17 October 2019
EMA/CHMP/620491/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revolade

International non-proprietary name: eltrombopag

Procedure No. EMEA/H/C/001110/II/0049

Note

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

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List of abbreviations

AA	Aplastic anemia
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
BCSH	British committee for standards in haematology
BUN	Blood urea nitrogen
CR	Complete response
CRADA	Cooperative research and development agreement
CsA	Cyclosporine A
CTCAE	Common terminology criteria for adverse events
DBIL	Direct bilirubin
DME	Designated medical events
EBMT	European group for blood and marrow transplantation
EMA	European medicines agency
EU	European union
FDA	Food and drug administration
GGT	Gamma-glutamyltransferase
GPI	Glucose phosphate isomerase
GSK	GlaxoSmithKline
h-ATG	Horse anti-thymocyte globulin
HCV	Hepatitis C virus
HRQL	Health-related quality of life
HSC	Hematopoietic stem cells
HSCP	Hematopoietic stem progenitor cells
HSCT	Hematopoietic stem cell transplantation
IST	Immunosuppressive therapy
ITP	Immune thrombocytopenia
MAA	Moderate aplastic anemia
MedDRA	Medical dictionary for regulatory activities
NHLBI	National heart, lung and blood institute
NIH	National institute of health
OR	Overall response
PK	Pharmacokinetics
QoL	Quality of life
r-ATG	Rabbit anti-thymocyte globulin
SAA	Severe aplastic anemia
SAE	Serious adverse event
SOC	System organ class
TBIL	Total bilirubin
TPO	Thrombopoietin
TPO-R	Thrombopoietin-receptor
ULN	Upper limit of normal
US	United States of America
USPI	US prescribing information

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 3 April 2018 an application for a variation.

The following variation was requested:

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

Extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia for Revolade in combination with standard immunosuppressive therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 50 has also been submitted.

During the initial application, the MAH changed the proposed indication to adult and paediatric patients aged 12 years and above.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0280/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0280/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

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

Timetable	Actual dates
Submission date	3 April 2018
Start of procedure:	28 April 2018
CHMP Rapporteur Assessment Report	16 July 2018
PRAC Rapporteur Assessment Report	26 June 2018
PRAC members comments	4 July 2018
PRAC Outcome	12 July 2018
CHMP members comments	16 July 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 July 2018
Request for supplementary information (RSI)	26 July 2018
CHMP Rapporteur Assessment Report	24 October 2018
PRAC Rapporteur Assessment Report	22 October 2018
PRAC members comments	24 October 2018
PRAC Outcome	31 October 2018
CHMP members comments	5 November 2018
Updated CHMP Rapporteur Assessment Report	8 November 2018
Request for supplementary information (RSI)	15 November 2018
CHMP Rapporteur Assessment Report	5 February 2019
PRAC Rapporteur Assessment Report	5 February 2019
PRAC members comments	6 February 2019
PRAC Outcome	13 February 2019
CHMP members comments	18 February 2019
Updated CHMP Rapporteur Assessment Report	22 February 2019
Request for supplementary information (RSI)	28 February 2019
CHMP Rapporteur Assessment Report	31 May 2019
PRAC Rapporteur Assessment Report	30 May 2019
PRAC members comments	5 June 2019
PRAC Outcome	14 June 2019
CHMP members comments	11 June 2019
Updated CHMP Rapporteur Assessment Report	21 June 2019
An Oral explanation took place on:	24 June 2019
CHMP opinion:	27 June 2019

1.3. Steps taken for the re-examination procedure

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

Rapporteur: Milena Stain Co-Rapporteur: Sinan Bardakci Sarac

Timetable	Actual dates
Written notice to the EMA to request a re-examination of Revolade CHMP opinion of 27 June 2019	11 July 2019
Rapporteur's appointment	25 July 2019
Detailed grounds for the Re-examination (Appendix 2 of Final Opinion) submitted on	26 August 2019
Start of procedure:	27 August 2019
Rapporteur assessment report	30 September 2019
The ad hoc expert group meeting considered the grounds for re-examination (Annex 3)	7 October 2019
Joint Rapporteur's updated assessment report circulated on:	9 October 2019
An Oral explanation on the detailed grounds for re-examination took place on:	15 October 2019
CHMP opinion:	17 October 2019

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

Aplastic anemia is a life-threatening bone marrow disease characterised by tri-lineage marrow hypoplasia and lack of hematopoietic stem progenitor cells (HSCP), due to immune-mediated attack on the bone marrow. Aplastic anemia is characterised as "severe" (SAA) based on hypocellular bone marrow below 30% and pancytopenia, with at least 2 of the following: absolute neutrophil count (ANC) < 500/μL; platelet counts < 20x103/μL; reticulocytes < 20x103/μL (or < 60x103/μL via automated counter).

The MAH initially applied for the following indication: "Revolade in combination with standard immunosuppressive therapy for the first-line treatment of adult and paediatric patients 2 years and older with severe aplastic anemia."

During the initial application, the MAH changed the proposed indication to adult and paediatric patients aged 12 years and above.

2.1.2. Epidemiology

Aplastic anemia is a rare disease, with an annual incidence of approximately 2 cases per million people and with a higher incidence in East-Asian countries (about 4-7 cases per million). There is no significant difference in incidence between men and women. The incidence has a biphasic age distribution with peaks from 10 to 25 years and above 60 years. Reported incidence in children and adolescent per million was 1.7 in the group of 0 to 14 years and 2.2 in 15 to 24 years.

2.1.3. Clinical presentation, diagnosis and prognosis

SAA is recognised as a chronic disease with frequent flares of the immune process and the need for long-term immunosuppression. There is evidence that depletion of primitive hematopoietic stem and progenitor cells is profound, demonstrating that immune attack against the most primitive stem cells is paramount. Even with recovery of blood counts following successful immunosuppressive therapy (IST), a significant quantitative stem cell defect persists, suggesting either ongoing immune destruction or persistent depletion of stem cells.

2.1.4. Management

The first-line treatment of choice is allogeneic hematopoietic stem cell transplantation (HSCT) for those who are eligible and have an available donor; it is the preferred option when feasible as it is curative. Yet less than 30% of subjects are suitable candidates for optimal HSCT because of a lack of a matched sibling donor, the lead time to identify a suitable unrelated donor, age, comorbidities, or access to transplantation.

For subjects who are not suitable candidates for HSCT, IST is the therapy of choice worldwide. Rosenfeld *et al* reported that approximately half of subjects with SAA treated with an IST regimen of h-ATG + CsA had a durable recovery and an excellent long-term survival, and these outcomes were related to the quality of the hematologic recovery. Recent survival analyses support ATG + CsA vs. transplantation as the first-line therapy in subjects over 40 years. The IST regimen of choice is h-ATG for 4 days + CsA for 6 months.

The outcomes remain poor for subjects who have an insufficient response or relapse, and approximately 40% of unresponsive subjects die within 5 years of diagnosis. Although h-ATG + CsA represented a major advance in the treatment of SAA, incomplete responses, relapses, and primary refractoriness limit the success of this therapy. Intensification of the IST with other immunosuppressive agents including r-ATG, alemtuzumab, or high dose cyclophosphamide or with the addition of sirolimus or mycophenolate to IST, do not improve the response rates. Thus, other regimens are needed to address these limitations and provide an alternative to stem cell transplantation.

About the product

Eltrombopag is an orally bioavailable, small-molecule thrombopoietin (TPO)-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signalling cascades that induce proliferation and differentiation from bone marrow progenitor cells. Eltrombopag has been investigated in multiple clinical development programs and it is currently approved in the European Union for use in chronic immune thrombocytopenia, chronic hepatitis C virus associated thrombocytopenia and refractory severe aplastic anemia.

Revolade is currently authorised for the following indications:

- Revolade is indicated for the treatment of patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1 of the SmPC).
- 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 of the SmPC).

- 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 of the SmPC).

The purpose of this submission is to seek approval for the use of eltrombopag in combination with standard immunosuppressive therapy for the first-line treatment of adult and paediatric patients 2 years and older with severe aplastic anemia.

The clinical summary documents supporting this submission focus primarily on findings from the pivotal Study AUS01T, a single center, single arm, non-randomized, Phase I/II trial investigating the efficacy and safety of horse antithymocyte globulin (h-ATG) + cyclosporine in combination with eltrombopag as experimental therapy in patients with severe aplastic anemia who have not received prior definitive immunosuppressive therapy.

Supportive data from other clinical trials in aplastic anemia included in the dossier are:

- Study E1201, a Novartis-sponsored trial in treatment-refractory Japanese patients provides supportive data for safety evaluation
- Study AUS28T and Study AUS18T, the pivotal and supportive trials, respectively, filed to gain approval in the refractory severe aplastic anemia population provide supportive safety data on the development of cytogenetic abnormalities
- Study E1202, a Novartis-sponsored trial in treatment-naïve Japanese patients with moderate aplastic anemia or severe aplastic anemia and PA17-0265/ Kadia et al 2015, an investigator-initiated trial in treatment-naïve patients diagnosed with aplastic anemia provide independent substantiation of the results from Study AUS01T.
- Studies 06-H-0034, 03-H-0193, 90-H-0146, and 97-H-0117, four historical trials evaluating h-ATG + cyclosporine in patients with severe aplastic anemia provide a safety and efficacy reference against which the data from Study AUS01T has been compared

2.2. Non-clinical aspects

2.2.1. Introduction

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

However, a revised environmental risk assessment report has been submitted of eltrombopag tablets and powder for oral suspension product addressing the following initially applied indication:

"Revolade in combination with standard immunosuppressive therapy for the first-line treatment of adult and paediatric patients 2 years and older with severe aplastic anemia."

The maximum recommended dose for severe aplastic anemia is 150 mg once daily.

2.2.2. Ecotoxicity/environmental risk assessment

Phase I ERA: Estimation of exposure

- ***Screening for Persistence, Bioaccumulation and Toxicity (PBT)***

As part of the screening for persistence, bioaccumulation and toxicity, the MAH provided $\log_{10}P_{OW}$ (>4.52). The octanol-water partition coefficient (P_{OW}) has been estimated at pH 5, 7 and 9 and 20 ºC using "Shake Flask Method" according to the OECD 107.

