Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Tocieta 25 mg, filmomhulde tabletten
Tocieta 50 mg, filmomhulde tabletten
Tocieta 75 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Product name] 25 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

[Product name] 50 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

[Product name] 75 mg film-coated tablets
Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

Excipient with known effect

[Product name] 25 mg film-coated tablets
Each film-coated tablet contains 58 mg of isomalt.

[Product name] 50 mg film-coated tablets
Each film-coated tablet contains 117 mg of isomalt.

[Product name] 75 mg film-coated tablets
Each film-coated tablet contains 175 mg of isomalt.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

[Product name] 25 mg film-coated tablets
Dark pink, round, biconvex film-coated tablet with “II” debossed on one side and with a diameter of approximately 8 mm.

[Product name] 50 mg film-coated tablets
Pink, round, biconvex film-coated tablet with “III” debossed on one side and with a diameter of approximately 10 mm.

[Product name] 75 mg film-coated tablets
Red to brown, round, biconvex film-coated tablet with “IV” debossed on one side and with a diameter of approximately 12 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Product name] is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

[Product name] 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) (see sections 4.2 and 5.1).

[Product name] is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1).

[Product name] is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see section 5.1).

4.2 Posology and method of administration

Eltrombopag treatment should be initiated by and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications.

Posology

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts.

Eltrombopag is available as powder for oral suspension under other brand names. The powder for oral suspension may lead to higher eltrombopag exposure than the tablet formulation (see section 5.2). When switching between the tablet and the powder for oral suspension formulations, platelet counts should be monitored weekly for 2 weeks.

Immune (primary) thrombocytopenia
The lowest dose of eltrombopag to achieve and maintain a platelet count ≥ 50,000/µl should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

Adults and paediatric population aged 6 to 17 years
The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

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

Monitoring and dose adjustment
After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count ≥ 50,000/µl as necessary to reduce the risk for bleeding. A daily dose of 75 mg must not be exceeded.

Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag full blood counts (FBCs), including platelet count and peripheral blood

smears, should be assessed weekly until a stable platelet count (≥ 50,000/µl for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

Table 1 Dose adjustments of eltrombopag in ITP patients

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day*.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 250,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg.

* For patients taking 25 mg eltrombopag once every other day, increase dose to 25 mg once daily.

♦ For patients taking 25 mg eltrombopag once daily, consideration should be given to dosing at 12.5 mg once daily or alternatively a dose of 25 mg once every other day.

Eltrombopag can be administered in addition to other ITP medicinal products. The dose regimen of concomitant ITP medicinal products should be modified, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

It is necessary to wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

The standard eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily.

Discontinuation
Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of eltrombopag therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. In non-splenectomised patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section 4.4).

Chronic hepatitis C (HCV) associated thrombocytopenia
When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications.

In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50,000-75,000/µl. Platelet counts > 75,000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen
Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East-/Southeast-Asian ancestry or patients with mild hepatic impairment (see section 5.2).

Monitoring and dose adjustment
The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided (see Table 2).

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

A dose of 100 mg eltrombopag once daily must not be exceeded.

Table 2 Dose adjustments of eltrombopag in HCV patients during antiviral therapy

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

* For patients taking 25 mg eltrombopag once daily, consideration should be given to reinitiating dosing at 25 mg every other day.

♦ On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

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

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

Severe aplastic anaemia
Initial dose regimen
Eltrombopag should be initiated at a dose of 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). The treatment should not be initiated when the patient has existing cytogenetic abnormalities of chromosome 7.

Monitoring and dose adjustment
Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting eltrombopag (see section 5.1). The dose of eltrombopag should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥ 50,000/µl. For patients taking 25 mg once daily, the dose should be increased to 50 mg daily before increasing the dose amount by 50 mg. A dose of 150 mg daily must not be exceeded. Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dosage regimen of eltrombopag modified based on platelet counts as outlined in Table 3.

Table 3 Dose adjustments of eltrombopag in patients with severe aplastic anaemia

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag to maintain platelet counts.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; for at least one week. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 50 mg.

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders
For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50%.

If counts remain stable after 8 weeks at the reduced dose, then eltrombopag must be discontinued and blood counts monitored. If platelet counts drop to < 30,000/µl, haemoglobin drops to < 9 g/dl or absolute neutrophil count (ANC) to < 0.5 x 10^9/l, eltrombopag may be reinitiated at the previous effective dose.

Discontinuation
If no haematological response has occurred after 16 weeks of therapy with eltrombopag, therapy should be discontinued. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate *(*see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of eltrombopag (see section 4.8).

Special populations

Renal impairment
No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2).

Hepatic impairment
Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section 4.4).

If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment an interval of 3 weeks should be observed before increasing the dose.

No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Chronic HCV patients and SAA patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily (see section 5.2). After initiating the dose of

eltrombopag in patients with hepatic impairment an interval of 2 weeks should be observed before increasing the dose.

There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events (TEEs), in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

Elderly
There are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between patients aged at least 65 years and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section 5.2).

There are limited data on the use of eltrombopag in HCV and SAA patients aged over 75 years. Caution should be exercised in these patients (see section 4.4).

East-/Southeast-Asian patients
For adult and paediatric patients of East-/Southeast-Asian ancestry including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily (see section 5.2).

Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

Paediatric population
Eltrombopag is not recommended for use in children under the age of 1 year with ITP due to insufficient data on safety and efficacy.

The safety and efficacy of eltrombopag has not been established in children and adolescents (< 18 years) with chronic HCV related thrombocytopenia. No data are available.

The safety and efficacy of eltrombopag has not been established in children and adolescents (<18 years) with SAA. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Oral use
The tablets should be taken at least two hours before or four hours after any products containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) such as antacids, dairy products (or other calcium containing food products), or mineral supplements (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤ 35 g/l or model for end stage liver disease (MELD) score ≥ 10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/l) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

Combination with direct-acting antiviral agents
Safety and efficacy have not been established in combination with direct-acting antiviral agents approved for treatment of chronic hepatitis C infection.

Risk of hepatotoxicity
Eltrombopag administration can cause abnormal liver function and severe hepatotoxicity, which might be life-threatening (see section 4.8).

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated fractionation should be performed. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥ 3 times the upper limit of normal [x ULN] in patients with normal liver function, or ≥ 3 x baseline or > 5 x ULN, whichever is the lower, in patients with pre-treatment elevations in transaminases) and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

Caution is required when administering eltrombopag to patients with hepatic disease. In ITP and SAA patients a lower starting dose of eltrombopag should be used. Close monitoring is required when administering to patients with hepatic impairment (see section 4.2).

Hepatic decompensation (use with interferon)
Hepatic decompensation in patients with chronic hepatitis C: Monitoring is required in patients with low albumin levels (≤ 35 g/l) or with MELD score ≥ 10 at baseline.

Chronic HCV patients with liver cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In two controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) occurred more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/l) or with a MELD score ≥ 10 at baseline, there was a 3-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35 g/l) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks.

Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for

discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/thromboembolic complications

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n=1,439), 38 out of 955 patients (4%) treated with eltrombopag and 6 out of 484 patients (1%) in the placebo group experienced TEEs. Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤ 35 g/l) or MELD ≥ 10 had a 2-fold greater risk of TEEs than those with higher albumin levels; those aged ≥60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for 2 weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count > 200,000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical studies in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of TEEs of any aetiology.

