 on-treatment death in the 6 to <12 months subgroup and 1 post-treatment death in the chronic subgroup), both due underlying malignancies.

In summary, when a comparison is made, deaths for haemorrhage were reported in 1.9% (2 deaths) of the 105 eltrombopag-treated patients enrolled in the TAPER study and 0% of the 365 eltrombopag-treated patients enrolled in the four ITP registration studies.

Since in the literature, it is stated that the frequency of death from haemorrhage in ITP patients with platelet counts <30 G/L is estimated to be between 1.6 and 3.9% per patient-year, influenced by several factors and since in both of the reported deaths from TAPER study the patient had loss the response to eltrombopag and their platelets counts were not stabilized, there seems to be a consistency between the reported rates in the study and literature. Nonetheless, beyond that, the sample size and design of TAPER study precludes to reach any conclusion about the association with the risk of haemorrhage and the ITP chronological stage of the disease.

Thus, events suggesting lack of efficacy from TAPER study cannot be viewed as conclusive. However, weighting them up with the overall high response rates and the decrease in the rates of bleeding observed in the study, they can be viewed as not concerning.

Another aspect that should be also pointed out is that, although not specifically in ITP patients in the early stages of disease, bone marrow reticulin fibrosis risk have been already assessed with the long-term use of eltrombopag

The risk for development or progression of reticulin fibres within the bone marrow with TPO-AR treatment is already known thought its relevance has not been not clearly elucidated. Current product information of eltrombopag already warns about the need of taking into account this potential risk and states that analysis to detect cellular morphologic abnormalities should be perform prior to treatment initiation and periodically after. It is also stated that treatment discontinuation and bone marrow biopsy should be considered in patients who develop new or worsening morphological abnormalities or cytopenia.

Moreover, although limited, safety results provided in this procedure (from EXTEND and TAPER analyses) do not suggest an increase of this risk in patients with <6 months from diagnosis. Thus, having this in regard and taking into consideration that the risk of bone marrow reticulin formation will be continuously assess through periodically PSURs, it is considered that no additional measures are necessary in this regard, beyond the already included warning in product information.

No pharmacovigilance data from this population have been provided. Although pharmacovigilance data could have been useful to support the remaining safety data provided, it is acknowledged that available pharmacovigilance data so far (including its off-label use), have already been periodically assessed and will continue to be assessed in the future through PSURs.

In summary, the data provided from ad-hoc analyses show that eltrombopag safety profile seems to be similar for all the ITP subgroups, irrespective of time form diagnosis.

Of note, although expected to be comparable, no long-term safety data have been provided for the

subgroup of patients with < 6 months from diagnosis within this procedure. Neither the updated ad-hoc analysis of TAPER study (J2411 study), nor the patients included in EXTEND study, provide long-term safety data beyond 6.5 months of treatment.

However, the long-term safety of eltrombopag is already known from studies conducted in patients >6 months from ITP diagnosis, showing an acceptable safety profile. Although it is disappointed that no more efforts were made by the company to generate evidence in this population, since eltrombopag safety profile is expected to be similar in ITP patients, regardless time from diagnosis, no more data are requested in this regard.

Lastly, as stated in the efficacy section, limited sample size and the uncontrolled character of most of the body of data, preclude a robust interpretation of results based solely on clinical trials, being necessary to also take into account as supportive, the real-world evidence provided. In this regard, submitted safety data from real-world evidence are overall in line with the already known safety profile of eltrombopag.

2.5.2. Conclusions on clinical safety

The two ad-hoc analyses presented (n=88 patients with less than 6 months from diagnosis and treated with eltrombopag) show that the safety profile of eltrombopag seems comparable across all ITP categories, i.e., irrespective of time from diagnosis. The majority of the reported AEs were in accordance with the known safety profile of eltrombopag and their incidence rates showed no relevant differences in patients with < 6 months from diagnosis when compared with those with more than 6 months.

Although expected to be comparable, no long-term safety data (beyond 6 months) have been provided for the subgroup of patients with less than 6 months from diagnosis within this procedure. Neither the updated ad-hoc analysis of TAPER study (J2411 study), nor the patients included in EXTEND study, provides long-term safety data beyond 6.5 months.

However, the long-term safety of eltrombopag is already known from studies conducted in patients >6 months from ITP diagnosis, showing an acceptable safety profile Since eltrombopag safety profile is expected to be similar in ITP patients regardless time from diagnosis, no more data are requested in this regard.