As the log_{10}Pow value is > 4.5 at pH 7, there is requirement to screen eltrombopag olamine for PBT.

In agreement with OSPAR, the PBT/vPvB assessment is required since the estimated log K_{OW} value is clearly above the cut-off of 4.5.

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

$PEC_{SURFACEWATER}$ was calculated and was above the trigger value for proceeding on to Phase II assessment.

$$\mathbf{PEC_{SURFACEWATER}} = \frac{\text{10 mg/inhabitant/day x 0.01}}{\text{200 L/inhabitant/day x 10}} = 0.00075 \text{ mg/L} = \mathbf{0.75\ \mu g/L}$$

The predicted environmental concentration (PEC) is given by the formula proposed in guideline EMEA/CHMP/SWP/4447/00 corr 2 and is calculated as the sum of all PECs for all indications for which eltrombopag is applied:

PECsurfacewater = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)

= (75 mg/inhabitant/day * 0.01) / (200 L/inhabitant/day * 10)

= 0.000375 mg/L = 0.375 µg/L for ITP

PECsurface water = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)

= (100 mg/inhabitant/day * 0.01) / (200 L/inhabitant/day * 10)

= 0.0005 mg/L = 0.5 µg/L for cHCV associated thrombocytopenia

PECsurface water **=** (DOSEai * Fpen) / (WASTEWinhab * DILUTION)

= (150 mg/inhabitant/day * 0.01) / (200 L/inhabitant/day * 10)

= 0.00075 mg/L = 0.75 µg/L for SAA

Overall PECsurface water = 0.375 µg/L + 0.5 µg/L + 0.75 µg/L = **1.625 µg/L**

Where:

DOSEai = 75 mg/patient/day for ITP;

= 100 mg/patient/day for cHCV associated thrombocytopenia

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

Fpen = 1% (default)

WASTEWinhab = 200 L/inhabitant/day

DILUTION = 10

The overall predicted environmental concentration (PEC), taking into account all indications, is **1.625 µg/L**, which exceeds the trigger value of 0.01 µg/L.

Phase II ERA: Environmental fate and effects analysis

Tier A- Initial environmental fate and effects

- ***Physico-chemical properties and fate***

Biodegradation

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

Adsorption / Desorption

As discussed in the Type II variation for HCV, eltrombopag was initially investigated for determination of activated sludge sorption isotherm according to OPPTS 835.1110 (Report SD2006/00091/00). However, no determination of the isotherm was possible in this study. This was due to the instability of the test material in aqueous solution at a concentration and pH relevant to the fate of the test material in the waste water treatment plant. At the time it was not possible to overcome these technical challenges and, therefore, it was concluded that those physico-chemical characteristics of eltrombopag that contributed to the failure of this study were the same as those which would likely give rise to a Koc value for eltrombopag of greater than 10'000 L/kg ostensibly triggering the need for a Phase II Tier B analysis in soil. However, since this submission it was found that another CRO with better analytical capabilities was able to conduct a soil/sludge adsorption study (OECD 106) with eltrombopag. In this study, the adsorption and desorption of eltrombopag was determined in three soils and two municipal sewage sludges using the batch equilibrium method according to the OECD test guideline no. 106. The following soils/sludges were used: soil I (Speyer 2.3; sandy loam), soil II (Hagenthal; silt loam), soil III (Mechtildshausen; loam), sludge I (Füllinsdorf) and sludge II (Sissach). In order to limit microbial degradation of the test item during the experiment, all soils and both sludge were treated by γ-irradiation before use.

Adsorption kinetics were determined for a soil/sludge-to-solution ratio of 1/100 (1 g soil to 100 mL 0.01 M $CaCl_2$) and a test item concentration of 0.027 µg/mL. For all soils and sludge species, the level of adsorption (adsorbed fraction of applied) almost reached equilibrium after 48 hours of agitation due to its high adsorption. The fraction of adsorption after 48 hours was 94.1%, 92.7% and 94.6% of the applied radioactivity for soils I to III, respectively and 95.8% and 95.5% for sludge I and II, respectively. The mass balance, determined for all soils/sludge after 48 hours of adsorption, showed overall mean recoveries of 99.9%, 104.4% and 105.4% for the soils and 113.3% and 108.8% for both sludges, respectively. The higher recoveries in both sludge species are due to the high amount of non-extractable radioactivity in comparison to the soils and the small amount of material combusted. The mean Koc adsorption value for the soils is 132,556 mL/g and 8,119 mL/g for the sludge. The adsorption showed to be independent of the cation exchange capacity, organic carbon or clay content of the soils. A slight dependence of the adsorption from the pH could be observed. Desorption kinetics were followed 2, 5, 24 and 48 hours after the 48 hours adsorption period. Very little desorption was observed for all soils/sludge throughout the experiment. The percent of the desorbed radioactivity amounted to 3.5%, 2.6%, 2.5%, 0.9% and 0.9% of adsorbed for soils I, II, III and sludge I and II, respectively after 48 hours of desorption. The mean Koc desorption value for the soils was 302,493 mL/g and 30,492 mL/g for the sludge.

Aerobic Transformation in Aquatic Sediment Systems

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

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

- ***Aquatic effects studies***

Toxicity data on algae, duckweed, daphnid and fish and microorganism were submitted for eltrombopag olamine. The main information of the conducted studies and the study results are summarised in the table below. The table contains also the results of the respiration inhibition test:

Table 1. Data on Effects Studies

Substance	Study	Results	Conclusions
	Green Algae (Scenedesmus subspicatus) *Growth and Yield Inhibition (72 h)* *(OECD 201)*		Eltrombopag olamine significantly adsorbed light at one of the wavelengths required for photosynthesis (460 nm) and that significant inhibition of growth occurred despite the use of the modified test design. Therefore, it is considered appropiate to change the test method to a Lemna Growth Inhibition Test (OECD 201).

Eltrombopag olamine	*Lemna minor* Growth and Yield Inhibition (7 days) (OECD 221)	Average Specific Growth rate: **E_rC_{50} (frond number)=4.1 mg/mL** **NOEC (frond number)= 0.45 mg/L** **E_rC_{50} (dry weight)= 7.2 mg/mL** **NOEC (dry weight)= 0.45 mg/L** Yield **E_rC_{50} (frond number)=1.2 mg/mL** **NOEC (frond number)= 0.45 mg/L** **E_rC_{50} (dry weight)= 1.2 mg/mL** **NOEC (dry weight)= 0.45 mg/L**	The drug substance eltrombopag olamine is **toxic to *Lemna minor*** at nominal concentrations as significant effects on growth relative to the control treatment were observed, under the conditions of the test.
	Daphnia magna Reproduction Test (OECD 211)	Reproduction: **EC_{50} (21 day)> 0.12 mg/L** **LOEC (21 day)=**	The drug substance was considered **provided of significant long-term toxicity to**

		0.34 mg/L **NOEC (21 day)= 0.12 mg/L** Immobility: **EC_{50} (21 day)> 0.19 mg/mL** **LOEC (21 day)= 0.34 mg/L** **NOEC (21 day)= 0.12 mg/L**	**aquatic invertebrates.**
	Fish (*Danio rerio*) Early-Life Stage Toxicity Test (OECD 210)	Hatching: **LOEC (28 day)= 0.53 mg/L** **NOEC (28 day)= 0.16 mg/L** Larval Survival: **LOEC (28 day)= 0.16 mg/L** **NOEC (28 day)= 0.052 mg/L** Length and Weight:	The drug substance was considered to be **provided of significant long-term toxicity to fish.**

		LOEC (28 day)= 0.16 mg/L **NOEC (28 day)= 0.052 mg/L**	
	Activated Sludge Respiratory Inhibition (OECD 209)	Respiration rate **EC50** >320 mg/L **NOEC = 32 mg/L**	The drug substance was considered **to be not toxic to activated sludge microbial populations.**

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

Based on the generated effect data the MAH carried out the risk characterisation in Tier A of the environmental risk assessment. In order to assess the risk to the aquatic environment it is required to calculate the PEC/PNEC ratios. Therefore the predicted no effect concentration (PNEC) has to be deduced from the NOEC values of the effects studies. In compliance with the guideline on environmental risk assessment the PNEC is calculated by applying an assessment factor (AF) to the no observed effect concentrations (NOEC) from relevant effect studies. A default assessment factor of 10 is applied to calculate the PNEC from the long-term toxicity test and the 10 to calculate anti-microbial effect study.

$PNEC_{WATER}$ = 52 µg/L /10 **= 5.20 µg/L** (based on lowest NOEC from all three trophic levels).

$PNEC_{MICROORGANISM}$ = 32,000 µg/L /10 **= 3,200 µg/L** (based on NOEC from Activate Sludge Respiration Inhibition study).

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

- ***Calculation of refined $PEC_{surfacewater}$***

The $PEC_{SURFACEWATER}$ has been refined as the sum all of each indication, based on prevalence of the diseases and treatment regimens. The new value has been considered for the PEC/PNEC ratios calculation.

The Tier A PEC is based on the "total residue approach", neglecting depletion by biotic and abiotic processes. The Phase II Tier A PECsurface water has been calculated using epidemiological data for all currently registered and newly applied for indications, i.e. cHCVaT, SAA, cITP and first line SAA (total PEC) based on the assumption that 100% of drug substance used enters the sewage treatment plant unchanged and passes through into the aquatic environment.

Immune (idiopathic) thrombocytopenia (ITP) is an autoimmune disorder characterised by autoantibody-induced platelet destruction and reduced platelet production, leading to a chronically low peripheral blood platelet count (<150,000/µL). As indicated by the term 'idiopathic', the exact etiology of ITP is unknown. Anti-platelet antibodies are thought to play a role in mediating destruction of platelets, and may impede the generation of platelets in the bone marrow. The prevalence of ITP in the population is known to be very low. As laid out in the latest EU Safety Risk Management Plan for eltrombopag the

prevalence of ITP in the EU is estimated to be 2.1 in 100,000 inhabitants.