No case of TEE was identified from a clinical study in refractory SAA, however the risk of these events cannot be excluded in this patient population due to the limited number of exposed patients. As the highest authorised dose is indicated for patients with SAA (150 mg/day) and due to the nature of the reaction, TEEs might be expected in this patient population.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, caution is required when administering eltrombopag to patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

In HCV clinical studies, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Bone marrow reticulin formation and risk of bone marrow fibrosis
Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin-receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing myelodysplastic syndrome (MDS)
There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS. TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage.

In clinical studies with a TPO-R agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported.

The diagnosis of ITP or SAA in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms, or abnormal signs such as increased peripheral blast cells.

The effectiveness and safety of eltrombopag have not been established for the treatment of thrombocytopenia due to MDS. [Product name] should not be used outside of clinical studies for the treatment of thrombocytopenia due to MDS.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA
Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of adult patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one patient had cytogenetic abnormality at Month 6.

In clinical studies with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of eltrombopag is appropriate.

Ocular changes
Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n=1,439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the eltrombopag group and 5% of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2% of the eltrombopag group and 2% of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

QT/QTc prolongation
A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical studies of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag
A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

Paediatric population
The above warnings and precautions for ITP also apply to the paediatric population.

Interference with laboratory tests
Eltrombopag is highly coloured and so has the potential to interfere with some laboratory tests. Serum discolouration and interference with total bilirubin and creatinine testing have been reported in patients taking eltrombopag. If the laboratory results and clinical observations are inconsistent, re-testing using another method may help in determining the validity of the result.

Excipients
Isomalt
Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors
Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% confidence interval [CI]: 82%, 126%) and $AUC_{0-\infty}$ 55% (90% CI: 42%, 69%). Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 5.2).

OATP1B1 and BCRP substrates
Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution (see section 5.2).

Cytochrome P450 substrates
In studies utilising human liver microsomes, eltrombopag (up to 100 μM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered (see section 5.2).

HCV protease inhibitors
Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg every 8 hours did not alter plasma telaprevir exposure.

Co-administration of a single dose of eltrombopag 200 mg with boceprevir 800 mg every 8 hours did not alter plasma boceprevir $AUC_{(0-\tau)}$, but increased C_{max} by 20%, and decreased C_{min} by 32%. The clinical relevance of the decrease in C_{min} has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

Effects of other medicinal products on eltrombopag

Ciclosporin
A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg ciclosporin (a BCRP inhibitor). The co-administration of 200 mg ciclosporin decreased the C_{max} and the $AUC_{0-\infty}$ of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg ciclosporin decreased the C_{max} and the $AUC_{0-\infty}$ of eltrombopag by 39% and 24%, respectively. Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count (see section 4.2). Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

Polyvalent cations (chelation)
Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption due to chelation (see sections 4.2 and 5.2).

Lopinavir/ritonavir
Co-administration of eltrombopag with lopinavir/ritonavir may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of a single 100 mg dose of eltrombopag with repeat dose lopinavir/ritonavir 400/100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{0-\infty}$ by 17% (90% CI: 6.6%, 26.6%). Therefore, caution should be used when co-administration of eltrombopag with lopinavir/ritonavir takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers
Eltrombopag is metabolised through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). Medicinal products that inhibit or induce a single enzyme are unlikely to

significantly affect plasma eltrombopag concentrations, whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

HCV protease inhibitors
Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg every 8 hours or telaprevir 750 mg every 8 hours with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Medicinal products for treatment of ITP
Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

Food interaction
The administration of eltrombopag tablet or powder for oral suspension formulations with a high-calcium meal (e.g. a meal that included dairy products) significantly reduced plasma eltrombopag $AUC_{0-\infty}$ and C_{max}. In contrast, the administration of eltrombopag 2 hours before or 4 hours after a high- calcium meal or with low-calcium food [< 50 mg calcium] did not alter plasma eltrombopag exposure to a clinically significant extent (see section 4.2).

Administration of a single 50 mg dose of eltrombopag in tablet form with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 59% and mean C_{max} by 65%.

Administration of a single 25 mg dose of eltrombopag as powder for oral suspension with a high-calcium, moderate-fat and moderate-calorie meal reduced plasma eltrombopag mean $AUC_{0-\infty}$ by 75% and mean C_{max} by 79%. This decrease of exposure was attenuated when a single 25 mg dose of eltrombopag powder for oral suspension was administered 2 hours before a high-calcium meal (mean $AUC_{0-\infty}$ was decreased by 20% and mean C_{max} by 14%).

Food low in calcium (< 50 mg calcium), including fruit, lean ham, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain, did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

[Product name] is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females
[Product name] is not recommended in women of childbearing potential not using contraception.

Breast-feeding
It is not known whether eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from [Product name] therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Fertility was not affected in male or female rats at exposures that were comparable to those in humans. However, a risk for humans cannot be ruled out (see section 5.3).

4.7 Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

Immune thrombocytopenia in adult and paediatric patients
The safety of eltrombopag was assessed in adult patients (N=763) using the pooled double-blind, placebo-controlled studies TRA100773A and B, TRA102537 (RAISE) and TRA113765, in which 403 patients were exposed to eltrombopag and 179 to placebo, in addition to data from the completed open-label studies (N=360) TRA108057 (REPEAT), TRA105325 (EXTEND) and TRA112940 (see section 5.1). Patients received study medication for up to 8 years (in EXTEND). The most important serious adverse reactions were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included nausea, diarrhoea, increased alanine aminotransferase and back pain.

The safety of eltrombopag in paediatric patients (aged 1 to 17 years) with previously treated ITP has been demonstrated in two studies (N=171) (see section 5.1). PETIT2 (TRA115450) was a two-part, double- blind and open-label, randomised, placebo-controlled study. Patients were randomised 2:1 and received eltrombopag (n=63) or placebo (n=29) for up to 13 weeks in the randomised period of the study. PETIT (TRA108062) was a three-part, staggered-cohort, open-label and double-blind, randomised, placebo-controlled study. Patients were randomised 2:1 and received eltrombopag (n=44) or placebo (n=21), for up to 7 weeks. The profile of adverse reactions was comparable to that seen in adults with some additional adverse reactions, marked ♦ in the table below. The most common adverse reactions in paediatric ITP patients 1 year and older (≥ 3% and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, pyrexia, abdominal pain, oropharyngeal pain, toothache and rhinorrhoea.

Thrombocytopenia with HCV infection in adult patients
ENABLE 1 (TPL103922 n=716, 715 treated with eltrombopag) and ENABLE 2 (TPL108390 n=805) were randomised, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of eltrombopag in thrombocytopenic patients with HCV infection who were otherwise eligible to initiate antiviral therapy. In the HCV studies the safety population consisted of all randomised patients who received double-blind study medicinal product during Part 2 of ENABLE 1 (eltrombopag treatment n=450, placebo treatment n=232) and ENABLE 2 (eltrombopag treatment n=506, placebo treatment n=252). Patients are analysed according to the treatment received (total safety double-blind population, eltrombopag n=955 and placebo n=484). The most important serious adverse reactions identified were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included headache, anaemia, decreased appetite, cough, nausea, diarrhoea, hyperbilirubinaemia, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza-like illness, asthenia, chills and oedema.