The limited sample size and the uncontrolled character of the most of the body of data, preclude a robust interpretation of results based solely on clinical trials, being necessary to also take into account as supportive, the real-world evidence provided. In this regard, the MAH has provided 7 literature reports from real-world studies as supportive evidence (n≈ 335 patients). Although with limited robustness, the safety profile of eltrombopag observed in patients less than 6 months from diagnosis seems similar when compared to patients with a longer time from diagnosis, and the type of reported adverse events are overall in line with the already known safety profile of eltrombopag.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 54.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 54.1 with the following content:

Safety concerns

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

Pharmacovigilance plan

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

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

Risk minimisation measures

Table Part V.3: Summary of pharmacovigilance activities and risk minimization activities by safety concerns

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

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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, there is no changes to the package leaflet and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Immune (idiopathic) thrombocytopenia (ITP) is an autoimmune disorder characterised by a low circulating platelet count (thrombocytopenia), decreased platelet production and increased platelet destruction. Thrombocytopenia places patients at risks for bruising, mucocutaneous bleeding and more seriously intracranial haemorrhage; although bleeding symptoms may not always be present. Diagnosis of ITP is one of exclusion, when the history, physical examination, complete blood count and examination of peripheral blood smear do not suggest other aetiology for the thrombocytopenia.

Before 2009, ITP was categorised based on the length of time from initial diagnosis into acute ITP, which lasted for up to 6 months from initial diagnosis, and chronic ITP, which lasted beyond 6 months from initial diagnosis (George et al 1996). In 2009, the International Working Group (IWG) released updated guidelines (Rodeghiero et al 2009), in which ITP was divided into newly diagnosed ITP (lasting up to 3 months from diagnosis), persistent ITP (lasting between 3 and 12 months from diagnosis) and chronic ITP (lasting more than 12 months from diagnosis). This classification was recently reaffirmed by the American Society of Hematology (ASH) (Neunert et al 2019) and a panel of international experts (Provan et al 2019).

Newly diagnosed ITP" was defined as all cases at first diagnosis. A new category, "persistent ITP," was introduced which included patients not reaching spontaneous remission or not maintaining complete response off therapy between 3 to 12 months from diagnosis. The IWG noted that the possibility of spontaneous remission is significant during this period and deferral of aggressive therapeutic approaches (such as splenectomy) should therefore be considered. The term "chronic ITP" was reserved for patients with ITP lasting for more than 12 months.

As part of this application, the proposed indication wording is as follows; additions are shown in **bold** text and deletions are marked in strikethrough (~~xxx~~):

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

3.1.2. Available therapies and unmet medical need

There are several guidelines including different treatment approaches in ITP, with the updated ASH 2019 guideline [Neunert *et al,* 2019] and the updated ICR [Provan *et al,* 2019] being the more relevant ones. Inferences regarding the efficacy of treatments are mainly based on platelet counts as the more reliable surrogate outcome measure. The major goal for treatment of ITP is to provide a platelet count that prevents major bleeding rather than correcting the platelet count to normal levels.

In newly diagnosed ITP (first 3 months), treatment is aimed at rapidly obtaining a safe platelet count (> 30 x 10^9/L) to prevent or stop haemorrhages and to ensure an acceptable quality of life, avoiding as much as possible treatment-related adverse effects. In both updated guidelines, corticosteroids, unless contraindicated, remain the standard initial treatment of newly diagnosed patients, although they should be used for a limited time (≤ 6 weeks). Use of IV Ig, or IV anti-D where available, may be another appropriate first-line treatment in patients with bleeding, at high risk for bleeding, who require a surgical procedure, or who are unresponsive or contraindicated to prednisone.

Most adult patient relapse upon cessation of steroid treatment. Patients still remaining thrombocytopenic after 3 months from diagnosis or initial treatment (corticosteroids, IVIg, anti-D) are classified in persistent (between 3 to 12 months) or chronic (after at least 12 months).

While the old guidelines did not specifically address patients with persistent ITP (between 3 to 12 months) due to lack of robust efficacy/safety data, the updated guidelines propose different treatment approaches for this refractory population. Usual second-line treatment options are TPO-RA, rituximab and splenectomy, nevertheless, there is no solid evidence that defines the best strategy. Each of these second-line treatments may be effective therapy and therefore the choice of treatment should be individualised based on duration of ITP, frequency of bleeding episodes requiring hospitalisation or rescue

medication, comorbidities, age of the patient, medication adherence, medical and social support networks, patient values and preferences, cost and availability.

