

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets

Revolade 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Revolade 25mg film-coated tablets

Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

Revolade 50mg film-coated tablets

Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

25mg: White, round, biconvex film-coated tablet (approximately 10.3 mm in diameter) debossed with 'GS NX3' and '25' on one side.

50mg: Brown, round, biconvex film-coated tablet (approximately 10.3 mm in diameter) debossed with 'GS UFU' and '50' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revolade 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).

Revolade is indicated for the treatment of paediatric patients aged 6 years 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).

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

Revolade is indicated in combination with standard immunosuppressive therapy for the first-line treatment of adult and adolescent patients 12 years and older with severe aplastic anemia.

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

4.2 Posology and method of administration

Revolade 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

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

Immune (primary) thrombocytopenia

The lowest dose of Revolade to achieve and maintain a platelet count $\geq 50\,000/\mu\text{l}$ should be used. Dose adjustments are based upon the platelet count response. Revolade must not be used to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting Revolade and decreased within 1 to 2 weeks after discontinuation.

Adults and paediatric population aged 6 to 17 years

The recommended starting dose of Revolade is 50 mg once daily. For patients of East-/Southeast-Asian ancestry Revolade should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Monitoring and dose adjustment

After initiating Revolade, the dose must be adjusted to achieve and maintain a platelet count $\geq 50\,000/\mu\text{l}$ 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 Revolade and the dose regimen of Revolade modified based on platelet counts as outlined in Table 1. During therapy with Revolade full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count ($\geq 50\,000/\mu\text{l}$ 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 Revolade 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*.
$\geq 50\,000/\mu\text{l}$ to $\leq 150\,000/\mu\text{l}$	Use lowest dose of Revolade and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
>150 000/ μl to $\leq 250\,000/\mu\text{l}$	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 Revolade; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $\leq 100\,000/\mu\text{l}$, reinstitute therapy at a daily dose reduced by 25 mg.

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

♦ For patients taking 25 mg Revolade once daily, consideration should be given to dosing at 25 mg once every other day.

Revolade 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 Revolade.

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 Revolade dose adjustment, either decrease or increase, would be 25 mg once daily.

Discontinuation

Treatment with Revolade should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of Revolade 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 Revolade 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 Revolade. The aim of treatment with Revolade 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/ μ l. Platelet counts >75 000/ μ l should be avoided. The lowest dose of Revolade needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen

Revolade 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 Revolade 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 Revolade dose adjustments should be avoided (see Table 2).

During antiviral therapy, the dose of Revolade 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/ μ l. 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 Revolade once daily must not be exceeded.

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

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

* For patients taking 25 mg Revolade 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 Revolade dose reductions should be avoided.

Discontinuation

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

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

First-line Severe Aplastic Anemia

Initiate Revolade concurrently with standard immunosuppressive therapy.

Initial Dose Regimen:

The recommended initial *dose regimen* is listed in Table 3. Do not exceed the initial dose of Revolade.

Table 3. Recommended Initial Revolade Dose Regimen in the First-Line Treatment of Severe Aplastic Anemia

Age	Dose Regimen
Patients 12 Years and Older	150 mg once daily for 6 months

For patients with severe aplastic anemia of East-/Southeast-Asian ancestry or those with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, C), decrease the initial Revolade dose by 50 % as listed in Table 4.

If baseline ALT or AST levels are $> 6 \times$ ULN, do not initiate Revolade until transaminase levels are $< 5 \times$ ULN. Determine the initial dose for these patients based on Table 3 or Table 4.

Table 4. Recommended Initial Revolade Dose Regimen for Patients of Asian Ancestry or Those with Mild, Moderate, or Severe Hepatic Impairment (Child-Pugh Class A, B, C) in the First-Line Treatment of Severe Aplastic Anemia

Age	Dose Regimen
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Patients 12 Years and Older	75 mg once daily for 6 months
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Table 5. Dose of standard immunosuppressive therapy administered with Revolade in the first-line SAA pivotal study

Agent	Dose administered in the pivotal study
Horse antithymocyte globulin (h-ATG)	40 mg/kg/day, based on actual body weight, administered intravenously on Days 1 to 4 of the 6-month treatment period.
Cyclosporine* (therapeutic dose for 6 months, from Day 1 to Month 6, adjusted to obtain a target therapeutic trough level between 200 and 400 micrograms/L)	<u>Patients aged 12 years and older:</u> 3 mg/kg, based on actual body weight, orally every 12 hours (total daily dose of 6 mg/kg/day) for 6 months, starting on Day 1. <i>Patients >20 years of age with a body mass index >35 or patients aged 12 to 20 years with a body mass index >95th percentile:</i> 3 mg/kg, based on adjusted body weight [#] , orally every 12 hours (total daily dose of 6 mg/kg/day) for 6 months, starting on Day 1.
Cyclosporine (maintenance dose, from Month 6 to Month 24)	<u>For patients who achieve a hematologic response at 6 months:</u> 2 mg/kg/day administered orally at a fixed dose for an additional 18 months.