Severe aplastic anaemia in adult patients
The safety of eltrombopag in adult patients with SAA was assessed in a single-arm, open-label study (N=43) in which 11 patients (26%) were treated for > 6 months and 7 patients (16%) were treated for > 1 year (see section 5.1). The most common adverse reactions occurring in at least 10% of patients

included headache, dizziness, cough, oropharyngeal pain, rhinorrhoea, nausea, diarrhoea, abdominal pain, transaminases increased, arthralgia, pain in extremity, muscle spasms, fatigue and pyrexia.

Severe aplastic anaemia in paediatric population
The safety of eltrombopag in paediatric patients with refractory/relapsed (cohort A; n=14) or treatmentnaive (cohort B; n=37) SAA was assessed in an open-label, uncontrolled, intra-patient dose escalation study (total N=51) (see also section 5.1 for study details). Adverse events of special interest, including acute kidney injury, hepatotoxicity, thromboembolic events, and clonal evolution or cytogenetic abnormality, were reported in 29 (56.9%), 39 (76.5%), 2 (3.9%), and 1 (2.0%) patients, respectively. Overall, the frequency, type and severity of adverse reactions observed for eltrombopag in paediatric patients with SAA were consistent with those observed in adult patients with SAA.

List of adverse reactions
The adverse reactions in the adult ITP studies (N=763), paediatric ITP studies (N=171), the HCV studies (N=1,520), the adult SAA study (N=43), the paediatric SAA study (N=51) and post-marketing reports are listed below by MedDRA system organ class and by frequency (tables 4, 5 and 6). Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

Table 4 Adverse reactions in the ITP study population

System organ class	Frequency	Adverse reaction
Infections and infestations	Very common	Nasopharyngitis♦, upper respiratory tract infection♦
	Common	Pharyngitis, influenza, oral herpes, pneumonia, sinusitis, tonsillitis, respiratory tract infection, gingivitis
	Uncommon	Skin infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Rectosigmoid cancer
Blood and lymphatic system disorders	Common	Anaemia, eosinophilia, leukocytosis, thrombocytopenia, haemoglobin decreased, white blood cell count decreased
	Uncommon	Anisocytosis, haemolytic anaemia, myelocytosis, band neutrophil count increased, myelocyte present, platelet count increased, haemoglobin increased
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Common	Hypokalaemia, decreased appetite, blood uric acid increased
	Uncommon	Anorexia, gout, hypocalcaemia
Psychiatric disorders	Common	Sleep disorder, depression
	Uncommon	Apathy, mood altered, tearfulness
Nervous system disorders	Common	Paraesthesia, hypoaesthesia, somnolence, migraine
	Uncommon	Tremor, balance disorder, dysaesthesia, hemiparesis, migraine with aura, neuropathy peripheral, peripheral sensory neuropathy, speech disorder, toxic neuropathy, vascular headache
Eye disorders	Common	Dry eye, vision blurred, eye pain, visual acuity reduced
	Uncommon	Lenticular opacities, astigmatism, cataract cortical, lacrimation increased, retinal haemorrhage, retinal pigment epitheliopathy, visual impairment, visual acuity tests abnormal, blepharitis, keratoconjunctivitis sicca

Ear and labyrinth disorders	Common	Ear pain, vertigo
Cardiac disorders	Uncommon	Tachycardia, acute myocardial infarction, cardiovascular disorder, cyanosis, sinus tachycardia, electrocardiogram QT prolonged
Vascular disorders	Common	Deep vein thrombosis, haematoma, hot flush
	Uncommon	Embolism, thrombophlebitis superficial, flushing
Respiratory, thoracic and mediastinal disorders	Very common	Cough♦
	Common	Oropharyngeal pain♦, rhinorrhoea♦
	Uncommon	Pulmonary embolism, pulmonary infarction, nasal discomfort, oropharyngeal blistering, sinus disorder, sleep apnoea syndrome
Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Mouth ulceration, toothache♦, vomiting, abdominal pain*, mouth haemorrhage, flatulence * Very common in paediatric ITP
	Uncommon	Dry mouth, glossodynia, abdominal tenderness, faeces discoloured, food poisoning, frequent bowel movements, haematemesis, oral discomfort
Hepatobiliary disorders	Very common	Alanine aminotransferase increased†
	Common	Aspartate aminotransferase increased†, hyperbilirubinaemia, hepatic function abnormal
	Uncommon	Cholestasis, hepatic lesion, hepatitis, drug-induced liver injury
Skin and subcutaneous tissue disorders	Common	Rash, alopecia, hyperhidrosis, pruritus generalised, petechiae
	Uncommon	Urticaria, dermatosis, cold sweat, erythema, melanosis, pigmentation disorder, skin discolouration, skin exfoliation
Musculoskeletal and connective tissue disorders	Very common	Back pain
	Common	Myalgia, muscle spasm, musculoskeletal pain, bone pain
	Uncommon	Muscular weakness
Renal and urinary disorders	Common	Proteinuria, blood creatinine increased, thrombotic microangiopathy with renal failure‡
	Uncommon	Renal failure, leukocyturia, lupus nephritis, nocturia, blood urea increased, urine protein/creatinine ratio increased
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Common	Pyrexia*, chest pain, asthenia *Very common in paediatric ITP
	Uncommon	Feeling hot, vessel puncture site haemorrhage, feeling jittery, inflammation of wound, malaise, sensation of foreign body
Investigations	Common	Blood alkaline phosphatase increased
	Uncommon	Blood albumin increased, protein total increased, blood albumin decreased, pH urine increased
Injury, poisoning and procedural complications	Uncommon	Sunburn

♦ Additional adverse reactions observed in paediatric studies (aged 1 to 17 years).

† Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

‡ Grouped term with preferred terms acute kidney injury and renal failure

Table 5 Adverse reactions in the HCV study population (in combination with anti-viral interferon and ribavirin therapy)

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Urinary tract infection, upper respiratory tract infection, bronchitis, nasopharyngitis, influenza, oral herpes
	Uncommon	Gastroenteritis, pharyngitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Hepatic neoplasm malignant
Blood and lymphatic system disorders	Very common	Anaemia
	Common	Lymphopenia
	Uncommon	Haemolytic anaemia
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hyperglycaemia, abnormal loss of weight
Psychiatric disorders	Common	Depression, anxiety, sleep disorder
	Uncommon	Confusional state, agitation
Nervous system disorders	Very common	Headache
	Common	Dizziness, disturbance in attention, dysgeusia, hepatic encephalopathy, lethargy, memory impairment, paraesthesia
Eye disorders	Common	Cataract, retinal exudates, dry eye, ocular icterus, retinal haemorrhage
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Palpitations
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea, oropharyngeal pain, dyspnoea exertional, productive cough
Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Vomiting, ascites, abdominal pain, abdominal pain upper, dyspepsia, dry mouth, constipation, abdominal distension, toothache, stomatitis, gastrooesophageal reflux disease, haemorrhoids, abdominal discomfort, varices oesophageal
	Uncommon	Oesophageal varices haemorrhage, gastritis, aphthous stomatitis
Hepatobiliary disorders	Common	Hyperbilirubinaemia, jaundice, drug-induced liver injury
	Uncommon	Portal vein thrombosis, hepatic failure
Skin and subcutaneous tissue disorders	Very common	Pruritus
	Common	Rash, dry skin, eczema, rash pruritic, erythema,

		hyperhidrosis, pruritus generalised, alopecia
	Uncommon	Skin lesion, skin discolouration, skin hyperpigmentation, night sweats
Musculoskeletal and connective tissue disorder	Very common	Myalgia
	Common	Arthralgia, muscle spasms, back pain, pain in extremity, musculoskeletal pain, bone pain
Renal and urinary disorders	Uncommon	Thrombotic microangiopathy with acute renal failure†, dysuria
General disorders and administration site conditions	Very common	Pyrexia, fatigue, influenza-like illness, asthenia, chills
	Common	Irritability, pain, malaise, injection site reaction, non-cardiac chest pain, oedema, oedema peripheral
	Uncommon	Injection site pruritus, injection site rash, chest discomfort
Investigations	Common	Blood bilirubin increased, weight decreased, white blood cell count decreased, haemoglobin decreased, neutrophil count decreased, international normalised ratio increased, activated partial thromboplastin time prolonged, blood glucose increased, blood albumin decreased
	Uncommon	Electrocardiogram QT prolonged