Available treatment modalities have different mechanisms of action and can be broadly categorised into those that are given only once (or for only 1 course) and are intended to induce a long-term response (rituximab, splenectomy) and those that need continued or chronic administration (low-dose corticosteroids, immunosuppressive agents, TPO-RAs).

TPO-RAs (eltrombopag, romiplostim) have provided excellent responses (>60%) in splenectomised and non-splenectomised patients. Response to continued TPO-RAs persists for up to 6 to 8 years and often allows other ITP therapy to be reduced or discontinued. Cessation of treatment will lead to the return of thrombocytopenia in most cases, but some patients (10%-30%) may achieve a durable response after TPO-RAs are tapered and withdrawn.

Rituximab shows a response of 60% of patients. Long-term durable responses occur in 20% to 25% of adult patients. Prior to treatment, hepatitis B status should be determined, and vaccination against encapsulated gram-positive bacteria should be given.

Splenectomy provides long-term efficacy in approximately 60% of cases. Nonetheless, splenectomy is invasive, irreversible, associated with postoperative complications, and its effectiveness is currently unpredictable, leading many physicians and patients toward postponement and use of alternative approaches. Both guidelines suggest that, if splenectomy is deemed necessary, surgery should be deferred for at least 12 to 24 months from diagnosis (chronic ITP) due to potential for spontaneous remission in the first year.

Fostamatinib represents an option in chronic ITP for adult refractory to the previous treatments. It offers an alternative mechanism for reducing platelet destruction; it may provide response rates of 43% but stable responses of only 18%.

Other medical therapies for patients failing previous therapies are immunosuppressive agents, such as mycophenolate mofetil, cyclosporine A or azathioprine. Danazol and dapsone are "corticosteroid-sparing" agents that may be particularly useful in some patients (e.g., those in whom splenectomy is contraindicated or if other agents are unavailable. Vinca alkaloids are not a chronic therapy option because of neurological toxicity.

3.1.3. Main clinical studies

No new clinical studies have been provided. Instead, to support the efficacy and safety of eltrombopag in patients with ITP ≤ 6 months, the MAH has provided two ad-hoc analyses of subgroups from: 1) ITP registration studies; 2) Interim analysis of ongoing phase II TAPER study (study J2411) (1st *cut-off date of 15-Oct-2020 [N=85]; and 2nd updated cut-off 22-Oct-2021 [N=105] after RSI*). In them eltrombopag efficacy and safety were explored among different patient subgroups by time from ITP diagnosis.

In addition, an updated PK/PD modelling has been provided aimed to evaluate whether the influence of time since diagnosis may provide clinically relevant differences in platelet counts in ITP adult patients receiving eltrombopag.

All this has been complemented with real world evidence of the already use of eltrombopag in patients with less than 6 months from ITP diagnosis in clinical practice.

3.2. Favourable effects

PK/PD modelling show that no clinically relevant changes in platelet count levels were predicted between patients with <6 month and ≥6 month diagnosis across the 4 weeks after the start of treatment. With the use of eltrombopag irrespective of time from diagnosis, minimal changes are expected in platelet count levels, which lack of any clinical relevance.

Pivotal studies ([TRA100773A], [TRA100773B], [TRA102537/RAISE] and [TRA108057/REPEAT]), which support the initial authorisation of eltrombopag, included patients with < 6 months from diagnosis. Nineteen of the 299 patients included in the ad-hoc analysis from ITP registration studies had < 6 months from ITP diagnosis. Specifically, 5 adult patients with newly diagnosed ITP [<3 months from diagnosis] and 41 patients with persistent ITP [3 months to < 12 months from diagnosis] were treated with eltrombopag. In total, **16 patients** had less than 6 months from ITP diagnosis and were treated with eltrombopag.

Platelet count responses achieved show that eltrombopag raises platelet counts irrespective of time from diagnosis in a relevant proportion of patients. The proportions of responders after up to 6 weeks of treatment was **80%** (4/5) (newly diagnosed ITP), **45.5%** (5/11) (persistent ITP; 3 to <6 months), **66.7%** (20/30) (persistent ITP; 6 to 12 months) and **68.2%** (116/170) (chronic ITP). These achieved platelet counts translated into a reduction in bleeding events.