* Dose of cyclosporine may need to be adjusted to achieve the above recommended target trough levels when cyclosporine is used concomitantly with other therapies; refer to the appropriate cyclosporine prescribing information.

[#] Calculated as the midpoint between the ideal body weight and actual body weight.

Monitoring and Dose Adjustment:

Perform clinical hematology and liver tests regularly throughout therapy with Revolade.

Table 6. Dose Adjustments of Revolade for Elevated Platelet Counts in the First-line Treatment of Severe Aplastic Anemia.

Platelet Count Result	Dose Adjustment or Response
$> 200 \times 10^9/L$ to $\leq 400 \times 10^9/L$	Decrease the daily dose by 25 mg every 2 weeks to the lowest dose that maintains platelet count $\geq 50 \times 10^9/L$.
$> 400 \times 10^9/L$	Discontinue Revolade for one week. Once the platelet count is $< 200 \times 10^9/L$, reinitiate Revolade at a daily dose reduced by 25 mg.

Table 7 summarises the recommendations for dose interruption, reduction, or discontinuation of Revolade in the management of elevated liver transaminase levels and thromboembolic events.

Table 7. Recommended Dose Modifications for Revolade for ALT and AST Elevations and Thromboembolic Events.

Event	Recommendation
ALT or AST Elevations	<u>Increase in ALT or AST $> 6 \times ULN$</u> Discontinue Revolade. Once ALT or AST is $< 5 \times ULN$, reinitiate Revolade at the same dose. <u>Increase in ALT or AST $> 6 \times ULN$ after reinitiating Revolade</u> Discontinue Revolade and monitor ALT or AST at least every 3 to 4 days. Once ALT or AST is $< 5 \times ULN$, reinitiate Revolade at a daily dose reduced by 25 mg compared to the previous dose.

	<u>If ALT or AST returns to > 6 x ULN on the reduced dose</u> Reduce the daily dose of Revolade by 25 mg until ALT or AST is < 5 x ULN.
Thromboembolic events (e.g., deep vein thrombosis (DVT), pulmonary embolus (PE), stroke, myocardial infarction)	Discontinue Revolade but remain on horse antithymocyte globulin (h-ATG) and cyclosporine

The total duration of Revolade treatment is 6 months.

Refractory Severe Aplastic Anaemia

Initial dose regimen

Revolade should be initiated at a dose of 50 mg once daily. For patients of East-/Southeast-Asian ancestry, Revolade 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 Revolade (see section 5.1). The dose of Revolade should be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count $\geq 50\,000/\mu\text{l}$. 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 Revolade and the dosage regimen of Revolade modified based on platelet counts as outlined in Table 8.

Table 8 Dose adjustments of Revolade 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.
$\geq 50\,000/\mu\text{l}$ to $\leq 150\,000/\mu\text{l}$	Use lowest dose of Revolade to maintain platelet counts.
>150 000/ μl to $\leq 250\,000/\mu\text{l}$	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 Revolade; for at least one week. Once the platelet count is $\leq 100\,000/\mu\text{l}$, reinstitute 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 Revolade may be reduced by 50%.

If counts remain stable after 8 weeks at the reduced dose, then Revolade 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) <0.5 $\times 10^9/\text{l}$ Revolade may be reinitiated at the previous effective dose.

Discontinuation

If no haematological response has occurred after 16 weeks of therapy with Revolade, therapy should be discontinued. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of

Revolade is appropriate (see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 8) or important liver test abnormalities also necessitate discontinuation of Revolade (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 Revolade with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2).

Hepatic impairment

Revolade 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 Revolade is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of Revolade 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 refractory severe aplastic anaemia patients with hepatic impairment should initiate Revolade at a dose of 25 mg once daily (see section 5.2). After initiating the dose of Revolade 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 Revolade, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

In a clinical trial in definitive immunosuppressive therapy-naïve severe aplastic anemia patients with baseline AST/ALT $> 5 \times$ ULN were ineligible to participate. The initial dose of Revolade in patients with hepatic impairment in the first-line setting should be determined as necessary based on clinical judgement, tolerability, and close monitoring of liver function.

Elderly

There are limited data on the use of Revolade in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of Revolade, overall no clinically significant differences in safety of Revolade 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 Revolade 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, Revolade should be initiated at a dose of 25 mg once daily for the treatment of ITP, HCV-associated thrombocytopenia, and refractory SAA (see section 5.2). For the treatment of patients with first-line SAA refer to Posology and method of administration.

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

Paediatric population

Revolade is not recommended for use in children under the age of one year with ITP due to insufficient data on safety and efficacy. In paediatric clinical trials, subjects between 1 to 5 years of age were administered Revolade as a powder for oral suspension formulation. Revolade is only available as tablets and cannot be used in patients who are unable to swallow Revolade tablets whole. The safety and efficacy of Revolade has not been established in children and adolescents (<18 years) with chronic HCV related thrombocytopenia or SAA. No data are available.

Method of administration

Oral use.