Chronic hepatitis C (cHCV) infection is a serious disease, especially for those with significant thrombocytopenia (<100 Gi/L). In this population, the annualised incidence rate for hepatocellular carcinoma or clinical hepatic decompensation (ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis) is approximately 8%. Every year more than 7% die or undergo liver transplantation. Over a 5-year period 1 out of 4 such patients will die. The aetiology of thrombocytopenia in HCV-infected patients is multi-fold and severity correlates with the severity of liver disease. Approximately 20% of HCV-infected individuals develop liver cirrhosis, with thrombocytopenia as a clinical marker of progression to more severe hepatic impairment. Consequently, low platelet counts are predictive of poorer outcomes. Thrombocytopenia is also caused, or further aggravated, by interferon-based antiviral therapy due to its myelosuppressive effects. Eltrombopag, working as a supporting care agent to increase the platelet count prior to and throughout interferon-based treatment of HCV infection initiate and help optimise and maintain the dose and duration of their antiviral therapy, improving the likelihood of achieving a sustained virologic response (SVR). In Europe, the HCV prevalence estimates show high variability between countries ranging from ≤ 0.5% in the northern European countries to ≥ 3% in the Romania and rural areas in Greece, Italy and Russia. The prevalence of thrombocytopenia in patients with HCV infection is estimated to be 5.8 %. Based on an EU population of 512.596.403 in January 2018, these results in 891’918 patients with cHCV associated thrombocytopenia or a prevalence of 174 in 100’000 for the EU.

Severe aplastic anaemia (SAA) is a rare, life-threatening, acquired bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack of haematopoietic stem and progenitor cells (HSPC) due to an immune-mediated attack on the bone marrow. There is no standard of care for SAA patients with an insufficient response to immunosuppressive therapy who do not have suitable donor for bone marrow transplantation.

For SAA no data on prevalence is available, however, information on incidence with a maximum of 2.54 cases in 1 million people found within the EU countries for which information is available, shows that SAA is a very rare disease. In the absence of prevalence data, the market penetration factor for SAA has been calculated based on the maximum incidence for this disease for the EU.

PECsurface water = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)

= (75 mg/inhabitant/day * 0.000021) / (200 L/inhabitant/day * 10)

= **0.0007875 µg/L for ITP.**

PECsurface water = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)

= (100 mg/inhabitant/day * 0.00174) / (200 L/inhabitant/day * 10)

= **0.087 µg/L for cHCV associated thrombocytopenia.**

PECsurface water = (DOSEai * Fpen) / (WASTEWinhab * DILUTION) = (150 mg/inhabitant/day * 0.00000254) / (200 L/inhabitant/day * 10) = **0.00019 µg/L for SAA.**

Where:

DOSEai = 75 mg/patient/day for ITP; = 100 mg/patient/day for cHCV associated thrombocytopenia = 150 mg/patient/day for 6 months for SAA

Fpen = 2.1 in 100’000 inhabitants; 0.0021 % for ITP

= 174 in 100'000 inhabitants; 0.174 % for cHCV associated thrombocytopenia.

= 0.254 in 100’000 inhabitants; 0.000254 % for SAA

WASTEWinhab = 200 L/inhabitant/day DILUTION = 10

Overall PECsurface water = 0.0007875 µg/L + 0.087 µg/L + 0.00019 µg/L = 0.088 µg/L.

$PEC_{surface\ water}$ = 0.088 µg/L

- ***Calculation of $PEC_{microorg}$***

Based on the default dilution factor of 10 used between surface water and sewage treatment plants, the PECmicroorg is ten times higher than the PECsurface water.

$PEC_{microorg}$ = 0.88 µg/L

- ***Calculation of $PEC_{groundwater}$***

According to the guideline, the PECgroundwater can be assumed to be typically 0.25 times the PECsurfacewater. This leads to a PECgroundwater of 0.022µg/L for eltrombopag free acid.

$PEC_{groundwater}$ = 0.022 µg/L

- ***Outcome of Tier A fate and effects analysis***

Surface water assessment

Refined $PEC_{surface\ water}$ = 0.088 µg/L

$PNEC_{surface\ water}$ = 5.2 µg/L

$PEC/PNEC_{surface\ water}$ = 0.088 µg/L / 5.2 µg/L **= 0.017**

Microorganisms / sewage treatment plant assessment

$PEC_{microorg.}$ = 0.88 µg/L

$PNEC_{microorg}$ = 3'200 µg/L

$PEC/PNEC_{microorg.}$ = 0.88 µg/L / 3' 200 µg/L = **0.000275**

Groundwater assessment

$PEC_{groundwater.}$ = 0.022 µg/L

$PNEC_{groundwater}$ = 12.0 µg/L

$PEC/PNEC_{groundwater}$ = 0.022 µg/L / 12.0 µg/L = **0.0018**

Table 2. Hazard/risk assessment eltrombopag olamine

Hazard/risk criterion	Data requirement
n-octanol/water coefficient (log Kow) > 3	Fish bioconcentration study conducted in Tier B
Adsorption – Desorption: sludge Koc < 10'000	Sorption to sludge below the trigger value for a Tier

	B terrestrial assessment. No terrestrial assessment required.
PECsurface water / PNECsurface water < 1	0.088 µg/L /5.2 µg/L = 0.017
PECmicroorg / PNECmicroorg < 0.1	0.88 µg/L /3'200 µg/L = 0.000275
PECgroundwater / PNECgroundwater < 1	0.022 µg/L /12.0 µg/L = 0.0018

Tier B: Extended Environmental Fate and Effects Analysis

- **Water sediment effects**

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

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

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

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

Tier B toxicity data for eltrombopag olamine

Development of sediment-dwelling organisms (OECD 218)	EC50 (emergence) = 130 mg/kg LOEC (emergence) = 185 mg/kg NOEC (emergence) = 104 mg/kg NOEC (development) = 104 mg/kg

Source: (Report 2016N274772_0)

- **Calculation of $PEC_{sediment}$**

PECsurface water refinement and PECsludge calculation

In Tier B the PECsurface water may be refined with information from STP modelling using the SimpleTreat model by incorporating adsorption of substances to sewage sludge in STPs, using the data from the estimation of the adsorption coefficient in sewage sludge from two sewage treatment plants.

Applying SimpleTreat STP modelling and an Elocalwater of 2136.75 mg/day (see calculation presented below) and using REACH Guidance on information requirements and chemical safety assessment Chapter R16.: Environmental Exposure Estimation (European Chemicals Agency, ECHA, October 2012) suggests 53 % elimination of eltrombopag from waste water (35.03 % via primary sludge and 17.79 % via surplus sludge) and 47.18 % emission of eltrombopag to effluent (Eltrombopag SimpleTreat.pdf).

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

ITP: 75 mg/inhabitant/day * 1 * 0.000021 * 10'000 inhabitants = 15.75 mg/day

cHCVaT: 100 mg/inhabitant/day * 1 * 0.00174 * 10'000 inhabitants = 1740 mg/day

SAA: 150 mg/inhabitant/day * 1 * 0.000254 * 10'000 = 381 mg/day

Sum $Elocal_{water}$ = 15.75 + 1740 + 381 = 2136.75 mg/day

With:
DOSEai = 75 mg/patient/day for ITP

= 100 mg/patient/day for cHCV associated thrombocytopenia = 150 mg/patient/day for 6 months for SAA

CAPACITYstp = 10'000 inhabitants (R.16 Table R.16-10)

$F_{excreta}$ = 100 %

F_{pen} = 2.1 in 100'000 inhabitants; 0.0021 % for ITP

= 174 in 100'000 inhabitants; 0.174 % for cHCV associated thrombocytopenia

= 0.254 in 100'000 inhabitants; 0.000254 % for SAA

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

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

= (2130.75 mg/day * 0.4718)/(200 L/inhabitant/day * 10'000 inhabitants * 10) = 0.050 µg/L

With:

$Elocal_{water}$ = 2130.75 mg/day

$Fstp_{water}$ = 47.18 %

$WASTEW_{inhab}$ = 200 L/inhabitant/day (R.16 Table R.16-10)

CAPACITYstp = 10'000 inhabitants (R.16 Table R.16-10)

FACTOR: Kp_{susp} = Foc_{susp} * Koc = 0.1 * 8'188.5 L/kg = 811.85 L/kg (R.16 Equation 16-6)

Foc_{susp}: 0.1 $kg_{oc}*kg_{solid}^{-1}$ (R.16 Table R.16-9)

Koc = (8'534 L/kg + 7'703 L/kg) / 2 = 8'188.5 L/kg (average from Koc from two sludges, see Table 4.1)
Dilution = 10

While the risk ratio calculated for surface waters in Tier A does not indicate a risk for this environmental compartment and therefore no refinement is required, it can be noted that applying the refined Tier B $PEC_{surface\ water}$ for the calculation of the risk ratio results in a $PEC/PNEC_{surface}$ water of 0.0096.

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

The $PEC_{sediment}$ can be calculated following REACH Guidance on information requirements and chemical

safety assessment Chapter R16.: Environmental Exposure Estimation (European Chemicals Agency, ECHA, October 2012):

$PEC_{local\ sed}$ = ($K_{susp\text{-}water}$ / RHO_{susp}) * $PEC_{local\ water}$ * 1000 = (3314.8 L/m^3 / 1150 kg/m^3) * 0.05 µg/L * 1000 = 144.12 µg/kg (Equation R.16-35)

With:

RHO_{susp} = 1'150 kg/m^3 (Equation R. 16-16)
$K_{susp\text{-}water}$ = $Fwater_{susp}$ + $Fsolid_{susp}$* (Kp_{susp} /1000) * RHO_{solid} =

0.9 $m_{water}{}^3/m_{susp}{}^3$ + 0.1 $m_{solid}{}^3/m_{susp}{}^3$ * (13'255.6 L/kgsolid / 1000) * 2500 kg/m^3 = 3314.8 L/m^3 (Equation R.16-7)

With:

RHO_{solid} = 2'500 kg/m^3 (Table R. 16.9)

Kp_{susp} = Foc_{susp} * Koc_{soil} = 0.1 kg_{oc}/kg_{solid} * 132'556 L/kg = 13'255.6 L/kg_{solid} (Equation

R.16.6)

Koc_{soil} = 132'556 ml/g (Average from three soils, i.e. 155'386, 97'529 and 144'754 mL/g)

Foc_{susp} = 0.1 kg_{oc}/kg_{solid} (Table 16.9)

In order to account for the fact that the effect concentration of the sediment toxicity study is expressed as a dry weight concentration, the $PEC_{sediment}$ calculated above, which relates to wet sediment is multiplied with a conversion factor of 4.6, resulting in a dry weight $PEC_{sediment}$ of 662.96 µg/kg.