In the first submitted interim ad-hoc analysis (n=82/105) of the ongoing phase II TAPER study*; cut-off date of 15-Oct-2020*), **56 patients** were treated with eltrombopag and have less than 6 months from diagnosis (n=38: newly diagnosed ITP; n= 18: 3 to <6 months). In this analysis, platelet count responses (≥50×10^9/L at least once) increased in a relevant proportion of patients (ranged from **80.0%** to **94.4%** by Week 9 across all ITP categories). Similar rates were observed for platelet threshold of ≥30 $\times10^9$/L (ranged from **80.0%** to **100%**) and for threshold of ≥100 $\times10^9$/L (ranged from **68.8%** to **80.0%)**. Results from supportive efficacy endpoints, which reflect more sustained or durable responses, also showed favorable results for eltrombopag treatment (ranging from **68.8%** to **83.3%** across the ITP categories).

With respect to bleeding events, results were also in line with those from ad-hoc analysis from parent studies; the proportion of patients without bleeding increased during eltrombopag treatment in all ITP categories at Week 4: newly diagnosed ITP [patients without bleeding increased from 39.5% (15/38) at baseline to **84.8%** (28/33)], 3 to <6 months [from 61.1% (11/18) to **94.4%** (17/18)], 6 to ≤12 months [from 50.0% (8/16) to **86.7%** (13/15)] and >12 months [from 70.0% (7/10) to **100%** (9/9).

In the second analysis submitted (n=105; *cut-off date: 21-Oct-2021*), 51 patients fell in the category of newly diagnosed ITP (< 3 months) and 21 belonged to the category of persistent ITP (3 to <6 months). Efficacy results did not differ from those observed in the previous analysis. The proportion of patients achieving platelet counts levels **≥50 G/L** at least once by Week 9 was high and comparable across ITP categories by time since diagnosis (ranging from **84.3%** to **94.4%**). High response rates were also observed for the platelet count threshold of **≥30 G/L** (ranged from **88.2**% to **100%**) and for **≥100 G/L** threshold (ranging from **72.2% to 86.7%)** across ITP categories. Similarly, more **durable response rates** (response rates ≥50 G/L on at least 6 out of 8 consecutive assessments in the first 6 months on study without rescue therapy) were observed, ranging from **70.6% to 81.0%** across the ITP categories.

Those increases in platelet counts continue to translate to the relevant benefit, which is reduced bleeding rates across the ITP categories.

Effectiveness data through literature review from recent real-world evidence (period time from 2014 till 2021) show that eltrombopag is frequently used-off label during clinical practice in patients with < 6 months once lack of response to first-line has been confirmed. Data from ≈335 patients provided show

the achievement of clinically relevant platelet responses in a considerable proportion of patients with < 6 months from diagnosis (ranged from 67%-90%] suggesting that the effect is the same regardless of time since diagnosis. The majority of the publications also report a decrease in bleeding rates and some of them also report a decrease in the use of rescue medication or concomitant ITP therapy. Since these results are in line with those achieved in ad-hoc analyses from clinical trials, they can be considered as supportive.

3.3. Uncertainties and limitations about favourable effects

Regarding the PK/PD model, the unbalanced proportion of patients with time since diagnosis <6 months could affect the final conclusion obtained. Therefore, the current population PK/PD model should be considered of low-impact (descriptive) for supporting the current extension of indication.

Favourable effects observed come from ad-hoc analyses and have not yet been confirmed specifically by a controlled trial in patients with less than 6 months from diagnosis.

The number of subjects with ITP ≤ 6 months included in the ad-hoc analysis from pivotal trials, which provide the greatest robustness, is limited (n=19 patients; 16 treated with eltrombopag). This number is even more limited when analysing more restricted subgroups regarding time from diagnosis (< 3 months: 5 patients; ≥ 3 to < 6 months: 11 patients). This limited sample size must be taken into account when interpreting the results (especially in the comparison made with the placebo group, where only 3 patients had < 6 months from diagnosis).

Due to the fact that parent studies did not collect patient data at time of diagnosis, data were analysed through the open label study TRA105325/EXTEND, which included patients from the parent studies that continued treatment until eltrombopag became commercially available and where time from diagnosis was collected. As an open study, its robustness is limited, particularly when subgroup ad-hoc analyses are attempted.

Regarding updated ad-hoc analysis of the ongoing phase II TAPER study (CETB115J2411; *cut-off date of 21-Oct-2021)*, 72 patients treated with eltrombopag had ≤ 6 months from diagnosis. Although favourable effects were also observed, limitations of a non-controlled study (single-arm) should be kept in mind as they hind the assessment of causality of the treatment effect and therefore, results should be interpreted with caution. The MAH has provided, as requested, the study protocol, SAP and in-depth details of the ad-hoc statistical analysis, since this documentation had not been previously provided within this procedure.