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

4.3 Contraindications

Hypersensitivity to Revolade 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 Revolade 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 ≤ 35 g/l) compared with the group overall. Treatment with Revolade 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

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

In a single-arm open-label clinical trial in definitive immunosuppressive therapy-naïve SAA patients who received Revolade concurrently with h-ATG and cyclosporine, ALT or AST >3 x ULN with total bilirubin >1.5 x ULN was reported in 43.5 % (40/92) of patients. None of these elevations resulted in discontinuation.

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

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin should be measured prior to initiation of Revolade, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Revolade 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. Revolade should be discontinued if ALT levels increase (≥ 3 times the upper limit of normal [$\times$ ULN] in patients with normal liver function, or $\geq 3 \times$ baseline or $>5 \times$ 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.

In the first-line setting of severe aplastic anemia, ALT, AST, and bilirubin should be measured prior to initiation of Revolade. During treatment, increases in ALT levels should be managed as recommended in Table 7.

Isolated cases of severe liver injury were identified in clinical trials. The elevation of liver laboratory values occurred approximately three months after initiation of Revolade. In all cases, the event resolved following Revolade discontinuation. No cases were identified from clinical trials in refractory SAA, however the number of exposed patients in this indication was limited. As the highest authorized dose is given to patients in SAA indication (150 mg/day) and due to the nature of the reaction, drug induced liver injury might be expected in this patient's population

Caution is required when administering Revolade to patients with hepatic disease. In ITP and SAA patients a lower starting dose of Revolade 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 Revolade 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. Revolade 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. Revolade 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 Revolade 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 Revolade 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. Revolade 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 Revolade once daily for 2 weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving Revolade 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 Revolade experienced the thrombotic complication at a platelet count $>200\,000/\mu\text{l}$ and within 30 days of the last dose of Revolade. Revolade is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In Revolade clinical studies in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering Revolade 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 Revolade 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.

Revolade 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 Revolade to patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of Revolade

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with Revolade. Following discontinuation of Revolade, 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 Revolade treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with Revolade 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 Revolade.

In HCV clinical studies, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and Revolade. 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

Revolade 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 Revolade, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of Revolade, 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 Revolade 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 Revolade have not been established for the treatment of thrombocytopenia due to MDS. Revolade 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 Revolade increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II refractory SAA clinical study with Revolade 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 Revolade 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 Revolade therapy and one patient had cytogenetic abnormality at Month 6.

In clinical studies with Revolade in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of Revolade 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 Revolade, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of Revolade is appropriate.

Ocular changes

Cataracts were observed in toxicology studies of Revolade 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 Revolade group and 5% of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients

receiving interferon, ribavirin and Revolade (2% of the Revolade 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 Revolade 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 Revolade

A loss of response or failure to maintain a platelet response with Revolade 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

Revolade 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 Revolade. If the laboratory results and clinical observations are inconsistent, re-testing using another method may help in determining the validity of the result.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Revolade on other medicinal products

HMG CoA reductase inhibitors

Administration of Revolade 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 Revolade, 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 Revolade 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, Revolade (up to 100 μ M) 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 Revolade 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 Revolade and CYP450 substrates are co-administered (see section 5.2).

HCV protease inhibitors

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

Co-administration of a single dose of Revolade 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 Revolade

Ciclosporin

A decrease in Revolade 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 Revolade by 25% and 18%, respectively. The co-administration of 600 mg ciclosporin decreased the C_{max} and the $AUC_{0-\infty}$ of Revolade by 39% and 24%, respectively. Revolade 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 Revolade is co-administered with ciclosporin. Revolade dose may need to be increased based on these platelet counts.

Polyvalent cations (chelation)

Revolade chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of Revolade 75 mg with a polyvalent cation-containing antacid (1 524 mg aluminium hydroxide and 1 425 mg magnesium carbonate) decreased plasma Revolade $AUC_{0-\infty}$ by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62%, 76%). Revolade 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 Revolade absorption due to chelation (see sections 4.2 and 5.2).

Lopinavir/ritonavir

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

CYP1A2 and CYP2C8 inhibitors and inducers

Revolade 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 Revolade concentrations, whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) Revolade 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 Revolade 200 mg did not alter plasma Revolade exposure to a clinically significant extent.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with Revolade in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining Revolade 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 Revolade tablet with a high-calcium meal (e.g. a meal that included dairy products) significantly reduced plasma Revolade $AUC_{0-\infty}$ and C_{max} . In contrast, the administration of Revolade 2 hours before or 4 hours after a high-calcium meal or with low-calcium food [<50 mg calcium] did not alter plasma Revolade exposure to a clinically significant extent (see section 4.2).

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

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 Revolade 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 Revolade in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females

Revolade is not recommended in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether Revolade / metabolites are excreted in human milk. Studies in animals have shown that Revolade 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 Revolade 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

Revolade has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of Revolade, 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 Revolade 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 Revolade 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 Revolade 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 Revolade (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 Revolade (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 ($\geq 3\%$ 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 Revolade) and ENABLE 2 (TPL108390 n=805) were randomised, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of Revolade 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 (Revolade treatment n=450, placebo treatment n=232) and ENABLE 2 (Revolade treatment n=506, placebo treatment n=252). Patients are analysed according to the treatment received (total safety double-blind population, Revolade 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.