The $PNEC_{sediment}$, based on the NOEC for the development of the sediment-dwelling larvae of Chironomus riparius (Table 5-1) including an assessment factor of 100, is 1'040 µg/L. The risk ratio for sediment therefore calculates as:

$PEC/PNEC_{sediment}$ = 662.96 µg/kg / 1'040 µg/kg = **0.64**

- **Bioaccumulation**

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

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

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

The uptake and depuration rate constants, k1 and k2, were determined to be 4.4148 and 0.1515 for the

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

Tier B bioaccumulation data

Bioconcentration in fish (OECD 305)	**Low concentration: 0.0025 mg/L** BCFss= 14 L/kg BCFk=29 L/kg BCFss lip-normalised= 336 L/kg **Low concentration: 0.025 mg/L** BCFss= 14 L/kg BCFk=29 L/kg BCFss lip-normalised= 130 L/kg

Source: (Report 2011N113982_01

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

Summary of main study results

Substance (INN/Invented Name): Eltrombopag olamine			
CAS-number: 496775-62-3			
PBT screening		Result	Conclusion
Bioaccumulation potential-log *K*ow	92/69/EEC Method A8 (shake-flask method)	log Dow > 4.1 at pH 5 log Dow = 4.52 at pH 7 log Dow = 0.96 at pH 9	Potential PBT (Y)

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF (steady-state lipid-normalised) (OECD 305)	336 (low concentration) and 130 (high concentration)	not B
Persistence	DT50 (total water and sediment) (OECD 308)	DT at 12ºC 653, 3244 days (sediment) 1043, 3116 days (total system)	vP
Toxicity	NOEC Fish, Early Life Stage Toxicity (OECD 210)	NOEC =52 µg/L	not T
PBT-statement :	The compound is neither considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	1.625	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} sludge = 8'534 and 7'703 mL/g	
		K_{oc} soil = 155'386, 97'529 and 144'754 mL/g K_d sludge = 2'355 and 2'148 mL/g K_d soil = 1'538, 1'307 and 1'723 mL/g	
Ready Biodegradability Test	OECD 302 C	Not inherently biodegradable	

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

		CT50			
Sediment dwelling organism	OECD 218	NOEC	104	mg/kg	*Chironomus riparius*

2.2.3. Discussion on non-clinical aspects

Phase I. Estimation of exposure

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

The predicted environmental concentration (PEC) for eltrombopag is 0.75 µg/L which exceeds the trigger value of 0.01 µg/L as given by EMEA (2006) and therefore an environmental assessment Phase II –Tier A was performed. As eltrombopag can be prescribed for the treatment of more than one indication, the $PEC_{surface\ water}$ has been calculated as the sum all of each indication PECs. This PEC value is 1.625 µg/L, which exceeds the trigger value of 0.01 µg/L. The assessment therefore proceeds to Phase II – Tier A.

Phase II Tier A. Environmental fate and effects analysis

Guideline on the environmental risk assessment of medical products for human use (EMEA/CHMP/SWP/4447/00) advises the Ready Biodegradability test (OECD 301) instead of the OECD 302C performed by MAH. Since eltrombopag is not considered biodegradable and the MAH proposes to perform a Tier B assessment, there is no concern regarding this issue. Eltrombopag has been found to quickly dissipate from the water phase into the sediment (OECD 308). The half-life determined in the study on transformation in total water/sediment systems exceeds 120 days, thus being very persistent considering the DT_{50} values of >1000 d at 12ºC in total system and the DT_{50} values of 653 and 3244 d at 12ºC in sediment. Therefore, an assessment for sediment has been presented in Phase II-Tier B of the current environmental risk assessment (OECD 218). Eltrombopag shows a low potential for adsorption to sludge (K_{oc}<10000), indicate the unlikely affinity to bind to sewage sludge in the SPT, thus a terrestrial assessment in Phase II Tier B is not considered necessary. Significant toxicity to aquatic species, i.e. Lemna (OECD 201), Daphnia magna (OECD 211) and fish (OECD 210) has been observed, with the fish species *Danio rerio* (zebra fish) being the most sensitive of the aquatic species tested. Based on PEC values calculated by the MAH, the risk for aquatic organisms in surface water and groundwater as well as for microorganisms in activated sludge microorganisms can be considered to be low.

Phase II Tier B. Extended environmental fate and effects analysis

A study on toxicity to the sediment-dwelling larvae of *Chironomus riparius* (OECD 218) was triggered and revealed no toxicity. $PEC_{SEDIMENT}$ for eltrombopag and the ratio $PEC_{SEDIMENT}/PNEC_{SEDIMENT}$ were recalculated considering the $PEC_{SURFACEWATER}$ value calculated as the sum all of each indication PECs, based on prevalence of the diseases and treatment regimens. The result indicates that eltrombopag does not constitute a risk to sediment compartments. As eltrombopag has a Log Pow value which is >3 in the environmental pH range, a fish bioaccumulation study (OECD 305) was conducted. As shown in the bioconcentration study in *Oncorhynchus mykiss*, eltrombopag cannot be considered bioaccumulative based on the maximum Biocencentration Factors at steady state (BCF_{SS}) of 336-130, as the BCF remains below the criteria for a bio-accumulative substance.

2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application lead to a significant increase in environmental exposure further to the use of eltrombopag.

However, considering the above data, eltrombopag is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3. Summary of design for pivotal Study AUS01T

Study design, objectives, population	No. of subjects analyzed Treatment/duration	Endpoints
Non-randomized, single-center, IIT study investigating eltrombopag as experimental therapy in combination with standard IST regimen of h-ATG + CsA in subjects with SAA who have not received prior definitive IST.	**123 subjects analyzed** Cohort 1: 30 Cohort 2: 31 Cohort 3: 31 Extension Cohort: 31 (still recruiting) **Treatment** Cohort 1: h-ATG on Days 1-4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 6. Cohort 2: h-ATG on Days 1-4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 3. Following amendment 15 to the protocol (beginning with subject 46), responders at month 6 received maintenance dose of CsA from month 6 to month 24. Cohort 3 and Extension Cohort: all 3 drugs started concurrently on Day 1: h-ATG on Days 1-4, + CsA and eltrombopag from Day 1 to month 6. Responders at month 6 received maintenance dose of CsA from month 6 to month 24. Study participation is considered complete for an individual subject after 5 years,	**Primary (efficacy)**: Complete response rate at 6 months following h-ATG/ CsA/ eltrombopag **Primary (safety)**: Toxicity profile in the 6 months following h-ATG/CsA/ eltrombopag **Secondary**: Complete response rates at 3 and 12 months and yearly thereafter Overall response rates at 3, 6 12 months and yearly thereafter Duration of complete response Duration of overall response Overall survival Change from baseline to post-baseline assessments in PROMIS Global Health, Sleep Disturbance, Applied Cognition-Abilities, Anxiety and Depression scores Change from baseline to post-baseline assessments in FACT- Anemia, Thrombocytopenia and Neutropenia scores Duration of response in subjects responding at month 6

Reference: [Study AUS01T]

Table 4. Summary of supportive studies and historical controls

	Contribution to the dossier	Subjects and Treatment
r-ATG +CsA in combination with eltrombopag in ATG treatment-naïve subjects with SAA: safety and efficacy		
[Study E1202]	Supportive efficacy and safety data from ATG treatment-naïve Japanese subjects with MAA or SAA; used to provide independent substantiation of the results of Study US01T	N=10 (3 MAA and 7 SAA) r-ATG + CsA + Eltrombopag 75 mg/day[a]
Eltrombopag alone in ATG-based treatment-refractory subjects with SAA: safety		
[Study E1201]	Supportive safety data from treatment-refractory Japanese subjects with MAA or SAA	N=21 Eltrombopag 100 mg/day[a]
Eltrombopag alone in IST-refractory subjects with SAA: development of cytogenetic abnormalities		
[Study US28T]	Supportive safety data on the development of cytogenetic abnormalities from NIH-sponsored trial in treatment-refractory subjects with SAA	N=43 Eltrombopag 150 mg/day
[Study US18T]	Supportive safety data on the development of cytogenetic abnormalities from NIH- sponsored trial in treatment-refractory subjects with SAA	N=40 Eltrombopag 150 mg/day[a]
h-ATG + CsA in combination eltrombopag in treatment-naïve subjects with SAA conducted at a non-NIH site: efficacy		
[Boddu et al (2017)] and abstract [Kadia et al (2015)]	Investigator-initiated trial (PI: Tapan Kadia, from MD Anderson Cancer Center). Treatment-naïve subjects with AA or SAA. Data used to provide independent substantiation of the results of Study US01T	N=14 h-ATG + CsA + G-CSF + Eltrombopag 150 mg/day[a] N=17 h-ATG + CsA + G-CSF
Published data from studies with h-ATG + CsA alone in subjects with SAA conducted at the NIH site (historical data)		
[Scheinberg et al (2011)]	Historical efficacy and safety data for h-ATG + CsA alone in subjects with SAA	N=60 h-ATG + CsA
[Scheinberg et al (2009)]	Historical efficacy and safety data for h-ATG + CsA alone in subjects with SAA	N=42 h-ATG + CsA
[Rosenfeld et al (2003)]	Historical efficacy and safety data for h-ATG + CsA alone in subjects with SAA	N=122 h-ATG + CsA
[Tisdale et al (2000)]	Historical efficacy and safety data for h-ATG + CsA alone in subjects with SAA	N=16 h-ATG + CsA

a. maximum dose of eltrombopag.
AA: aplastic anemia. **h-ATG**: horse-antithymocyte globulin - **CR**: complete remission - **CsA**: cyclosporine A - **IST**: immunosuppressive treatment - **MAA**: moderate aplastic anemia - **OR**: overall remission - **ORR**: overall response rate - **OS**: overall survival - **PK**: pharmacokinetic - **PR**: partial response - **QoL** quality of life - **r-ATG**: rabbit-antithymocyte globulin - **SAA**: severe aplastic anemia - **SAEs**: serious adverse events

2.3.2. Pharmacokinetics

The studies used to assess the PK in naïve adult and adolescents (aged between 6-18 years) SAA patients are shown in table 5 and 6. No PK study in children between 2 and 5 years old has been conducted.