Data from real-world evidence show the same trend as data from clinical trials and can be considered as supportive. Robust evidence that can be drawn from routine clinical setting is limited, and therefore, interpretation of data must be done with caution. Single arm studies, small sample sizes, potential selection bias in retrospective studies or concomitant treatment used as rescue therapy influencing response rates, are aspects, among other, that should be kept in mind when data are interpreted.

3.4. Unfavourable effects

The unfavourable effects of the product are already included in sections 4.4, 4.8 and 5.1 of the approved SmPC. The safety profile of eltrombopag in the population of subjects with ITP < 6 months seems similar to that observed in the ITP ≥ 6 months population with no relevant differences between them.

The majority of the reported AEs in the ad-hoc analyses were in accordance with the known safety profile of eltrombopag and their incidence rates showed no relevant differences in patients with < 6 months from diagnosis when compared with those ≥ than 6 months:

In the EXTEND study, data from 16 included eltrombopag treated patients with less than 6 months from diagnosis do not seem to reveal any specific pattern or safety concern when compared with patients with >6 months. The type of adverse events more commonly reported in patients with less 6 months from ITP diagnosis (fatigue, constipation, headache and nasopharyngitis) are manageable in clinical practice.

In the initial interim ad-hoc analysis of TAPER study (*cut-off date:15-Oct-2020*; n=82, of which 56 patients treated with eltrombopag had ITP< 6 months), adverse events analysis showed similar rates between all the ITP subgroups [81.6% (31/38) (<3 months), 94.4% (17/18) (3 to <6 months); 87.5% (14/16) (6 to ≤12 months) and 70% (7/10) (>12 months)]. With regards to treatment-related adverse events (TEAEs) no increase was seen in patients with less than 6 months from diagnosis [21,1% (8/38) (<3 months), 38.9% (7/18) (3 to <6 months); 18.8% (3/16) (6 to ≤12 months) and 50.0% (5/10) (>12 months)]. Treatment-related SAEs was also comparable across ITP categories [2.6% (1/38) (<3 months), 0 % (3 to <6 months); 12.5% (2/16) (6 to ≤12 months) 0% (>12 months)]; as well as treatment-related adverse events leading to discontinuation [0% (<3 months); 0% (3 to <6 months); 6.3% (1/16) (6 to ≤12 months); 0% (>12 months)].

In the updated ad-hoc analysis (*cut-off date: 21-Oct-2021*), the inclusion of 23 additional patients (n=105, of which 72 patients treated with eltrombopag had ITP< 6 months), do not significantly modify the previously observed safety results. Incidence of TEAE (29.4% [15/51], 47.6% [10/21], 33.3% [6/18], 46.7% [7/15]) and treatment-related SAEs (3.9% [2/51], 0%, 16.7% [3/18], 0%) continue without differing greatly across ITP categories in newly diagnosed to chronic ITP, respectively. The overall rate of treatment-related adverse events leading to discontinuation and of dose adjustment/interruption were also comparable in all ITP categories.
The reported adverse events in TAPER study concur with the already known ones for eltrombopag. The most commonly reported adverse events (>10% in all patients) were headache (17.6% vs. 38.1% vs. 11.1.% vs. 20.0%), and thrombocytopenia (21.6% vs. 23.8% vs. 11.1% vs 0%) in newly diagnosed to chronic ITP, respectively; followed by hepatobiliary laboratory abnormalities, diarrhoea, nausea, asthenia, epistaxis and petechiae (*cut-off date:21-Oct-2021*).

Real world evidence submitted show that safety profile of eltrombopag observed in patients less than 6 months from diagnosis (n ≈ 335 patients with newly and persistent ITP) seems similar when compared to patients with a longer time from diagnosis, and the type of reported adverse events are overall in line with the already known safety profile of eltrombopag. Frequently reported non-serious AES were headache and hepatobiliary laboratory abnormalities. More frequently reported SAEs were related to thrombosis complications and hemorrhages events in non-responsive patients.

The risk for thrombotic/thromboembolic complications with eltrombopag treatment is already known and the SmPC already includes the warning that caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism.

3.5. Uncertainties and limitations about unfavourable effects

Although expected to be comparable, no long-term safety data (beyond 6 months) have been provided for the subgroup of patients with less than 6 months from diagnosis within this procedure. Neither the updated ad-hoc analysis of TAPER study (J2411 study), nor the patients included in EXTEND study, provide long-term safety data beyond 6.5 months in this population. However, the long-term safety of eltrombopag is already known from studies conducted in patients >6 months from ITP diagnosis.