† Grouped term with preferred terms oliguria, renal failure and renal impairment

Table 6 Adverse reactions in the SAA study population

System organ class	**Frequenc**	**Adverse reaction**
Blood and lymphatic system disorders	Common	Neutropenia, splenic infarction
Metabolism and nutrition disorders	Common	Iron overload, decreased appetite, hypoglycaemia, increased appetite
Psychiatric disorders	Common	Anxiety, depression
Nervous system disorders	Very common	Headache, dizziness
	Common	Syncope
Eye disorders	Common	Dry eye, cataract, ocular icterus, vision blurred, visual impairment, vitreous floaters
Respiratory, thoracic and mediastinal disorders	Very common	Cough, oropharyngeal pain, rhinorrhoea
	Common	Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea, nausea, abdominal pain
	Common	Oral mucosal blistering, oral pain, vomiting, abdominal discomfort, constipation, gingival bleeding, abdominal distension, dysphagia, faeces discoloured, swollen tongue, gastrointestinal motility disorder, flatulence
Hepatobiliary disorders	Very common	Transaminases increased
	Common	Blood bilirubin increased (hyperbilirubinemia), jaundice
	Not known	Drug-induced liver injury
Skin and subcutaneous tissue disorders	Common	Petechiae, rash, pruritus, urticaria, skin lesion, rash macular
	Not	Skin discolouration, skin hyperpigmentation

	known	
Musculosketal and connective tissue disorders	Very common	Arthralgia, pain in extremity, muscle spasms
	Common	Back pain, myalgia, bone pain
Renal and urinary disorders	Common	Chromaturia
General disorders and administration site conditions	Very common	Fatigue, pyrexia, chills
	Common	Asthenia, oedema peripheral, malaise
Investigations	Common	Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/thromboembolic events (TEEs)
In 3 controlled and 2 uncontrolled clinical studies among adult ITP patients receiving eltrombopag (n=446), 17 patients experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n=6), pulmonary embolism (n=6), acute myocardial infarction (n=2), cerebral infarction (n=2), embolism (n=1) (see section 4.4).

In a placebo-controlled study (n=288, Safety population), following 2 weeks' treatment in preparation for invasive procedures, 6 of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1%) patients in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count > 200,000/µl

No specific risk factors were identified in those patients who experienced a TEE with the exception of platelet counts ≥ 200,000/µl (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n=1,439), 38 out of 955 patients (4%) treated with eltrombopag experienced a TEE and 6 out of 484 patients (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag versus < 1% for placebo) (see section 4.4). Patients with low albumin levels (≤ 35 g/l) or MELD ≥ 10 had a 2-fold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)
Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11%) than in the placebo arm (6%). In patients with low albumin levels (≤ 35 g/l) or MELD score ≥ 10 at baseline, there was a 3-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Hepatotoxicity
In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum ALT, AST and bilirubin were observed (see section 4.4).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in adults with chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality. In two placebo-controlled studies in paediatric patients (aged 1 to 17 years) with chronic ITP, ALT ≥ 3 x ULN was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥ 3 x ULN was reported in 34% and 38% of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥ 1.5 x ULN was reported in 76% and 50% of the eltrombopag and placebo groups, respectively.

In the single-arm phase II monotherapy refractory SAA study, concurrent ALT or AST > 3 x ULN with total (indirect) bilirubin > 1.5 x ULN were reported in 5% of patients. Total bilirubin > 1.5 x ULN occurred in 14% of patients.

Thrombocytopenia following discontinuation of treatment
In the 3 controlled clinical ITP studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% and 8% of the eltrombopag and placebo groups, respectively (see section 4.4).

Increased bone marrow reticulin
Across the programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In a small number of ITP patients, eltrombopag treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities
In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of adult patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one patient had cytogenetic abnormality at Month 6.

Haematologic malignancies
In the single-arm, open-label study in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) patient has been diagnosed with MDS or AML in each study.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consideration should be given to oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Platelet counts should be closely monitored. Treatment with eltrombopag should be reinitiated in accordance with dosing and administration recommendations (see section 4.2).

In the clinical studies there was one report of overdose where the patient ingested 5000 mg of eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin. The platelet counts

were 672,000/µl on Day 18 after ingestion and the maximum platelet count was 929,000/µl. All events were resolved without sequelae following treatment.

Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells.

Clinical efficacy and safety

Immune (primary) thrombocytopenia (ITP) studies
Two phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year. The single-arm phase II study TAPER (CETB115J2411) evaluated the safety and efficacy of eltrombopag and its ability to induce sustained response after treatment discontinuation in 105 adult ITP patients who relapsed or failed to respond to first-line corticosteroid treatment.

Double-blind placebo-controlled studies
RAISE:
197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medicinal products at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6-month treatment period based on individual platelet counts. All patients initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28% of eltrombopag-treated patients were maintained on ≤ 25 mg and 29 to 53% received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥ 3 prior ITP therapies and 36% had a prior splenectomy.

Median platelet counts at baseline were 16,000/µl for both treatment groups and in the eltrombopag group were maintained above 50,000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained < 30,000/µl throughout the study.

Platelet count response between 50,000-400,000/µl in the absence of rescue treatment was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period, p <0.001 (Table 7). Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the 6-month treatment period.

Table 7 Secondary efficacy results from RAISE

	Eltrombopag N=135	**Placebo N=62**
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75% of assessments in the target range (50,000 to 400,000/µl), n (%)	51 (38)	4 (7)
p-value [a]	<0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
p-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
p-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
p-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
p-value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33%) patients treated with eltrombopag who were taking an ITP medicinal product at baseline permanently discontinued all baseline ITP medicinal products.

At baseline, more than 70% of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20% reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% from Day 15 to the end of treatment throughout the 6-month treatment period.

TRA100773B:
The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥ 50,000/µl at Day 43 from a baseline of < 30,000/µl; patients who withdrew prematurely due to a platelet count > 200,000/µl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated ITP were randomised 2:1 eltrombopag (n=76) to placebo (n=38) (Table 8).

Table 8 Efficacy results from TRA100773B

	Eltrombopag N=76	**Placebo N=38**
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥ 50,000/µl after up to 42 days of dosing (compared to a baseline count of < 30,000/µl), n (%)	43 (59)	6 (16)
p-value [a]	<0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
p-value [a]	0.029	

a Logistic regression model adjusted for randomisation stratification variables.