Definitive immunosuppressive therapy-naïve severe aplastic anemia in adult and paediatric patients

The safety of Revolade administered in combination with horse antithymocyte globulin (h-ATG) and cyclosporine to patients with severe aplastic anemia who had not received prior definitive immunosuppressive therapy (i.e., ATG therapy, alemtuzumab, or high dose cyclophosphamide) was evaluated in a single-arm, sequential cohort study (see Clinical studies). A total of 154 patients were enrolled and 153 were dosed in this study, of which 92 patients were enrolled to the cohort where

Revolade, h-ATG, and cyclosporine were initiated concurrently at the recommended dose and schedule (Cohort 3 regimen): Revolade up to 150 mg once daily on Day 1 to Month 6 (D1-M6) in combination with h-ATG on Days 1 to 4 and cyclosporine for 6 months, followed by low dose of cyclosporine (maintenance dose) for an additional 18 months for patients who achieved a hematologic response at 6 months. The median duration of exposure to Revolade in this cohort was 183 days with 83.7% of patients exposed for >12 weeks. Adverse drug reactions for the first-line SAA study population (N=92) are shown in Table 11.

The most common adverse drug reactions occurring in at least 10% of patients were alanine aminotransferase increased, aspartate aminotransferase increased, and blood bilirubin increased (including ocular icterus)

Refractory severe aplastic anaemia in adult patients

The safety of Revolade in refractory severe aplastic anaemia 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.

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 definitive immunosuppressive therapy-naïve SAA (first-line SAA) study population (N=92), the SAA studies (N=43) and post-marketing reports are listed below by MedDRA system organ class and by frequency. 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ to $< 1/1\ 000$); not known (cannot be estimated from the available data).

Table 9: 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 10: 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 11: Definitive immunosuppressive therapy-naïve SAA (first-line SAA) study population

Revolade in combination with standard immunosuppressive therapy

System organ class	Frequency	Adverse reaction
Gastrointestinal disorders	common	Nausea, Diarrhoea, Abdominal pain
Skin and subcutaneous tissue disorders	common	Rash, Skin discolouration including hyperpigmentation
Investigations	very common	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased (including ocular icterus)

The only adverse drug reaction associated with Revolade reported in definitive immunosuppressive therapy-naïve SAA patients not previously reported in the refractory SAA study population is skin discolouration including skin hyperpigmentation (5.4 %). In definitive immunosuppressive therapy-naïve SAA patients, blood bilirubin increased was reported more frequently (17.4 %) than in the refractory SAA study population.

New or worsening liver function laboratory abnormalities (CTCAE Grade 3 and Grade 4) in the Revolade D1-M6 cohort were 15.2% and 2.2% for AST, 26.4% and 4.3% for ALT, and 12.1% and 1.1% for bilirubin, respectively.

Paediatric patients

The safety assessment of Revolade in definitive immunosuppressive therapy-naïve paediatric SAA patients 2 to 17 years old is based on 37 patients enrolled in the single-arm, sequential cohort study: 2 patients aged 2 to 5 years, 12 patients aged 6 to 11 years, and 23 patients aged 12 to 17 years (*see Clinical Studies*). The safety profile in paediatric patients was consistent with the safety profile observed in the overall population.

Table 12: SAA study population

System organ class	Frequency	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, gingival bleeding, abdominal pain
	Common	Oral mucosal blistering, oral pain, vomiting, abdominal discomfort, constipation, 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* * Cases of drug-induced liver injury have been reported in patients with ITP and HCV
Skin and subcutaneous tissue disorders	Common	Petechiae, rash, pruritus, urticaria, skin lesion, rash macular
	Not known	Skin discolouration, skin hyperpigmentation
Musculoskeletal 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 Revolade (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 Revolade 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 Revolade 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 $\geq 200\ 000/\mu\text{l}$ (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n=1 439), 38 out of 955 patients (4%) treated with Revolade 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 Revolade versus < 1% for placebo) (see section 4.4). Patients with low albumin levels ($\leq 35\text{ g/l}$) 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 Revolade 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. Revolade 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 Revolade, 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 Revolade 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 Revolade 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 Revolade and placebo groups, respectively. Most patients receiving Revolade 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 Revolade 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 Revolade 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, Revolade treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities

In the single-arm study in patients with definitive immunosuppressive therapy-naïve SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. In the entire study across all cohorts, clonal cytogenetic evolution occurred in 15 out of 153 (10%) patients. Of the 15 patients who experienced a cytogenetic abnormality, 7 patients had the loss of chromosome 7, six of which occurred within 6.1 months; 4 patients had chromosomal aberrations which were of unclear significance; 3 patients had a deletion of chromosome 13, which is considered a good prognostic factor in aplastic anemia; and 1 patient had a follow-up bone marrow assessment at 5 years with features of dysplasia with hypercellularity concerning for potential development of MDS. In the Revolade D1-M6 cohort, 7 patients had a new cytogenetic abnormality reported of which 4 had the loss of chromosome 7, occurring within 6.1 months. It is unclear whether these findings occurred due to the underlying disease, the immunosuppressive therapy, and/or treatment with Revolade.