The limited sample size of the ad-hoc analyses (n=88 eltrombopag treated patients with ITP < 6 months) and the uncontrolled character of most of the submitted data, preclude a robust interpretation of results based solely on clinical trials, being necessary to also take into account as supportive, the real-world

evidence provided. In this regard, although it must be taken into account that robust evidence that can be drawn from routine clinical setting is limited, and that, consequently, interpretation of data should be done with caution, submitted safety data from real-world evidence are overall in line with the already known safety profile of eltrombopag.

Two haemorrhagic deaths of the 105 eltrombopag-treated patients (1.9%) were reported in the TAPER study in patients <6 months from diagnosis (on-treatment deaths due to central nervous system haemorrhage and intracranial haemorrhage), one with newly diagnosed ITP and other in the subgroup of 3 to < 6 months from ITP diagnosis.

Although the investigator did not consider these two deaths related to eltrombopag, they can be considered as lack of efficacy, also if taken into account the discontinuation rates due to lack of efficacy observed.

Since in the literature, it is stated that the frequency of death from haemorrhage in ITP patients with platelet counts <30 G/L is estimated to be between 1.6 and 3.9% per patient-year, influenced by several factors and since in both of the reported deaths from TAPER study the patient had loss the response to eltrombopag and their platelets counts were not stabilized, there seems to be a consistency between the reported rates in the study and literature. Nonetheless, beyond that, the sample size and design of TAPER study precludes to draw any conclusion about the association with the risk of haemorrhage and the ITP chronological stage of the disease.

Thus, events suggesting lack of efficacy from TAPER study cannot be viewed as conclusive. However, weighting them up with the overall high response rates and the decrease in the rates of bleeding observed in the study, they can be viewed as not concerning.

3.6. Effects Table

Table 24. Effects Table for eltrombopag in adult ITP ≤ 6 months from diagnosis, refractory to other treatments

Favourable effect	Short description	Unit	Eltrombopag	Control	Uncertainties / Strength of evidence
Platelet response *Ad-hoc analysis EXTEND study*[1]	Proportion of responders (platelet count of ⩾ 50 G/L) up to 6 weeks of treatment.	% (n/Nº evaluable)	ITP < 3 months **80%** (4/5) ITP ≥3 to <6 months **45.5%** (5/11) ITP ≥6 to ≤12 months **66.7%** (20/30) ITP >12 months **68.2%** (116/170)	ITP < 3 months **0%** ITP ≥3 to <6 months **100%** (1/1) ITP ≥6 to ≤12 months **22.2%** (2/9) ITP >12 months **10.6%** (7/66)	-Very limited number of patients in placebo group regarding <6 months subgroups. -Open label -Data from parent studies
Platelet response *Updated Ad-hoc analysis TAPER Study (CETB115J2411study*[2]*)*	Platelet count ≥50 G/L at least once by Week 9 Day 1 (~Day 57)	% (n/Nº evaluable)	ITP < 3 months **84.3%** (43/51) ITP ≥3 to <6 months **90.5%** (19/21) ITP ≥6 to ≤12 months **94.4%** (17/18) ITP >12 months **86.7%** (13/15)		- Uncontrolled
Complete platelet response rate *Updated Ad-hoc analysis TAPER Study (CETB115J2411study*[2]*)*	Platelet count ≥100 G/L at least once by Week 9 Day 1 (~Day 57)	% (n/Nº evaluable)	ITP < 3 months **74.5%** (38/51) ITP ≥3 to <6 months **76.2%** (16/21) ITP ≥6 to ≤12 months **72.2%** (13/18) ITP >12 months **86.7%** (13/15)		-Uncontrolled