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count (≤ 15,000/µl, > 15,000/µl) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count ≤ 15,000/µl the median platelet counts did not reach the target level (>50,000/µl), although in both studies 43% of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42% of patients with baseline platelet count ≤ 15,000/µl treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60% of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

Open-label non-controlled studies
REPEAT (TRA108057):
This open-label, repeat-dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

EXTEND (TRA105325):
Eltrombopag was administered to 302 ITP patients in this open-label extension study, 218 patients completed 1 year, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 years. The median baseline platelet count was 19,000/µl prior to eltrombopag administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were 85,000/ µl, 85,000/ µl, 105,000/ µl, 64,000/ µl, 75,000/ µl, 119,000/ µl and 76,000/ µl, respectively.

TAPER (CETB115J2411):
This was a single-arm phase II study including ITP patients treated with eltrombopag after first-line corticosteroid failure irrespective of time since diagnosis. A total of 105 patients were enrolled on the study and started eltrombopag treatment on 50 mg once daily (25 mg once daily for patients of East-/Southeast-Asian ancestry). The dose of eltrombopag was adjusted during the treatment period based on individual platelet counts with the goal to achieve a platelet count ≥100,000/µl.

Of the 105 patients who were enrolled in the study and who received at least one dose of eltrombopag, 69 patients (65.7%) completed treatment and 36 patients (34.3%) discontinued treatment early.

Analysis of sustained response off treatment
The primary endpoint was the proportion of patients with sustained response off treatment until Month 12. Patients who reached a platelet count of ≥100,000/µl and maintained platelet counts around 100,000/µl for 2 months (no counts below 70,000/µl) were eligible for tapering off eltrombopag and treatment discontinuation. To be considered as having achieved a sustained response off treatment, a patient had to maintain platelet counts ≥30,000/µl, in the absence of bleeding events or the use of rescue therapy, both during the treatment tapering period and following discontinuation of treatment until Month 12.

The duration of tapering was individualised depending on the starting dose and the response of the patient. The tapering schedule recommended dose reductions of 25 mg every 2 weeks if the platelet counts were stable. After the daily dose was reduced to 25 mg for 2 weeks, the dose of 25 mg was then only administered on alternate days for 2 weeks until treatment discontinuation. The tapering was done in smaller decrements of 12.5 mg every second week for patients of East-/Southeast-Asian ancestry. If a relapse (defined as platelet count <30,000/µl) occurred, patients were offered a new course of eltrombopag at the appropriate starting dose.

Eighty-nine patients (84.8%) achieved a complete response (platelet count ≥100,000/µl) (Step 1, Table 9) and 65 patients (61.9%) maintained the complete response for at least 2 months with no platelet counts below 70,000/µl (Step 2, Table 9). Forty-four patients (41.9%) were able to be tapered off eltrombopag until treatment discontinuation while maintaining platelet counts ≥30,000/µl in the absence of bleeding events or the use of rescue therapy (Step 3, Table 9).

The study met the primary objective by demonstrating that eltrombopag was able to induce sustained response off treatment, in the absence of bleeding events or the use of rescue therapy, by Month 12 in 32 of the 105 enrolled patients (30.5%; p<0.0001; 95% CI: 21.9, 40.2) (Step 4, Table 9). By Month 24, 20 of the 105 enrolled patients (19.0%; 95% CI: 12.0, 27.9) maintained sustained response off treatment in the absence of bleeding events or the use of rescue therapy (Step 5, Table 9).

The median duration of sustained response after treatment discontinuation to Month 12 was 33.3 weeks (min-max: 4-51), and the median duration of sustained response after treatment discontinuation to Month 24 was 88.6 weeks (min-max: 57-107).

After tapering off and discontinuation of eltrombopag treatment, 12 patients had a loss of response, 8 of them re-started eltrombopag and 7 had a recovery response.

During the 2-year follow-up, 6 out of 105 patients (5.7%) experienced thromboembolic events, of which 3 patients (2.9%) experienced deep vein thrombosis, 1 patient (1.0%) experienced superficial vein thrombosis, 1 patient (1.0%) experienced cavernous sinus thrombosis, 1 patient (1.0%) experienced cerebrovascular accident and 1 patient (1.0%) experienced pulmonary embolism. Of the 6 patients, 4 patients experienced thromboembolic events that were reported at or greater than Grade 3, and 4 patients experienced thromboembolic event that were reported as serious. No fatal cases were reported.

Twenty out of 105 patients (19.0%) experienced mild to severe haemorrhage events on treatment before tapering started. Five out of 65 patients (7.7%) who started tapering experienced mild to moderate haemorrhage events during tapering. No severe haemorrhage event occurred during tapering. Two out of 44 patients (4.5%) who tapered off and discontinued eltrombopag treatment experienced mild to moderate haemorrhage events after treatment discontinuation until Month 12. No severe haemorrhage event occurred during this period. None of the patients who discontinued eltrombopag and entered the second year follow-up experienced haemorrhage event during the second year. Two fatal intracranial haemorrhage events were reported during the 2-year follow-up. Both events occurred on treatment, not in the context of tapering. The events were not considered to be related to study treatment.

The overall safety analysis is consistent with previously reported data and the risk-benefit assessment remained unchanged for the use of eltrombopag in patients with ITP.

Table 9 Proportion of patients with sustained response off treatment at Month 12 and at Month 24 (full analysis set) in TAPER

		All patients N=105		**Hypothesis testing**	
		n (%)	**95% CI**	**p-value**	**Reject H0**
Step 1:	Patients who reached platelet count ≥100,000/µl at least once	89 (84.8)	(76.4, 91.0)		
Step 2:	Patients who maintained stable platelet count for 2 months after reaching 100,000/µl (no counts <70,000/µl)	65 (61.9)	(51.9, 71.2)		
Step 3:	Patients who were able to be tapered off eltrombopag until treatment discontinuation, maintaining platelet count ≥30,000/µl in the absence of bleeding events or use of any rescue therapy	44 (41.9)	(32.3, 51.9)		
Step 4:	Patients with sustained response off treatment until Month 12, with platelet count maintained ≥30,000/µl in the absence of bleeding events or use of any rescue therapy	32 (30.5)	(21.9, 40.2)	<0.0001*	Yes
Step 5:	Patients with sustained response off treatment from Month 12 to Month 24, maintaining platelet count ≥30,000/µl in the absence of bleeding events or use of any rescue therapy	20 (19.0)	(12.0, 27.9)		

N: The total number of patients in the treatment group. This is the denominator for percentage (%) calculation.
n: Number of patients in the corresponding category.
The 95% CI for the frequency distribution was computed using Clopper-Pearson exact method. Clopper-Pearson test was used for testing whether the proportion of responders was >15%. CI and p-values are reported.
* Indicates statistical significance (one-sided) at the 0.05 level.

Results of response on treatment analysis by time since ITP diagnosis
An ad-hoc analysis was conducted on the n=105 patients by time since ITP diagnosis to assess the early response to eltrombopag across four different ITP categories by time since diagnosis (newly diagnosed ITP <3 months, persistent ITP 3 to <6 months, persistent ITP 6 to ≤12 months, and chronic ITP >12 months). 49% of patients (n=51) had an ITP diagnosis of <3 months, 20% (n=21) of 3 to <6 months, 17% (n=18) of 6 to ≤12 months and 14% (n=15) of >12 months.