In the phase II refractory SAA clinical study with Revolade 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 Revolade 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 Revolade 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 Revolade, 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.

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 Revolade and thus limit absorption. Platelet counts should be closely monitored. Treatment with Revolade 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 5 000 mg of Revolade. 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/ μ l on Day 18 after ingestion and the maximum platelet count was 929 000/ μ l. All events were resolved without sequelae following treatment.

Because Revolade 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 Revolade.

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. Revolade 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 Revolade in adult patients with previously treated ITP. Overall, Revolade 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 Revolade 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, Revolade (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 Revolade was adjusted during the 6-month treatment period based on individual platelet counts. All patients initiated treatment with Revolade 50 mg. From Day 29 to the end of treatment, 15 to 28% of Revolade 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/ μ l for both treatment groups and in the Revolade group were maintained above 50 000/ μ l at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained < 30 000/ μ l throughout the study.

Platelet count response between 50 000-400 000/ μ l in the absence of rescue treatment was achieved by significantly more patients in the Revolade treated group during the 6-month treatment period, $p < 0.001$. Fifty-four percent of the Revolade-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 13 Secondary efficacy results from RAISE

	Revolade 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)
<i>p</i> -value ^a	<0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
<i>p</i> -value ^a	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
<i>p</i> -value ^a	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
<i>p</i> -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)
<i>p</i> -value ^a	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33%) patients treated with Revolade 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 Revolade-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 Revolade (n=76) to placebo (n=38).

Table 14 Efficacy results from TRA100773B

	Revolade N=74	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)
<i>p</i> -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)
<i>p</i> -value ^a	0.029	

a Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to Revolade relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count ($\leq 15\ 000/\mu\text{l}$, $>15\ 000/\mu\text{l}$) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count $\leq 15\ 000/\mu\text{l}$ the median platelet counts did not reach the target level ($>50\ 000/\mu\text{l}$), although in both studies 43% of these patients treated with Revolade responded after 6 weeks of treatment. In addition, in the RAISE study, 42% of patients with baseline platelet count $\leq 15\ 000/\mu\text{l}$ treated with Revolade responded at the end of the 6-month treatment period. Forty-two to 60% of the Revolade-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 Revolade has demonstrated no loss of response.

EXTEND (TRA105325):

Revolade 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 $19\ 000/\mu\text{l}$ prior to Revolade administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were $85\ 000/\mu\text{l}$, $85\ 000/\mu\text{l}$, $105\ 000/\mu\text{l}$, $64\ 000/\mu\text{l}$, $75\ 000/\mu\text{l}$, $119\ 000/\mu\text{l}$ and $76\ 000/\mu\text{l}$, respectively.

TAPER (CETB115J2411):

This was a single-arm phase II study including ITP patients treated with Revolade after first-line corticosteroid failure irrespective of time since diagnosis. A total of 105 patients were enrolled on the study and started Revolade treatment on 50 mg once daily (25 mg once daily for patients of East-/Southeast-Asian ancestry). The dose of Revolade was adjusted during the treatment period based on individual platelet counts with the goal to achieve a platelet count $\geq 100\ 000/\mu\text{l}$.

Of the 105 patients who were enrolled in the study and who received at least one dose of Revolade, 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 $\geq 100\ 000/\mu\text{l}$ and maintained platelet counts around $100\ 000/\mu\text{l}$ for 2 months (no counts below $70\ 000/\mu\text{l}$) were eligible for tapering off Revolade and

treatment discontinuation. To be considered as having achieved a sustained response off treatment, a patient had to maintain platelet counts $\geq 30\,000/\mu\text{l}$, 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 $< 30\,000/\mu\text{l}$) occurred, patients were offered a new course of Revolade at the appropriate starting dose.

Eighty-nine patients (84.8%) achieved a complete response (platelet count $\geq 100\,000/\mu\text{l}$) (Step 1, Table 15) and 65 patients (61.9%) maintained the complete response for at least 2 months with no platelet counts below $70\,000/\mu\text{l}$ (Step 2, Table 15). Forty-four patients (41.9%) were able to be tapered off Revolade until treatment discontinuation while maintaining platelet counts $\geq 30\,000/\mu\text{l}$ in the absence of bleeding events or the use of rescue therapy (Step 3, Table 15).

The study met the primary objective by demonstrating that Revolade 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 15). 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 15).

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 Revolade treatment, 12 patients had a loss of response, 8 of them re-started Revolade 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 Revolade 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 Revolade 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 Revolade in patients with ITP.