Durable response rate *Updated Ad-hoc analysis TAPER Study (CETB115J2411 Study[2])*	Platelet count ≥50 G/L on at least 6 out of 8 consecutive scheduled platelet assessments within first 6 months	% (n/Nº evaluable)	ITP < 3 months **70.6%** (36/51) ITP ≥3 to <6 months **81.0%** (17/21) ITP ≥6 to ≤12 months **72.2%** (13/18) ITP >12 months **80.0%** (12/15)		-Uncontrolled
Bleeding rate *Ad-hoc analysis EXTEND study[1]*	Proportion of patients without bleeding events at baseline and after 6 weeks of treatment (Day 43)	%, (n/Nº evaluable)	ITP < 3 months *Baseline* 20% (1/5) Week 6 **75%** (3/4) ITP ≥3 to <6 months *Baseline* 45.5% (5/11) Week 6 **90%** (9/10) ITP ≥6 to ≤12 months *Baseline* 36.7% (11/30) Week 6 **63.6%** (14/22) ITP >12 months *Baseline* 31.5% (53/168) *Week 6* **78.6%** (110/140)	ITP < 3 months *Baseline* **0** (0/2) Week 6 **0** (0/2) ITP ≥3 to <6 months *Baseline* **0** (0/1) Week 6 **100%** (1/1) ITP ≥6 to ≤12 months *Baseline* **50%** (5/10) Week 6 **75%** (6/8) ITP >12 months *Baseline* **25.4%** (16/63) *Week 6* **41.3%** (26/63)	-Very limited number of patients in placebo group<6 months subgroups. -Open label -Data from parent studies
Bleeding rates *Updated Ad-hoc analysis TAPER Study (CETB115J2411 Study[2])*	proportion of patients without bleeding at baseline and at Week 4	% (n)	ITP < 3 months *Baseline* 37.3% (19/51) *Week 4* **89.1%** (41/46) ITP ≥3 to <6 months *Baseline* 57.1% (12/21)		Uncontrolled

			Week 4 **95.2%** (20/21) ITP ≥6 to ≤12 months *Baseline* 50% (9/18) *Week 4* **88.2%** (15/18) ITP >12 months *Baseline* 73.3% (11/15) *Week 4* **92.9%** 13/14)		
Unfavourable effects					
SAEs *Updated Ad-hoc analysis TAPER Study (CETB115J2411 Study[2])*	treatment related	% (n/N)	ITP < 3 months **3.9%** (2/51) ITP ≥3 to <6 months **0** ITP ≥6 to ≤12 months **16.7%** (3/18) ITP >12 months **0**		Uncontrolled
Deaths *Updated Ad-hoc analysis TAPER Study (CETB115J2411Study[2])*	Fatal SAEs	% (n/N)	ITP < 3 months **2.0%** (1/51) ITP ≥3 to <6 months **4.8%** (1/21) ITP ≥6 to ≤12 months **5.6%** (1/18) ITP >12 months **0**		Central nervous system haemorrhage, intracranial haemorrhage, malignancy.
Treatment-related adverse events *Updated Ad-hoc analysis TAPER Study (CETB115J2411Study[2])*	All treatment related events reported	% (n/N)	ITP < 3 months **29.4%** (15/51) ITP ≥3 to <6 months **47.6%** (10/21) ITP ≥6 to ≤12 months **33.3%** (6/18) ITP >12		Uncontrolled

			months **46.7%** (7/15)		
Thrombotic events *Updated Ad-hoc analysis* *TAPER Study* *(CETB115J2411Study[2])*	Thrombotic events reported: - Pulmonary embolism - Deep vein thrombosis	% (n/N)	ITP < 3 months **0**% ITP ≥3 to <6 months **0%** ITP ≥6 to ≤12 months **5.6%** (1/18) ITP >12 months **0%** **----------** **---** ITP < 3 months **0**% ITP ≥3 to <6 months **0%** ITP ≥6 to ≤12 months **11.1%** (2/18) ITP >12 months **0%**		

Notes: Abbreviations: ITP: Immune Thrombocytopenia

(1) Ad-hoc analysis of extension study [EXTEND study]: after completion of their participation in parent studies [TRA100773A], [TRA100773B], [TRA102537/RAISE], [TRA108057/REPEAT]), the patients were offered to continue treatment with eltrombopag in the open-label study [TRA105325/EXTEND], until eltrombopag became commercially available. In this study, the date of ITP diagnosis was collected, which allowed derivation of time from ITP diagnosis to the first dose of eltrombopag or matching placebo in the parent study.

(2) Interim Ad-hoc analysis of TAPER study (CETB115J2411 study) (cut-off:21-Oct-2021): on-going phase II, open-label, prospective, single-arm, study to assess ability of eltrombopag to induce sustained remission in patients with ITP who are refractory or relapsed after first-line steroids.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

ITP is an uncommon orphan condition that may be life threatening and where limited therapeutic alternatives are available. Eltrombopag is regarded as a suitable therapeutic option able to increase platelet counts above a level which reduces the risk of bleeding events.

Overall, the clinical data presented are indicative of an increase in platelet counts in patients with ITP <6 months from diagnosis. The observed efficacy seems generally consistent among different subgroups (< 3 months, ≥ 3 to <6 months, ≥6 to ≤12 months, and > 12 months). This translate into a significant reduction in bleeding, which is the goal of ITP therapy.