Table 5. Overview of studies with a clinical pharmacology component for eltrombopag as therapy in SAA subjects (30-Sept-2016).

Study	Study Objective(s)	Study Design	Study population	N[a]/eltrombopag PK sampling	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)
Registration study					
[Study AUS01T]	Efficacy and safety	Phase I/II Non-controlled	Definitive IST-naïve SAA	PK sampling in 23 out of 30 subjects in cohort 1 - 21 subjects evaluable for PK analysis Serial sampling at Month 3: pre-dose, 2, 4, 6, and 8 h post dose with optional 24 h post-dose sample.	Three consecutive cohorts designed as Simon-2 stage. Only subjects enrolled in Cohort 1 had their blood samples used for PK assessments. **Cohort 1:** h-ATG (Day 1-4) + CsA (Day 1 to Month 6) + Eltrombopag (Day 14 to Month 6) Starting dose: 150 mg/day
Studies providing supportive PK data					
[Study E1201]	Efficacy and safety	Phase II Non-controlled	Japanese subjects with refractory, MAA or SAA	PK sampling in all 21 subjects Serial PK sampling at the starting dose of 25 mg in 5 subjects only: pre-dose, 1, 2, 4, 6, 8, and 24 h post dose on Day 14. All other subjects had sparse (pre-dose) samples taken on Day 14. For doses of 50, 75 and 100 mg: pre-dose samples were taken in all subjects 15 days after the new dose had started	Eltrombopag was administered as monotherapy starting at 25 mg/day and increased by 25 mg/day every 2 weeks up to 100 mg/day according to the platelet count.
[Study E1202]	Efficacy and safety	Phase II Non-controlled	Japanese subjects with MAA or SAA who had not received prior ATG/ALG-based IST	PK sampling in all 10 subjects 75, 50 and 25 mg: pre-dose samples on Day 15. For 75 mg only: additional 4 h post dose sample on Day 15	Eltrombopag was administered orally once daily at 75, 50 and 25 mg.

After the original cut-off (30-Sept-2016) the MAH updated PK with a new cut-off date (28-Feb-2018). Data from this period include PK results from subjects in Cohort 1 and from the Extension Cohort. The updated cut-off allowed assessment of PK parameters of eltrombopag in 33 subjects in Extension Cohort, of whom: 1 subject received daily eltrombopag at 37.5 mg (South-East Asian, 10 years), 6 subjects at 75 mg (3 non-Asians, of 6 to 7 years and 3 South-East Asians > 18 years), and the remaining 26 subjects at 150 mg. No PK data were collected in patients aged 2 to 5 years.

Table 6. Studies providing supportive PK data in healthy subjects, in subjects with ITP, and in subjects with CLD

Reference	Population (N)	Daily doses, duration	PK analysis
Matthys et al 2011	Healthy subjects (N = 33)	RD 100 mg to 200 mg, 5 days	Non-compartmental PK analysis
Gibiansky et al 2011	Healthy subjects (N = 111) Subjects with ITP (N = 88)	Healthy subjects: SD and RD, 5 mg to 75 mg, 10 days, RD 100 mg to 200 mg, 5 days ITP: 30 mg to 75 mg, 6 weeks	Population PK analysis, individual PK parameters derived by empirical Bayes estimation for a theoretical dose of 50 mg
Farrell et al 2013	Healthy subjects (N = 28) Subjects with CLD (N = 79)	Healthy subjects: SD 30 mg to 75 mg CLD: 12.5 mg to 75 mg, 14 days	Population PK analysis, individual PK parameters derived by empirical Bayes estimation for a theoretical dose of 50 mg

SD: single dose, RD: repeated dose

Pharmacokinetics in study AUS01T

To assess the pharmacokinetics in SAA naïve patients, preliminary data with original cut-off (30-Sept-2016) from the AUS01T were available. This Investigator Initiated Trial, sponsored by the National Heart, Lung, and Blood Institute, is a non-randomized, single-arm, single-center, PhaseI/II study investigating the standard regimen of horse anti-thymocyte globulin (h-ATG) and cyclosporine (CsA), in combination with eltrombopag as experimental therapy in subjects with SAA who have not received prior definitive IST.

The subjects were treated with IST, h-ATG + CsA, combined with eltrombopag as experimental therapy. The cohorts differed only by the treatment starting day and duration of eltrombopag and the addition of a CsA maintenance regimen.

Subjects received their starting dose of eltrombopag according to their age and ethnicity (East/South-East Asian or non-Asian). Eltrombopag 150 mg once daily was selected as the starting dose for non-Asian ≥12 year old subjects. h-ATG was administered at a dose of 40 mg/kg. CsA dosing was based on body weight, except for obese subjects (defined as a BMI >35 in subjects >20 years and > 95th percentile in subjects 12 to 20 years). Total daily dose of CsA for subjects ≥ 12 years and <12 years was 6 mg/kg/day and 12 mg/kg/day, respectively. For obese subjects the CsA dose was based on the adjusted body weight that was calculated as the midpoint between the ideal weight and actual body weight. CsA dosing was adjusted to obtain a therapeutic trough level between 200 to 400 µg/L. Eltrombopag starting doses in East/South-East Asian subjects were to be 50% lower than those in non-Asians.

The PK of eltrombopag was an exploratory objective of this study. Only subjects enrolled in Cohort 1 who had received once daily eltrombopag for at least 7 days prior to the landmark month 3 visit (to be at PK steady-state with no recent dose interruptions) were included in the PK assessments. Blood samples (2 mL) for PK analysis were collected at the following times: within 30 min prior to eltrombopag dosing (pre-dose sample), and at 2, 4, 6, and 8 h after eltrombopag dosing. An optional sample could be collected 24 h post-dose, prior to administration of eltrombopag on the next day. As the 24 h sample was not collected, the pre-dose sample was duplicated and analysed as a 24 h sample under the assumption that PK steady-state had been reached.

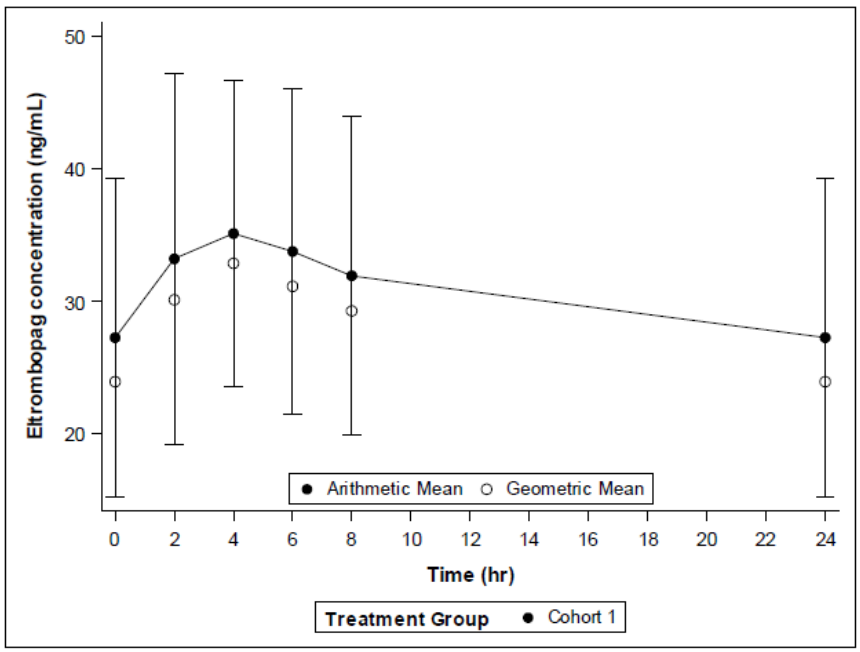
Twenty-one (21) subjects enrolled in Cohort 1 (AUST01) were evaluable for PK, 1 subject at the 100 mg dose, 1 subject at the 125 mg dose, and 19 subjects at the 150 mg dose. Three (3) out of 21 subjects were adolescents aged 12, 14, and 17 years (2 of them received 150 mg dose). There was no East/South-East Asian subject evaluable for the PK assessment. PK parameters are presented in table 7 and in figure 1.

Table 7. Summary of steady state PK parameters for eltrombopag at the 150 mg dose-Pharmacokinetic analysis set (cut-off 30-Sept-2016).

Parameter	Statistics	Cohort 1[a] N=19
Cmax (µg/mL)	Mean (SD)	36.8 (13.1)
	CV%	35.7
	Geo-mean	34.1
	Geo-CV%	44.2
	Median (Min; Max)	38.2 (12.4; 57.2)
Tmax (h)	Median (Min; Max)	4.0 (1.92; 6.0)
Ctrough (µg/mL)	Mean (SD)	27.2 (12.0)
	CV%	44.0
	Geo-mean	23.9
	Geo-CV%	65.8
	Median (Min; Max)	26.3 (3.62; 49.5)
AUClast (h.µg/mL)	Mean (SD)	737 (285)
	CV%	38.8
	Geo-mean	671
	Geo-CV%	51.3
	Median (Min; Max)	813 (179; 1230)

a. Only subjects on 150 mg leading dose are included in this output.