Until the cut-off date (22-Oct-2021), patients were exposed to eltrombopag for a median (Q1-Q3) duration of 6.2 months (2.3-12.0 months). The median (Q1-Q3) platelet count at baseline was 16,000/µl (7,800-28,000/µl).

Platelet count response (defined as a platelet count ≥50,000/µl at least once by Week 9 without rescue therapy) was achieved in 84% (95% CI: 71% to 93%) of newly diagnosed ITP patients, 91% (95% CI: 70% to 99%) and 94% (95% CI: 73% to 100%) of persistent ITP patients (i.e. with ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and in 87% (95% CI: 60% to 98%) of chronic ITP patients.

The rate of complete response, defined as platelet count ≥100,000/µl at least once by Week 9 without rescue therapy, was 75% (95% CI: 60% to 86%) in newly diagnosed ITP patients, 76% (95% CI: 53% to 92%) and 72% (95% CI: 47% to 90%) in persistent ITP patients (ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and 87% (95% CI: 60% to 98%) in chronic ITP patients.

The rate of durable response, defined as a platelet count ≥50,000/µl for at least 6 out of 8 consecutive assessments without rescue therapy during the first 6 months on study, was 71% (95% CI: 56% to 83%) in newly diagnosed ITP patients, 81% (95% CI: 58% to 95%) and 72% (95% CI: 47% to 90.3%) in persistent ITP patients (ITP diagnosis 3 to <6 months and 6 to ≤12 months, respectively), and 80% (95% CI: 52% to 96%) in chronic ITP patients.

When assessed with the WHO Bleeding Scale, the proportion of newly diagnosed and persistent ITP patients without bleeding at Week 4 ranged from 88% to 95% compared to 37% to 57% at baseline. For chronic ITP patients it was 93% compared to 73% at baseline.

The safety of eltrombopag was consistent across all ITP categories and in line with its known safety profile.

Clinical studies comparing eltrombopag to other treatment options (e.g. splenectomy) have not been conducted. The long-term safety of eltrombopag should be considered prior to starting therapy.

Paediatric population (aged 1 to 17 years)
The safety and efficacy of eltrombopag in paediatric patients have been investigated in two studies.

TRA115450 (PETIT2):
The primary endpoint was a sustained response, defined as the proportion of patients receiving eltrombopag, compared to placebo, achieving platelet counts ≥ 50,000/µl for at least 6 out of 8 weeks (in the absence of rescue therapy), between weeks 5 to 12 during the double-blind randomised period. Patients were diagnosed with chronic ITP for at least 1 year and were refractory or relapsed to at least one prior ITP therapy or unable to continue other ITP treatments for a medical reason and had platelet count < 30,000/µl. Ninety-two patients were randomised by three age cohort strata (2:1) to eltrombopag

(n=63) or placebo (n=29). The dose of eltrombopag could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of eltrombopag patients (40%) compared with placebo patients (3%) achieved the primary endpoint (Odds Ratio: 18.0 [95% CI: 2.3, 140.9] p <0.001) which was similar across the three age cohorts (Table 10).

Table 10 Sustained platelet response rates by age cohort in paediatric patients with chronic ITP

	Eltrombopag n/N (%) [95% CI]	**Placebo n/N (%) [95% CI]**
Cohort 1 (12 to 17 years)	9/23 (39%) [20%, 61%]	1/10 (10%) [0%, 45%]
Cohort 2 (6 to 11 years)	11/26 (42%) [23%, 63%]	0/13 (0%) [N/A]
Cohort 3 (1 to 5 years)	5/14 (36%) [13%, 65%]	0/6 (0%) [N/A]

Statistically fewer eltrombopag patients required rescue treatment during the randomised period compared to placebo patients (19% [12/63] vs. 24% [7/29], p=0.032).

At baseline, 71% of patients in the eltrombopag group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of eltrombopag patients reporting any bleeding was decreased to half of baseline (36%). In comparison, at Week 12, 55% of placebo patients reported any bleeding.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the open-label phase of the study and 53% (8/15) of patients were able to reduce (n=1) or discontinue (n=7) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

TRA108062 (PETIT):
The primary endpoint was the proportion of patients achieving platelet counts ≥ 50,000/µl at least once between weeks 1 and 6 of the randomised period. Patients were diagnosed with ITP for at least 6 months and were refractory or relapsed to at least one prior ITP therapy with a platelet count < 30,000/µl (n=67). During the randomised period of the study, patients were randomised by three age cohort strata (2:1) to eltrombopag (n=45) or placebo (n=22). The dose of eltrombopag could be adjusted based on individual platelet counts.
Overall, a significantly greater proportion of eltrombopag patients (62%) compared with placebo patients (32%) met the primary endpoint (Odds Ratio: 4.3 [95% CI: 1.4, 13.3] p=0.011).

Sustained response was seen in 50% of the initial responders during 20 out of 24 weeks in the PETIT 2 study and 15 out of 24 weeks in the PETIT study.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomised, double-blind, placebo-controlled studies. ENABLE 1 utilised peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilised peginterferon alfa-2b plus ribavirin. Patients did not receive direct acting antiviral agents. In both studies, patients with a platelet count of <75,000/µl were enrolled and stratified by platelet count (< 50,000/µl and ≥ 50,000/µl to < 75,000/µl), screening HCV RNA (< 800,000 IU/ml and ≥ 800,000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

Baseline disease characteristics were similar in both studies and were consistent with compensated cirrhotic HCV patient population. The majority of patients were HCV genotype 1 (64%) and had bridging fibrosis/cirrhosis. Thirty-one percent of patients had been treated with prior HCV therapies,

primarily pegylated interferon plus ribavirin. The median baseline platelet count was 59,500/µl in both treatment groups: 0.8%, 28% and 72% of the patients recruited had platelet counts < 20,000/µl, < 50.000/µl and ≥ 50,000/µl respectively.

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label eltrombopag to increase the platelet count to ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. The median time to achieve the target platelet count ≥ 90,000/µl (ENABLE 1) or ≥ 100,000/µl (ENABLE 2) was 2 weeks.

The primary efficacy endpoint for both studies was sustained virologic response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period.

In both HCV studies, a significantly greater proportion of patients treated with eltrombopag (n=201, 21%) achieved SVR compared to those treated with placebo (n=65, 13%) (see Table 11). The improvement in the proportion of patients who achieved SVR was consistent across all subgroups in the randomisation strata (baseline platelet counts (< 50,000 vs. > 50,000), viral load (< 800,000 IU/ml vs. ≥ 800,000 IU/ml) and genotype (2/3 vs. 1/4/6)).