Since the clinical data are limited, supporting data from real world evidence through literature review has also been provided, which show that eltrombopag is frequently used off-label during clinical practice in patients with <6 months from diagnosis and, although interpretation of data should be done with caution, results show the achievement of clinically relevant platelet responses in a considerable proportion of patients in patients with both newly and persistent IPT, in line with what has been observed in clinical trials.

From a safety point of view, no unexpected findings have been identified. Common adverse events include headache and hepatobiliary laboratory abnormalities. Serious adverse events include thrombotic and haemorrhages events in non-responsive patients. The risk for thrombotic/thromboembolic complications with eltrombopag treatment is already known and the SmPC already includes the warning that caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism.

3.7.2. Balance of benefits and risks

In this application, the MAH proposes to modify the ITP indication statement to remove the term "lasting 6 months or longer from diagnosis" to allow adult ITP patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) to be treated with eltrombopag after first-line treatment irrespective of time from initial diagnosis. Since only the adult ITP indication is sought to be extended with this submission, the paediatric indication will be separated into an individual statement.

To support this indication extension, the company based this application with two ad-hoc analyses of subgroups from: 1) ITP registration studies (19 patients; 16 treated with eltrombopag with ITP < 6 months); 2) Interim analysis of ongoing phase II TAPER study (CETB115J2411) (updated cut-off date of 21-Oct-2021) (n=105 patients: including 51 newly diagnosed ITP, 21 with ITP 3 to <6 months, 18 with ITP 6 to ≤12 months and 15 patients with chronic ITP). Eltrombopag efficacy and safety were explored among different patient subgroups by time from ITP diagnosis. In addition, an updated PK/PD modelling has been provided aiming at evaluating whether the influence of time since diagnosis may provide clinically relevant differences in platelet counts in ITP adult patients receiving eltrombopag.

Comparable rates of platelet responses were attained irrespective of time from diagnosis; therefore, they can be considered clinically relevant for subjects with ITP < 6 months. These similar platelet responses across ITP categories translate into a similarly reduction in the frequency and severity of bleeding events irrespective of time from diagnosis, which is the goal of ITP therapy. Consistency was observed between the two ad-hoc analyses.

Data from clinical trials have been complemented with real world evidence of the already use of eltrombopag in patients with less than 6 months from ITP diagnosis in clinical practice (n ≈335 patients with newly and persistent ITP). Support with data from real world evidence is considered relevant when a high off- label use in clinical practice is expected, such as in the case of TPO-AR. Data provided show that eltrombopag seems to be also effective when it is started in earlier stages of the disease and confirm that it exists an off-label use of eltrombopag already in patients with less than 6 months from diagnosis when response failure to first line therapy is confirmed, which is not unexpected according to what it is stablished current guidelines (Neunert et al, 2019; Provan et al, 2019). Although it must be taken into account that robust evidence that can be drawn from routine clinical settings is limited, and that, consequently, interpretation of data should be done with caution, results show the achievement of clinically relevant platelet responses in a considerable proportion of patients with newly and persistent ITP (ranged from 67%-to 90%), in line with what has been observed in ad-hoc analysis from clinical trials.

PK/PD modelling shows that no clinically relevant changes in platelet count levels were predicted between patients with <6 month and ≥6 months diagnosis across the 4 weeks after the start of treatment. With the use of eltrombopag irrespective of time from diagnosis, minimal changes are expected in platelet count levels, which lack of any clinical relevance. However, the unbalanced proportion of patients with time since diagnosis <6 months could affect the final conclusion obtained. Therefore, the current population PK/PD should be considered of low-impact (descriptive) for supporting the current extension of indication.

If taken into account the consistency observed in all the evidence submitted, all pointing in the same direction, and in the context of limited treatment options, benefits of the treatment overweigh the risks for patients with ITP who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) irrespective of time since initial ITP diagnosis.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Revolade remains positive. Current application is considered approvable.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of indication to include treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) irrespective of time since initial diagnosis, based on an ad-hoc analysis of Study TAPER (CETB115J2411); an ongoing phase II, open-label, prospective, single-arm study in
adult ITP patients who are refractory or relapsed after first-line steroids.
As a consequence sections 4.1 and 5.1 of the SmPC have been updated.
In addition, the MAH took the opportunity to make some minor amendments in section 4.8 of the SmPC for increased consistency.
An updated RMP version 54.1 has been submitted.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Revolade-H-C-1110/II/0068'