Figure 1. Geometric and arithmetic means of eltrombopag plasma concentrations over time - Pharmacokinetic analysis set (cut-off 30-Sept-2016).



Only subjects on 150 mg leading dose are included in this output.

Eltrombopag was absorbed with a peak plasma concentration occurring 2 to 6 hours after repeat oral administration. In the 19 subjects with PK at the dose 150 mg day (two of them were aged from 12-18 years), the geometric mean (geometric mean coefficient of variation - CV) C_{max} was 34.1 µg/mL (44%), AUC_{last} (equivalent to AUC_{0-24} post-dose, henceforth will be referred to as AUC) was 671 h.µg/mL (51%), and C_{trough} was 23.9 µg/mL (66%). Overall variability of PK parameters at 150 mg was moderate, with geometric mean CV below 66% for all parameters.

Subgroup analyses on exposure parameters (AUC, Cmax, and Ctrough) were performed by the actual dose administered at the time of PK assessment (100 mg, 125 mg, and 150 mg), gender, age group (<18 years and ≥18 years), race, and by hematological response at Month 3. The analysis by gender showed that Cmax, Ctrough, and AUC were approximately 35% to 50% higher in female as compared to male subjects (Table 8).

Table 8. PK results (AUC) by gender in AUS01T study (cut-off 30-Sept-2016).

		Cohort 1	
Parameter	Statistics	Female N=10	Male N=9
AUClast (h*ug/mL)	n	10	9
	Mean(SD)	845(171)	616(345)
	CV%	20.2	56.1
	Geo-mean	829	530
	Geo-CV%	21.0	65.6
	Median	841	441
	[Min; Max]	[604;1120]	[179;1230]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- Only subjects on 150 mg leading dose are included in this output.

These differences are considered within the magnitude of the observed overall variability of PK parameters. For the other subgroup analyses, no difference between subgroups was observed, suggesting in particular that exposure in the 2 adolescents was similar to that in adult subjects (Table 9).

Table 9. PK results (AUC) by age (<18 years *vs.* >18 years) in AUS01T study (cut-off 30-Sept-2016).

		Cohort 1	
Parameter	Statistics	< 18 years N=2	>= 18 years N=17
AUClast (h*ug/mL)	n	2	17
	Mean(SD)	638(278)	748(292)
	CV%	43.6	39.1
	Geo-mean	607	679
	Geo-CV%	47.5	53.1
	Median	638	813
	[Min; Max]	[441;834]	[179;1230]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- Only subjects on 150 mg leading dose are included in this output.

New cut-off data (28-Feb-2018) were provided as part of this application. Data from this period include PK results from subjects in Cohort 1 and and from the Extension Cohort. The updated cut-off allowed assessment of PK parameters of eltrombopag in 33 subjects in Extension Cohort, of whom: 1 subject received daily eltrombopag at 37.5 mg (South-East Asian, 10 years), 6 subjects at 75 mg (3 non-Asians, of 6 to 7 years and 3 South-East Asians > 18 years), and the remaining 26 subjects at 150 mg. No PK data were collected in patients aged 2 to 5 years.

Table 10. Summary of steady state PK parameters for eltrombopag at the 150 mg dose – Pharmacokinetic analysis set at 150 mg dose (cut-off 28-Feb-2018).

	Cohort 1 N=19	Extension Cohort N=26	Pooled Cohort 1 + Extension Cohort N=45
Cmax (µg/mL)	**n=19**	**n=26**	**n=45**
Mean (SD)	36.8 (13.1)	48.4 (18.4)	43.5 (17.2)
Coefficient of variation (%)	35.7	38.0	39.6
Geo-mean	34.1	45.0	40.1
Geo-coefficient of variation (%)	44.2	41.8	44.9
Median (Min;Max)	38.2 (12.4;57.2)	47.4 (15.0;87.4)	40.7 (12.4;87.4)
Tmax (h)	**n=19**	**n=26**	**n=45**
Median (Min;Max)	4.0 (1.92; 6.0)	5.98 (1.93;8.00)	4.00 (1.92;8.00)
Ctrough (µg/mL) at Days 8-30	**-**	**n=26**	**n=26**
Mean (SD)		31.0 (12.7)	31.0 (12.7)
Coefficient of variation (%)		40.9	40.9
Geo-mean		28.4	28.4
Geo-coefficient of variation (%)		46.9	46.9
Median (Min;Max)		27.8 ([8.77;54.7)	27.8 (8.77;54.7)
Ctrough (µg/mL) at Months 3/6	**n=19**	**n=21**	**n=40**
Mean (SD)	27.2 (12.0)	39.0 (16.2)	33.4 (15.4)
Coefficient of variation (%)	44.0	41.4	45.9
Geo-mean	23.9	35.4	29.4
Geo-coefficient of variation (%)	65.8	51.0	61.9
Median (Min;Max)	26.3 (3.62;49.5)	37.7 (11.8;73.5)	32.5 (3.62;73.5)
AUClast (h.µg/mL)	**n=19**	**n=26**	**n=45**
Mean (SD)	737 (285)	919 (347)	842 (332)
Coefficient of variation (%)	38.8	37.8	39.4
Geo-mean	671	855	772
Geo-coefficient of variation (%)	51.3	41.6	47.2
Median (Min;Max)	813 (179;1230)	867 (292;1690)	817 (179;1690)

Data cutoff: 28-Feb-2018
n is the number of patients with corresponding evaluable PK parameters. Geo: geometric.

Subgroup analyses by dose, gender, race, and by hematological response at Month 3 including subjects in Cohort 1 and Extension cohort are presented in table 11 and figure 2.

Table 11. Summary of dose-normalized PK parameters for eltrombopag by gender Pharmacokinetic analysis set (cut-off 28-Feb-2018).

		Cohort 1 + Extension Cohort			
Parameter	Statistics	E/SE Asian Female N=2	non-E/SE Asian Female N=30	E/SE Asian Male N=1	non-E/SE Asian Male N=17
Cmax (ug/mL)	n	2	30	1	17
	Mean(SD)	74.0(20.4)	49.5(16.8)	39.8(-)	33.9(12.3)
	CV%	27.5	33.9	-	36.4
	Geo-mean	72.6	46.6	39.8	31.5
	Geo-CV%	28.4	37.5	-	43.1
	Median	74.0	48.6	39.8	36.0
	[Min; Max]	[59.6;88.4]	[15.0;87.4]	[39.8;39.8]	[12.4;55.4]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- Dose-normalized PK parameter (Cthrough, Cmax and AUClast)= actual PK parameter X (150 / leading dose)
- PK parameters derived from PK samples collected at Month 3 for Cohort 1 subjects and at Day 8-30 for Extension Cohort subjects.
- Subjects < 12 years are excluded.
- Subject #133 was 20 years old asian female but the exact origin was missing. However, she started eltrombopag at a dose of 75 mg/day suggesting she was East or South-East (E/SE) Asian. For this summary, this subject was considered as E/SE Asian

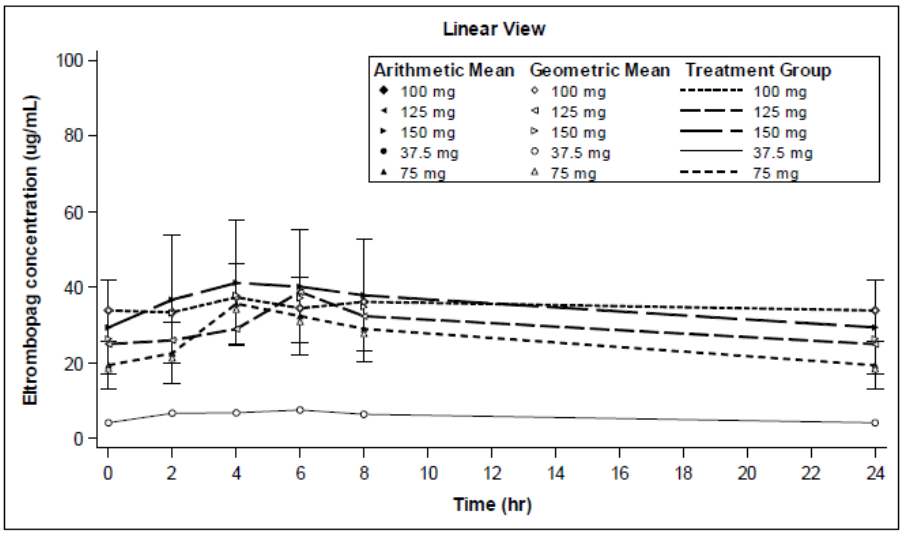
		Cohort 1 + Extension Cohort			
Parameter	Statistics	E/SE Asian Female N=2	non-E/SE Asian Female N=30	E/SE Asian Male N=1	non-E/SE Asian Male N=17
AUClast (h*ug/mL)	n	2	30	1	17
	Mean(SD)	1370(343)	954(317)	767(-)	670(277)
	CV%	25.0	33.2	-	41.4
	Geo-mean	1350	900	767	609
	Geo-CV%	25.7	37.3	-	50.6
	Median	1370	894	767	656
	[Min; Max]	[1130;1620]	[292;1690]	[767;767]	[179;1230]