Table 11 Virologic response in HCV patients in ENABLE 1 and ENABLE 2

	Pooled data		**ENABLE 1[a]**		**ENABLE 2[b]**	
Patients achieving target platelet counts and initiating antiviral therapy[c]	1,439/1,520 (95%)		680/715 (95%)		759/805 (94%)	
	Eltrombopag	**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**	**Placebo**
Total number of patients entering antiviral treatment phase	**n=956**	**n=485**	**n=450**	**n=232**	**n=506**	**n=253**
	% patients achieving virologic response					
Overall SVR [d]	21	13	23	14	19	13
HCV RNA Genotype						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6[e]	15	8	18	10	13	7
Albumin levels [f]						
≤ 35 g/l	11	8				
> 35 g/l	25	16				
MELD score[f]						
≥ 10	18	10				
< 10	23	17				

a Eltrombopag given in combination with peginterferon alfa-2a (180 µg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

b Eltrombopag given in combination with peginterferon alfa-2b (1.5 µg/kg once weekly for 48 weeks for genotype 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1400 mg orally in 2 divided doses)

c Target platelet count was ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. For ENABLE 1, 682 patients were randomised to the antiviral treatment phase; however, 2 patients then withdrew consent prior to receiving antiviral therapy

d *p*-value <0.05 for eltrombopag versus placebo

e 64% patients participating in ENABLE 1 and ENABLE 2 were genotype 1

f Post-hoc analyses

Other secondary findings of the studies included the following: significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, p<0.0001). A greater proportion of patients on eltrombopag did not require any antiviral dose reduction as compared to placebo (45% vs. 27%). Eltrombopag treatment delayed and reduced the number of peginterferon dose reductions.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with eltrombopag in all subsets of the paediatric population in secondary thrombocytopenia (see section 4.2 for information on paediatric use).

Severe aplastic anaemia

Eltrombopag was studied in a single-arm, single-centre, open-label study in 43 patients with SAA with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤ 30,000/µl.

The majority of patients, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 patients had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens. Patients with diagnosis of Fanconi anaemia, infection not responding to appropriate therapy, PNH clone size in neutrophils of ≥ 50%, where excluded from participation.

At baseline the median platelet count was 20,000/µl, haemoglobin was 8.4 g/dl, ANC was 0.58 x 10^9/l and absolute reticulocyte count was 24.3 x 10^9/l. Eighty-six percent of patients were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

The primary endpoint was haematological response assessed after 12 weeks of eltrombopag treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/µl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by > 1.5g/dl, or a reduction in ≥ 4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase > 0.5 x 10^9/l.

The haematological response rate was 40% (17/43 patients; 95% CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12. Eltrombopag was discontinued after 16 weeks if no haematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study. A total of 14 patients entered the extension phase of the trial. Nine of these patients achieved a multi-lineage response, 4 of the 9 remain on treatment and 5 tapered off treatment with eltrombopag and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months). The remaining 5 patients discontinued treatment, three due to relapse at the month 3 extension visit.

During treatment with eltrombopag 59% (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27% (10/37) became RBC transfusion independent (56 days without RBC transfusion). The longest platelet transfusion-free period for non-responders was 27 days (median). The longest platelet transfusion-free period for responders was 287 days (median). The longest RBC transfusion-free period for non-responders was 29 days (median). The longest RBC transfusion-free period for responders was 266 days (median).

Over 50% of responders who were transfusion-dependent at baseline, had >80% reduction in both platelet and RBC transfusion requirements compared to baseline.

Preliminary results from a supportive study (Study ELT116826), an ongoing non-randomised, phase II, single-arm, open-label study in refractory SAA patients, showed consistent results. Data are limited to 21 out of the planned 60 patients with haematological responses reported by 52% of patients at 6 months. Multilineage responses were reported by 45% of patients.

Paediatric population
The efficacy of oral eltrombopag in paediatric patients aged 2 to 17 years with refractory/relapsed (cohort A; n=14) or treatment-naive (cohort B; n=37) SAA was assessed in an open-label, uncontrolled, intra-patient dose escalation study (total N=51) (study CETB115E2201) (see also section 4.2). Cohort A consisted of 14 patients with refractory (6 patients) or relapsed (8 patients) SAA. These 14 patients received one of two treatment regimens: 1) eltrombopag plus horse antithymocyte globulin (hATG)/cyclosporine A (CsA) or 2) eltrombopag plus CsA. In cohort B, 37 ISTnaive SAA patients were treated with hATG and CsA in addition to eltrombopag. The treatment duration was 26 weeks with an additional 52-week follow-up period and long-term follow-up of up to three years.

Eltrombopag starting doses were 25 mg daily in patients aged from 1 to < 6 years and 50 mg daily in patients aged 6 to < 18 years, regardless of ethnicity. Intra-patient dose escalations were permitted every 2 weeks until the patient had either achieved the targeted platelet count or reached the maximum dose (150 mg), whichever occurred first.

The primary objective was to characterise the PK of eltrombopag at the highest individual steady-state dose (see section 5.2). Secondary efficacy objectives were to assess the overall response rate (ORR) and platelet response rate (PRR), and to evaluate platelet and red blood cell transfusion independence.

ORR was defined as the proportion of patients who had either a complete response (CR) or a partial response (PR). CR was defined as meeting the criteria platelet and red blood cell transfusion independence, normal age-adjusted haemoglobin, platelet count >100 x 10^9/l, and absolute neutrophil count > 1.5 x 10^9/l. PR was defined as meeting at least two or more of the following criteria: absolute reticulocyte count > 30 x 10^9/l, platelet count > 30 x 10^9/l, absolute neutrophil count >0.5 x 10^9/l above baseline with transfusion independence for at least 28 days for platelet transfusion and 56 days for red blood cell (RBC) transfusion. PRR was also defined as the proportion of patients who had either a complete response (CR) or a partial response (PR). CR was defined as meeting the criteria platelet count > 100 x 10^9/l. PR was defined as meeting the criteria platelet count > 30 x 10^9/l.

The median age of the overall population was 10 years old (range: 2 to 17 years), 54.9% of patients were male, and 58.8% of patients were Caucasian. The median body-mass index (BMI) was 17.9 kg/m^2. There were 12 patients aged < 6 years and 39 patients aged 6 to < 18 years. The ORR was 19.6% at Week 12, 52.9% at Week 26, 45.1% at Week 52, and 45.1% at Week 78 for all patients. The ORR was generally higher in Cohort A than in Cohort B (e.g. 71.4% vs. 45.9% at Week 26). The PRR was 47.1% at Week 12, 56.9% at Week 26, 51.0% at Week 52, and 49.0% at Week 78.

Twenty-eight (7 patients in Cohort A and 21 patients in Cohort B) of the 42 patients who were RBC transfusion-dependent at baseline achieved transfusion independence for at least 56 days during the study. The median of the longest RBC transfusion-free period was 266 days for 34 patients (range: 58 to 1,637), 321 days (range: 185 to 1,637 days) for Cohort A, and 262 days (range: 58 to 1,296 days) for Cohort B. Thirty-three (8 patients in Cohort A and 25 patients in Cohort B) of the 43 patients who were platelet transfusion-dependent at baseline achieved transfusion independence for at least 28 days during the study. The median of the longest platelet transfusion-free period was 263 days (range: 34 to 1 637 days) for 40 patients, 268 days (range: 36 to 1,637 days) for Cohort A, and 250 days (range: 34 to 1,289 days) for Cohort B.

Safety results were consistent with the known safety profile of eltrombopag (see section 4.8).

Efficacy results were not sufficient to conclude on the efficacy of eltrombopag in paediatric patients with SAA.

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 patients with ITP in studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP patients are presented (Table 12).

Table 12 Geometric mean (95% confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	AUC $_{(0-\tau)}$ [a] µg.h/ml	C_{max} [a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates.

Plasma eltrombopag concentration-time data collected in 590 patients with HCV enrolled in phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ estimates for adult patients with HCV enrolled in the phase III studies are presented for each dose studied in Table 13.