Table 15 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 $\geq 100\ 000/\mu\text{l}$ at least once	89 (84.8)	(76.4, 91.0)		
Step 2: Patients who maintained stable platelet count for 2 months after reaching $100\ 000/\mu\text{l}$ (no counts $< 70\ 000/\mu\text{l}$)	65 (61.9)	(51.9, 71.2)		
Step 3: Patients who were able to be tapered off Revolade until treatment discontinuation, maintaining platelet count $\geq 30\ 000/\mu\text{l}$ 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 $\geq 30\ 000/\mu\text{l}$ 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 $\geq 30\ 000/\mu\text{l}$ 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 response to Revolade 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 Revolade for a median (Q1-Q3) duration of 6.2 months (2.3-12.0 months). The median (Q1-Q3) platelet count at baseline was $16\ 000/\mu\text{l}$ (7 800-28 000/ μl).

Platelet count response, defined as a platelet count $\geq 50\ 000/\mu\text{l}$ 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 $\geq 100\ 000/\mu\text{l}$ 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 $\geq 50\ 000/\mu\text{l}$ 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 Revolade was consistent across all ITP categories and in line with its known safety profile.

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

Paediatric population (aged 1 to 17 years)

The safety and efficacy of Revolade 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 Revolade, compared to placebo, achieving platelet counts $\geq 50\ 000/\mu\text{l}$ 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 $< 30\ 000/\mu\text{l}$. Ninety-two patients were randomised by three age cohort strata (2:1) to Revolade (n=63) or placebo (n=29). The dose of Revolade could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of Revolade 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 16).

Table 16 Sustained platelet response rates by age cohort in paediatric patients with chronic ITP

	Revolade 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 Revolade 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 Revolade group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of Revolade 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 $\geq 50\ 000/\mu\text{l}$ 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 $< 30\ 000/\mu\text{l}$ (n=67). During the randomised period of the study, patients were randomised by three age cohort strata (2:1) to

Revolade (n=45) or placebo (n=22). The dose of Revolade could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of Revolade 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 Revolade 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 Revolade 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 Revolade (n=201, 21%) achieved SVR compared to those treated with placebo (n=65, 13%) (see Table 17). 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 17 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%)	
	Revolade	Placebo	Revolade	Placebo	Revolade	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
<i>HCV RNA Genotype</i>						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6 ^e	15	8	18	10	13	7
<i>Albumin levels ^f</i>						
≤ 35g/l	11	8				
> 35g/l	25	16				
<i>MELD score^f</i>						
≥ 10	18	10				
< 10	23	17				

- a Revolade 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 1 200 mg daily in 2 divided doses orally)
- b Revolade 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 1 400 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 Revolade 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 Revolade prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, *p*=<0.0001). A greater proportion of patients on Revolade did not require any antiviral dose reduction as compared to placebo (45% vs. 27%). Revolade treatment delayed and reduced the number of peginterferon dose reductions.

Definitive immunosuppressive therapy-naïve severe aplastic anemia study

Revolade in combination with horse antithymocyte globulin (h-ATG) and cyclosporine was investigated in a single-arm, single-center, open-label sequential cohort trial in patients with severe aplastic anemia who had not received prior definitive immunosuppressive therapy (i.e., ATG therapy, alemtuzumab, or high dose cyclophosphamide). The multiple cohorts differed by treatment start day and duration of Revolade-treatment and the initiation of low dose of cyclosporine (maintenance dose) for patients who achieved a hematologic response at 6 months. A total of 153 patients received Revolade in sequential cohorts:

- Revolade on Day 14 to Month 6 (D14-M6) plus h-ATG and cyclosporine (the trial's Cohort 1 regimen, n=30).

- Revolade on Day 14 to Month 3 (D14-M3) plus h-ATG and cyclosporine (the trial's Cohort 2 regimen, n=31), with half of the patients eligible to receive low dose of cyclosporine (maintenance dose) if they achieved a hematologic response at 6 months.
- Revolade on Day 1 to Month 6 (D1-M6) plus h-ATG and cyclosporine (the trial's Cohort 3 regimen, n=92), with all patients eligible to receive low dose of cyclosporine (maintenance dose) if they achieved a hematologic response at 6 months.

The starting dose of Revolade for adults and adolescent patients aged 12 to 17 years was 150 mg once daily (a reduced dose of 75 mg was administered for East-/Southeast Asians), 75 mg once daily for patients aged 6 to 11 years (a reduced dose of 37.5 mg was administered for East-/Southeast Asians), and 2.5 mg/kg once daily for patients aged 2 to 5 years (a reduced dose of 1.25 mg/kg was administered for East-/Southeast Asians). The dose of Revolade was reduced if the platelet count exceeded 200,000/microL and interrupted and reduced if it exceeded 400,000/microL.

All patients received h-ATG 40 mg/kg/day on Days 1 to 4 of the 6-month treatment period and a total daily dose of 6 mg/kg/day of cyclosporine for 6 months in patients aged 12 years and older or a total daily dose of 12 mg/kg/day for 6 months in patients aged 2 to 11 years. A 2 mg/kg/day maintenance dose of cyclosporine was administered for an additional 18 months to 15 patients who achieved a hematologic response at 6 months in the Revolade D14-M3 cohort and all patients who achieved a hematologic response at 6 months in the Revolade D1-M6 cohort.

Data from the recommended schedule of Revolade on Day 1 to Month 6 in combination with h-ATG and cyclosporine (the trial's Cohort 3 regimen) are presented below. This cohort had the highest complete response rates.