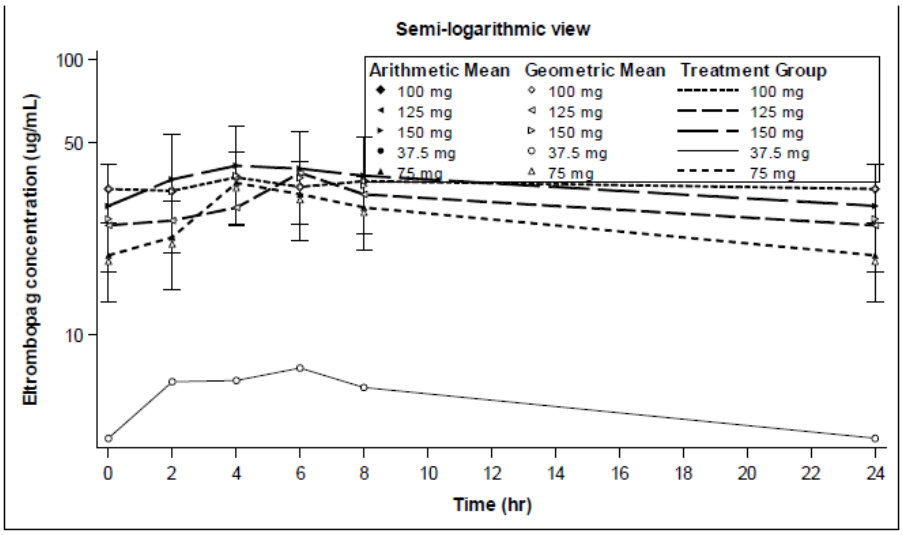
- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- Dose-normalized PK parameter (Cthrough, Cmax and AUClast)= actual PK parameter X (150 / leading dose)
- PK parameters derived from PK samples collected at Month 3 for Cohort 1 subjects and at Day 8-30 for Extension Cohort subjects.
- Subjects < 12 years are excluded.
- Subject #133 was 20 years old asian female but the exact origin was missing. However, she started eltrombopag at a dose of 75 mg/day suggesting she was East or South-East (E/SE) Asian. For this summary, this subject was considered as E/SE Asian

		Cohort 1 + Extension Cohort			
Parameter	Statistics	E/SE Asian Female N=2	non-E/SE Asian Female N=30	E/SE Asian Male N=1	non-E/SE Asian Male N=17
Ctrough (ug/mL)	n	2	30	1	17
	Mean(SD)	45.5(11.2)	33.5(12.0)	27.0(-)	23.4(11.1)
	CV%	24.6	35.7	-	47.2
	Geo-mean	44.8	31.2	27.0	20.6
	Geo-CV%	25.2	42.4	-	64.2
	Median	45.5	31.9	27.0	22.0
	[Min; Max]	[37.6;53.4]	[8.77;54.7]	[27.0;27.0]	[3.62;49.5]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- Dose-normalized PK parameter (Cthrough, Cmax and AUClast)= actual PK parameter X (150 / leading dose)
- PK parameters derived from PK samples collected at Month 3 for Cohort 1 subjects and at Day 8-30 for Extension Cohort subjects.
- Subjects < 12 years are excluded.
- Subject #133 was 20 years old asian female but the exact origin was missing. However, she started eltrombopag at a dose of 75 mg/day suggesting she was East or South-East (E/SE) Asian. For this summary, this subject was considered as E/SE Asian

Figure 2. Geometric and arithmetic means of eltrombopag concentrations over time, by leading dose-Pharmacokinetics analysis set.





Cutoff date 28-Feb-2018

Table 12. Summary of dose-normalized PK parameters for eltrombopag by age Pharmacokinetic analysis set (cut-off 28-Feb-2018).

		Cohort 1 + Extension Cohort					
Parameter	Statistics	E/SE Asian 6-11 years N=1	non-E/SE Asian 6-11 years N=3	E/SE Asian 12-17 years N=0	non-E/SE Asian 12-17 years N=8	E/SE Asian >= 18 years N=3	non-E/SE Asian >= 18 years N=39
Cmax (ug/mL)	n	1	3	-	8	3	39
	Mean(SD)	30.2(-)	80.1(16.9)	-(-)	44.2(18.1)	62.6(24.4)	43.8(17.0)
	CV%	-	21.1	-	40.8	39.0	38.8
	Geo-mean	30.2	78.9	-	41.6	59.4	40.3
	Geo-CV%	-	21.5	-	37.7	41.5	46.0
	Median	30.2	79.0	-	36.3	59.6	42.7
	[Min; Max]	[30.2;30.2]	[63.8;97.6]	[-;-]	[26.2;81.2]	[39.8;88.4]	[12.4;87.4]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- Dose-normalized PK parameter (Cthrough, Cmax and AUClast)= actual PK parameter X (150 / leading dose)
- PK parameters derived from PK samples collected at Month 3 for Cohort 1 subjects and at Day 8-30 for Extension Cohort subjects.
- Subject #133 was 20 years old asian female but the exact origin was missing. However, she started eltrombopag at a dose of 75 mg/day suggesting she was East or South-East (E/SE) Asian. For this summary, this subject was considered as E/SE Asian
- No patient in the subgroup of 2-5 years provided PK data.

		Cohort 1 + Extension Cohort					
Parameter	Statistics	E/SE Asian 6-11 years N=1	non-E/SE Asian 6-11 years N=3	E/SE Asian 12-17 years N=0	non-E/SE Asian 12-17 years N=8	E/SE Asian >= 18 years N=3	non-E/SE Asian >= 18 years N=39
AUClast (h*ug/mL)	n	1	3	-	8	3	39
	Mean(SD)	551(-)	1320(387)	-(-)	827(353)	1170(426)	856(330)
	CV%	-	29.3	-	42.7	36.3	38.6
	Geo-mean	551	1280	-	767	1120	785
	Geo-CV%	-	32.4	-	42.5	38.6	40.1
	Median	551	1400	-	756	1130	864
	[Min; Max]	[551;551]	[902;1670]	[-;-]	[441;1460]	[767;1620]	[179;1690]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- Dose-normalized PK parameter (Cthrough, Cmax and AUClast)= actual PK parameter X (150 / leading dose)
- PK parameters derived from PK samples collected at Month 3 for Cohort 1 subjects and at Day 8-30 for Extension Cohort subjects.
- Subject #133 was 20 years old asian female but the exact origin was missing. However, she started eltrombopag at a dose of 75 mg/day suggesting she was East or South-East (E/SE) Asian. For this summary, this subject was considered as E/SE Asian
- No patient in the subgroup of 2-5 years provided PK data.

		Cohort 1 + Extension Cohort					
Parameter	Statistics	E/SE Asian 6-11 years N=1	non-E/SE Asian 6-11 years N=3	E/SE Asian 12-17 years N=0	non-E/SE Asian 12-17 years N=8	E/SE Asian >= 18 years N=3	non-E/SE Asian >= 18 years N=39
Ctrough (ug/mL)	n	1	3	-	8	3	39
	Mean(SD)	16.8(-)	40.9(15.7)	-(-)	28.4(13.9)	39.3(13.3)	30.2(12.4)
	CV%	-	38.4	-	49.0	33.8	41.1
	Geo-mean	16.8	38.4	-	25.6	37.8	27.1
	Geo-CV%	-	47.7	-	51.9	35.1	56.5
	Median	16.8	48.8	-	26.4	37.6	29.4
	[Min; Max]	[16.8;16.8]	[22.8;51.0]	[-;-]	[14.4;52.8]	[27.0;53.4]	[3.62;54.7]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- Dose-normalized PK parameter (Cthrough, Cmax and AUClast)= actual PK parameter X (150 / leading dose)
- PK parameters derived from PK samples collected at Month 3 for Cohort 1 subjects and at Day 8-30 for Extension Cohort subjects.
- Subject #133 was 20 years old asian female but the exact origin was missing. However, she started eltrombopag at a dose of 75 mg/day suggesting she was East or South-East (E/SE) Asian. For this summary, this subject was considered as E/SE Asian
- No patient in the subgroup of 2-5 years provided PK data.

Regarding PK results by age subgroup in a total of 50 non-Asian naïve SAA subjects, 3 of them were aged from 6 to 11 years, a total of 8 were aged 12-17 years and 39 subjects aged >18 years. These 50 subjects received from 75 to 150 mg/day of eltrombopag. Exposure to eltrombopag in the non-Asian SAA paediatric patients when PK parameters were dose-normalised was consistent with what was previously observed in paediatris ITP patients, in relation to the >12 years age group (Table 13).

Table 13. Summary of dose-normalized PK parameters for eltrombopag by age in non-East/South-East Asian SAA subjects.

	6-11 years N=3	12-17 years N=8	> 18 years N=39
DN-Cmax (µg/mL)	78.9 (21.5)	41.6 (37.7)	40.3 (46.0)
Tmax (h)	4 (3.92-4.08)	5.01 (4.00-6.00)	4.00 (1.92-8.00)
DN-AUClast (µg*h/mL)	1280 (32.4)	767 (42.5)	785 (48.1)
DN-Ctrough (µg/mL)	38.4 (47.7)	25.6 (51.9)	27.1 (56.5)

DN: Dose-normalized. Data are presented as Geo Means (CV% of Geo Means) except for Tmax, for which Median (MinMax) are presented. PK parameters in non-East/South-East Asians are presented normalized to a 150 mg dose.

Studies providing supportive PK data in healthy subjects, in subjects with ITP, and in subjects with CLD

Pharmacokinetics comparison SAA (study AUS01T) vs. non-SAA (healthy subjects, in subjects with ITP, and in subjects with CLD).

Pharmacokinetic results in Study AUS01T after the original cut-off (30-sept-2016) were compared with published data in healthy subjects *(Matthys et al 2011)*, in subjects with chronic immune thrombocytopenia (ITP), the first indication of eltrombopag *(Gibiansky et al 2011),* and in subjects with chronic liver disease (CLD) *(Farrell et al 2013).* The details of the studies and analyses from which the reference PK data was derived are summarised in table 6.

To enable comparisons between populations, the PK parameters obtained at 150 mg in Study AUS01T were adjusted to the theoretical dose for which empirical Bayes estimates for AUC and Cmax were calculated in the ITP and CLD publications (50 mg, Table 6), under the assumption of PK linearity.

When considering a similar dose (by dose-normalising to 50 mg), exposure in definitive IST-naïve subjects with SAA from Study AUS01T was between 2- to 3- fold higher than exposure in healthy subjects, and in subjects with ITP, whereas it was similar to the exposure in subjects with CLD (Table 14).

Table 14. Estimates of steady-state geometric mean Cmax and AUC following once-daily administration of eltrombopag in definitive IST-naïve SAA versus non-SAA subjects.