Table 13 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

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

$AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption and bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section 4.2). In a relative bioavailability study in adults, the eltrombopag powder for oral suspension delivered 22% higher plasma $AUC_{(0-\infty)}$ than the film-coated tablet formulation. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52%.

Distribution

Eltrombopag is highly bound to human plasma proteins (>99.9%), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation

Eltrombopag is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately

64% of plasma radiocarbon $AUC_{(0-\infty)}$. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination
Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59%) with 31% of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20% of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Pharmacokinetic interactions
Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50% was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter (IC_{50} value of 2.7 μM [1.2 μg/ml]). *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor (IC_{50} value of 2.7 μM [1.2 μg/ml]).

Special patient populations

Renal impairment
The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult patients with renal impairment. Following administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 32% to 36% lower in patients with mild to moderate renal impairment, and 60% lower in patients with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein-bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of eltrombopag have not been established in patients with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment
The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult patients with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of

eltrombopag was 41% higher in patients with mild hepatic impairment and 80% to 93% higher in patients with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein-bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111% (95% CI: 45% to 283%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see sections 4.2 and 4.4). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section 4.2).

Race
The influence of East-Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East-Asians) and 88 patients with ITP (18 East-Asians). Based on estimates from the population pharmacokinetic analysis, East-Asian ITP patients had approximately 49% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East-Asian patients who were predominantly Caucasian (see section 4.2).

The influence of East-/Southeast-Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East-Asians and 69 Southeast-Asians). Based on estimates from the population pharmacokinetic analysis, East-/Southeast-Asian patients had approximately 55% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2).

Gender
The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 23% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

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

Age
The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥ 75 years. Based on model estimate, elderly (≥ 65 years) patients had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

Paediatric population (aged 1 to 17 years)
The pharmacokinetics of eltrombopag have been evaluated in 168 paediatric ITP patients dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT-2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. The effects of race and sex on plasma eltrombopag CL/F estimates were consistent between paediatric and adult

patients. East-/Southeast-Asian paediatric ITP patients had approximately 43% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-Asian patients. Female paediatric ITP patients had approximately 25% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to male patients.

The pharmacokinetic parameters of eltrombopag in paediatric patients with ITP are shown in Table 14.

Table 14 Geometric mean (95% CI) steady-state plasma eltrombopag pharmacokinetic parameters in paediatric patients with ITP (50 mg once daily dosing regimen)

Age	**C_{max} (µg/ml)**	**AUC(0-□) (µg.hr/ml)**
12 to 17 years (n=62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n=68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n=38)	11.6 (10.4, 12.9)	162 (139, 187)

Data presented as geometric mean (95%CI). AUC(0-□) and C_{max} based on population PK post-hoc estimates.

Plasma eltrombopag PK data collected at the highest individual steady state dose from 38 paediatric patients with first-line (cohort B) or second-line (cohort A) SAA enrolled in study CETB115E2201 are presented after adjustment to a common 50 mg dose in Table 15. Overall, eltrombopag clearance was lower and eltrombopag plasma exposure was higher for patients aged 2 to < 6 years of age compared to patients aged 6 to < 18 years.

Table 15 Eltrombopag steady-state PK parameters in CETB115E2201, adjusted to a 50 mg dose, at the highest individual dose (Week 12 or later) by cohort and age group

Treatment	**Age group**	**Statistic**	**$AUC_{(0-\tau)}$ (µg.hr/ml)**	**C_{max} (µg/ml)**
Cohort A (N=11)	2 to < 6 years	n	1	1
		Geo-mean	272	16,1
		Geo-CV%		
	6 to < 18 years	n	5	7
		Geo-mean	306	14.5
		Geo-CV%	63.8	58,2
Cohort B (N=27)	2 to < 6 years	n	6	8
		Geo-mean	502	27,1
		Geo-CV%	65,6	40,6
	6 to < 18 years		10	15,
		Geo-mean	275	15,6
		Geo-CV%	52,6	47,2
Total patients (N=38)	2 to < 6 years	n	7	9,
		Geo-mean	460	25,6
		Geo-CV%	64,9	42,2
	6 to < 18 years	n	15	22
		Geo-mean	285	15,2
		Geo-CV%	54,2	49,5

Cohort A: eltrombopag administered as second-line treatment, Cohort B: eltrombopag administered as firstline treatment.

5.3 Preclinical safety data

Safety pharmacology and repeat-dose toxicity
Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure in adult ITP patients at 75 mg/day and 3 times the human clinical exposure in adult HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. At non-tolerated doses in pre-weaning juvenile rats dosed from Days 4-32 (approximately equating to a 2-year-old human at the end of the dosing period), ocular opacities were observed (histology not performed) at 9 times the maximum human clinical exposure in paediatric ITP patients at 75 mg/day, based on AUC. However, cataracts were not observed in juvenile rats given tolerated doses at 5 times the human clinical exposure in paediatric ITP patients, based on AUC. Cataracts have not been observed in adult dogs after 52 weeks of dosing at 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterised by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 or 0.8 times the human clinical exposure based on AUC in adult or paediatric ITP patients at 75 mg/day and 0.6 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in adult ITP patients and 3 and 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) and in dogs (52 weeks) at 4 or 2 times the human clinical exposure in adult ITP patients and 3 or 2 times the human clinical exposure in paediatric ITP patients at 75 mg/day and 2 times or equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

At poorly tolerated doses in rats and dogs (> 10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and>4 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short-term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times human clinical exposure in adult or paediatric ITP patients at 75 mg/day and ≤ 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Endosteal hyperostosis was observed in a 28-week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times or 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Carcinogenicity and mutagenicity

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 or 2 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times or 8 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day, based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Reproductive toxicity

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure in adult or adolescent (12-17 years old) ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV patients at 100 mg/day, based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioural or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

Phototoxicity

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 or 7 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) or ocular phototoxicity (≥ 4 times the human clinical exposure in adult or paediatric ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

Juvenile animal studies

At non-tolerated doses in pre-weaning rats, ocular opacities were observed. At tolerated doses, no ocular opacities were observed (see above subsection 'Safety pharmacology and repeat-dose toxicity'). In conclusion, taking into account the exposure margins based on AUC, a risk of eltrombopag-related cataracts in paediatric patients cannot be excluded. There are no findings in juvenile rats to suggest a greater risk of toxicity with eltrombopag treatment in paediatric vs. adult ITP patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, microcrystalline
Mannitol
Povidone
Isomalt (E 953)
Calcium silicate
Sodium starch glycolate
Magnesium stearate

Tablet coating
[Product name] 25 mg <and> <50 mg> film-coated tablets
Hypromellose
Titanium dioxide (E 171)
Iron oxide red (E 172)
Iron oxide yellow (E 172)
Triacetin

[Product name] 75 mg film-coated tablets
Hypromellose
Titanium dioxide (E171)
Iron oxide red (E 172)
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

[Product name] 25 mg, 50 mg and 75 mg film-coated tablets
oPA/Al/PVC-Al blisters packed in boxes containing 14, 28 or 84 film-coated tablets, unit-dose blisters packed in boxes containing 14x1, 28x1 or 84x1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zentiva, k.s.

U Kabelovny 130,
Dolní Měcholupy,
102 37 Praag 10
Tsjechië

8. MARKETING AUTHORISATION NUMBER(S)

RVG 130862
RVG 130863
RVG 130864

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 9 februari 2024

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.2, 4.8 en 5.1: 26 augustus 2026