In the Revolade D1-M6 cohort, the median age was 28 years (range 5 to 82 years) with 16.3 % and 28.3 % of patients $\geq$ 65 years of age and $<$ 18 years of age, respectively. 45.7 % of patients were male and the majority of patients were White (62.0 %).

The efficacy of Revolade in combination with h-ATG and cyclosporine was established on the basis of complete hematological response at 6 months. A complete response was defined as hematological parameters meeting all 3 of the following values on 2 consecutive serial blood count measurements at least one week apart: absolute neutrophil count (ANC) $>$ 1,000/microL, platelet count $>$ 100,000/microL and hemoglobin $>$ 10 g/dL. A partial response was defined as blood counts no longer meeting the standard criteria for severe pancytopenia in severe aplastic anemia equivalent to 2 of the following values on 2 consecutive serial blood count measurements at least one week apart: ANC $>$ 500/microL, platelet count $>$ 20,000/microL, or reticulocyte count $>$ 60,000/microL

Table 18: Efficacy results in definitive immunosuppressive therapy-naïve SAA patients.

	Rev/Pro D1-M6 + h-ATG + cyclosporine N=92
Month 3, n^a	88
Overall response, n (%)	66 (75.0)
[95 % CI]	[64.6, 83.6]
Complete response, n (%)	24 (27.3)
[95 % CI]	[18.3, 37.8]
Month 6, n^a	87
Overall response, n (%)	69 (79.3)
[95 % CI]	[69.3, 87.3]
Complete response, n (%)	38 (43.7)
[95 % CI]	[33.1, 54.7]

	Rev/Pro D1-M6 + h-ATG + cyclosporine N=92
Median duration of overall response, n ^b Months (95 % CI)	70 24.3 (21.4, NE)
Median duration of complete response, n ^b Months (95 % CI)	46 24.3 (23.0, NE)

**a The number of patients who reached the 3- or 6-month assessment or withdrew earlier is the denominator for percentage calculation*

^b Number of responders at any time

NE = not estimable

The overall and complete hematological response rates at Year 1 (N=78) are 56.4 % and 38.5 % and at Year 2 (N=62) are 38.7 % and 30.6 % respectively.

Paediatric patients

Thirty seven patients aged 2 to 17 years were enrolled in the single-arm, sequential-cohort trial. Of the 36 patients who reached the 6-month assessment point or withdrew earlier, the complete response rate at 6 months was 30.6 % (0/2 in patients aged 2 to 5 years, 1/12 in patients aged 6 to 11 years, and 10/22 in patients aged 12 to 17 years) and the overall response rate at 6 months was 72.2 % (2/2 in patients aged 2 to 5 years, 7/12 in patients aged 6 to 11 years, and 17/22 in patients aged 12 to 17 years). Out of 25 evaluable patients in the Revolade D1-M6 cohort, the complete response rate at 6 months was 28 % (7/12) and the overall response rate at 6 months was 68 %.

Refractory severe aplastic anaemia

Revolade was studied in a single-arm, single-centre open-label study in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count $\leq 30\,000/\mu\text{L}$.

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 $\geq 50\%$, were excluded from participation.

At baseline the median platelet count was $20\,000/\mu\text{L}$, haemoglobin was 8.4 g/dl, ANC was $0.58 \times 10^9/\text{L}$ and absolute reticulocyte count was $24.3 \times 10^9/\text{L}$. 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 Revolade treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to $20\,000/\mu\text{L}$ above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by $>1.5\text{g/dL}$, 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 $>0.5 \times 10^9/\text{L}$.

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. Revolade 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 Revolade 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 Revolade 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.

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma Revolade 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 Revolade AUC_(0-τ) and C_{max} estimates for ITP patients are presented (Table 19).

Table 19 Geometric mean (95% confidence intervals) of steady-state plasma Revolade pharmacokinetic parameters in adults with ITP

Revolade dose, once daily	N	AUC _(0-τ) ^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-τ) and C_{max} based on population PK post-hoc estimates.

Plasma Revolade 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 Revolade C_{max} and AUC_(0-τ) estimates for patients with HCV enrolled in the phase III studies are presented for each dose studied in Table 20.

Table 20 Geometric mean (95% CI) steady-state plasma Revolade pharmacokinetic parameters in patients with chronic HCV

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

Data presented as geometric mean (95% CI).

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

The pharmacokinetic parameters of Revolade after administration of Revolade 150mg to 45 patients with definitive immunosuppressive therapy-naïve severe aplastic anemia are shown in Table 21.

Table 21: Steady-state plasma Revolade pharmacokinetic parameters in patients with definitive immunosuppressive therapy-naïve severe aplastic anemia

Revolade dose (once daily)	N	Cmax (microg/mL)	AUCtau (microg.h/mL)
150 mg	45	40.1 (44.9 %)	772 (47.2 %)

Data presented as geometric mean (geometric mean coefficient of variation)

Absorption and bioavailability

Revolade is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of Revolade concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces Revolade exposure (see section 4.2). The absolute oral bioavailability of Revolade 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 Revolade solution dose was estimated to be at least 52%.

Distribution

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

Biotransformation

Revolade is primarily metabolised through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, Revolade accounted for approximately 64% of plasma radiocarbon AUC_{0-∞}. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of Revolade. 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 Revolade is extensively metabolised. The predominant route of Revolade excretion is via faeces (59%) with 31% of the dose found in the urine as metabolites. Unchanged parent compound (Revolade) is not detected in urine. Unchanged Revolade excreted in faeces accounts for approximately 20% of the dose. The plasma elimination half-life of Revolade is approximately 21-32 hours.

Pharmacokinetic interactions

Based on a human study with radiolabelled Revolade, glucuronidation plays a minor role in the metabolism of Revolade. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for Revolade glucuronidation. Revolade 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 Revolade.

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

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

Revolade 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 Revolade is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter (IC₅₀ value of 2.7 µM [1.2 µg/ml]). *In vitro* studies also demonstrated that Revolade is a breast cancer resistance protein (BCRP) substrate and inhibitor (IC₅₀ value of 2.7 µM [1.2 µg/ml]).

Special patient populations

Renal impairment

The pharmacokinetics of Revolade have been studied after administration of Revolade to adult patients with renal impairment. Following administration of a single 50 mg dose, the AUC_{0-∞} of Revolade 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 Revolade (active) concentrations for this highly protein-bound medicinal product were not measured. Patients with impaired renal function should use Revolade with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of Revolade have not been established in patients with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment

The pharmacokinetics of Revolade have been studied after administration of Revolade to adult patients with hepatic impairment. Following the administration of a single 50 mg dose, the AUC_{0-∞} of Revolade 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 Revolade (active) concentrations for this highly protein-bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of Revolade 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 Revolade $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma Revolade $AUC_{(0-\tau)}$ values.

Therefore, Revolade 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 Revolade at a dose of 25 mg once daily (see section 4.2).

Race

The influence of East-Asian ethnicity on the pharmacokinetics of Revolade 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 Revolade $AUC_{(0-\tau)}$ 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 Revolade 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 Revolade $AUC_{(0-\tau)}$ 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 Revolade 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 Revolade $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

The influence of gender on Revolade 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 Revolade $AUC_{(0-\tau)}$ as compared to male patients.

Age

The influence of age on Revolade 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 Revolade in patients ≥ 75 years. Based on model estimate, elderly (≥ 65 years) patients had approximately 41% higher plasma Revolade $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

Paediatric population (aged 1 to 17 years)

The pharmacokinetics of Revolade have been evaluated in 168 paediatric ITP patients dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT-2. Plasma Revolade apparent clearance following oral administration (CL/F) increased with increasing body weight. The effects of race and sex on plasma Revolade CL/F estimates were consistent between paediatric and adult patients. East-/Southeast-Asian paediatric ITP patients had approximately 43% higher plasma Revolade $AUC_{(0-\tau)}$ values as compared to non-Asian patients. Female paediatric ITP patients had approximately 25% higher plasma Revolade $AUC_{(0-\tau)}$ values as compared to male patients.

The pharmacokinetic parameters of Revolade in paediatric patients with ITP are shown in Table 22.

Table 22 Geometric mean (95% CI) steady-state plasma Revolade pharmacokinetic parameters in paediatric patients with ITP (50 mg once daily dosing regimen)

Age	C _{max} (µg/ml)	AUC _(0-τ) (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-τ) and C_{max} based on population PK post-hoc estimates

5.3 Preclinical safety data

Safety pharmacology and repeat-dose toxicity

Revolade 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 Revolade 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

Revolade 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). Revolade 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, Revolade was marginally positive (<3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that Revolade does not pose a genotoxic risk to humans.

Reproductive toxicity

Revolade 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, Revolade 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. Revolade should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Revolade 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). Revolade 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 Revolade was likely via lactation.

Phototoxicity

In vitro studies with Revolade 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 Revolade 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 Revolade-related cataracts in paediatric patients cannot be excluded. There are no findings in juvenile rats to suggest a greater risk of toxicity with Revolade treatment in paediatric vs. adult ITP patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Revolade 25mg film-coated tablets

Tablet core

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Sodium starch glycolate

Tablet coating

Hypromellose

Macrogol 400

Polysorbate 80

Titanium dioxide (E171)

Revolade 50 mg film-coated tablets

Tablet core

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Sodium starch glycolate

Tablet coating

Hypromellose

Iron oxide red (E172)

Iron oxide yellow (E172)

Macrogol 400

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 30°C.

6.4 Nature and contents of container

Film-coated tablets

Aluminum blisters (PA/Alu/PVC/Alu) in a carton containing 14 or 28 film-coated tablets and multipacks containing 84 (3 packs of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.5 Special precautions for disposal

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

Product Registration Holder

Novartis Corporation (Malaysia) Sdn. Bhd.
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Malaysian Package Leaflet

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18 Aug 2023

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Novartis Pharma AG, Basel, Switzerland