Study	Population	Dose	N	Cmax (µg/mL)	AUC (µg.h/mL)
[Study AUS01T]	Definitive IST-naive SAA	150 mg	19	34.1	671
		Normalized to a theoretical 50 mg dose		11.3	224
Matthys et al 2011	Healthy subjects	150 mg	8	22.8	239
Gibiansky et al 2011	ITP	Empirical Bayes estimate for a 50 mg dose	88	7.5	99
Farrell et al 2013	CLD	Empirical Bayes estimate for a 50 mg dose	79	15.2	221

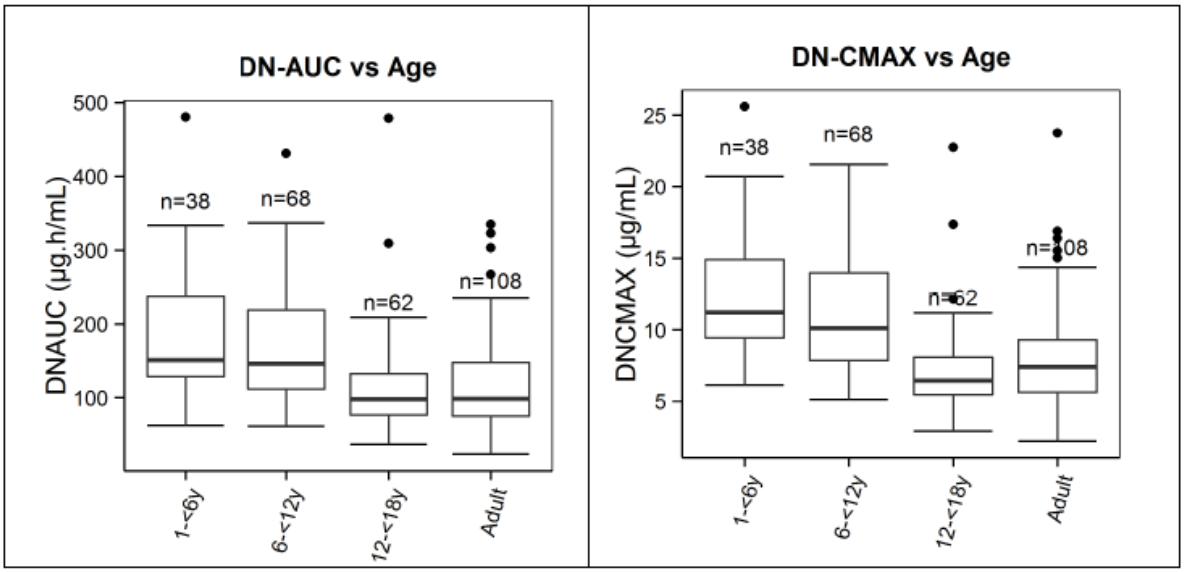
After the updated cut-off (28-Feb-2018) the MAH provided PK data in ITP patients by age subgroup (Table 15 and Figure 3). These results showed similar exposure to eltrombopag (AUC, Cmáx and Ctrough) between adults and children aged 12-17 years. However, PK behaviour was found to be similar between younger patients (i.e. 6-11 years and 1-5 years). Comparing exposures between patients aged >12 years (including adults) vs ≤11 years, exposure to eltrombopag was higher in younger group (Cmax and AUC were approximately 50-65% higher and Ctrough was approximately 40% higher, in relation to >12 years group).

Table 15. Summary of dose normalized PK parameters for eltrombopag by subgroup in ITP patients.

Covariate	N	DN-AUCtau (µg.h/mL)	DN-Cmax (µg/mL)	DN-Ctrough (µg/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)
Age							
12-17 Years	62	103 (91.1, 116)	6.80 (6.17, 7.50)	2.43 (2.08, 2.85)	4.0 (2.0-6.0)	51.9 (48.4, 55.7)	0.49 (0.43, 0.55)
6-11 Years	68	153 (137, 170)	10.3 (9.42, 11.2)	3.55 (3.06, 4.11)	4.0 (2.0-6.0)	50.3 (47.4, 53.3)	0.33 (0.29, 0.36)
1-5 Years	38	162 (139, 187)	11.6 (10.4, 12.9)	3.48 (2.76, 4.40)	4.0 (2.0-4.0)	46.9 (42.9, 51.2)	0.22 (0.19, 0.25)
Adult	108	101 (91.4, 113)	7.03 (6.44, 7.68)	2.54 (2.21, 2.91)	4.0 (1.0-6.0)	44.0 (41.8, 46.3)	0.49 (0.44, 0.55)

Data presented as geometric mean (95% CI), except tmax presented as median (minimun, maximum)
DN: dose normalized to 50 mg
Source: Report 2013N181329_00 (TRA108062, TRA115450) submitted to NDA 207027 (SN 0000)

Figure 3. Plasma eltrombopag dose-normalized (to 50mg) AUC(0-tau) and Cmax by covariates in ITP patients.



Median (line inside box), Interquartile Range (IQR, box), 1.5x IQR (whiskers), outliers (points)
Source: Report 2013N181329_00 (TRA108062, TRA115450) submitted to NDA 207027 (SN 0000)

Studies providing supportive PK data Japanese naïve and refractory patients

The absence of East/South-East Asian subjects in the study PK dataset on study AUS01T did not allow for the characterisation of differences in ethnic exposure. Therefore, comparisons with other studies were performed using PK data from the 2 supportive Japanese studies in refractory aplastic anemia (Study E1201) and definitive IST-naïve aplastic anemia (Study E1202).

Description of Japanese Studies

- Study E1201

This was a non-randomized, open-label, phase II study to assess the efficacy and safety of eltrombopag monotherapy in Japanese subjects with moderate or more severe AA with a platelet count < 30,000/µL who were refractory to ATG-based IST, who had relapsed after ATG-based IST, or who were ineligible for ATG-based IST. Treatment with eltrombopag was started at 25 mg/day and adjusted according to the platelet count. Twenty-one subjects were enrolled in the study. All were evaluable for the PK assessment. The details of the studies and analyses are summarized in Table 5.

Exposure to eltrombopag (AUC, Cmax) was measured at steady-state (Day 15) and was considered similar to the previously reported values in Japanese ITP subjects. Trough concentrations increased with ascending dose from 25 to 100 mg. No substantial difference was apparent in the PK of eltrombopag monotherapy when comparing Japanese AA and ITP subjects.

- Study E1202

This was a non-randomized, open label, single-arm, phase II study to evaluate the efficacy and safety of eltrombopag in combination with rabbit ATG/CsA in Japanese subjects with moderate or more severe AA who had not received prior ATG/ALG-based immunosuppressive therapy.

Subjects who were considered eligible in Screening and in the Day 1 tests started treatment with rabbit ATG/CsA on Day 1 (start of treatment). Treatment with eltrombopag was started on Day 15 (± 3 days). The dose of eltrombopag was 75 mg/day initially and could be decreased according to the platelet count or safety. Rabbit ATG was administered at a dose of 2.5 to 3.75 mg/kg/day for 5 days. CsA was administered until Week 26. Eltrombopag was administered until Week 26 unless meeting the stopping or withdrawal criteria. Ten (10) subjects were enrolled in the study. All were evaluable for the PK assessment (day 15 trough, steady-state) described in Table 5.

Trough concentrations increased with ascending dose from 25 to 75 mg.

Pharmacokinetics comparison: study AUS01T vs. Japanese studies (naïve and refractory studies)

For the comparison of eltrombopag exposure between definitive IST-naïve AA subjects of Asian (Study E1202) to subjects of non-Asian origin (Study AUS01T, cut-off 30-Sept-2016), stead-state Ctrough was used. The geometric mean Ctrough at 75 mg in the 10 Japanese subjects receiving 75 mg eltrombopag (20.4 µg/mL) was similar to the geometric mean Ctrough in non-Japanese subjects receiving twice the dose at 150 mg eltrombopag (23.9 µg/mL). The observation of similar exposure for a 2-fold difference in dose is consistent with the previously identified ethnic sensitivity factor (2-fold higher exposure in Asian compared to non-Asian) (Table 16).

Table 16. Estimates of steady-state PK parameters of eltrombopag following once daily administration in Japan (Studies E1201 and E1202) versus non-Japan population (AUS01T Study cut-off 30-Sept-2016).

Study	Population	Dose	n	Ctrough (µg/mL)) Geometric mean (Geometric mean CV%)	Ctrough (µg/mL) Median (range)
[Study AUS01T]	Non-Japanese definitive IST-naive SAA	150 mg	19	23.9 (66%)	26.3 (3.6 – 49.5)
		Normalized to a theoretical 75 mg dose		12.0 (66%)	11.8 (1.8 – 24.8)
[Study E1201]	Japanese refractory MAA and SAA	75 mg	20	9.9 (146%)	13.7 (1.0 – 37.3)
[Study E1202]	Japanese IST-naive MAA and SAA	75 mg	10	20.4 (41%)	21.3 (8.1 – 34.9)

Source: Individual CSRs.

Results in Japanese subjects suggest that Aat the same dose, average exposure in refractory AA (Study E1201) is approximately 2-fold lower than exposure in definitive IST-naïve AA (Study E1202). The generally high variability on Ctrough (CV% = 146%) could contribute to this difference, as the ranges of

individual Ctrough values between Study E1201 (1.0 – 37.3 µg/mL) and Study E1202 (8.1 - 34.6 µg/mL) were overlapping.

The origin of a possible overexposure in subjects with definitive IST-naïve AA receiving eltrombopag as a combination with CsA and ATG was investigated. The hypothesis that CsA, combined with eltrombopag in E1202 and AUS01T could increase eltrombopag exposure (CsA being a BCRP inhibitor and eltrombopag being a BCRP substrate) was assessed. A formal clinical drug-drug interaction study was carried out to assess the effect of CsA on the plasma PK of eltrombopag (Zhang et al 2015). This was a Phase I, open-label, randomized, three-period crossover study in healthy adult subjects. Results showed that there was no increase in eltrombopag exposure when eltrombopag was co-administered with CsA at the doses of 200 mg or 600 mg. A statistically significant decrease in eltrombopag exposure was observed when it was coadministered with CsA, but it was not considered clinically meaningful (Zhang et al 2015). Therefore it is unlikely that the combination with CsA was responsible for the increased exposure to eltrombopag when it is combined with CsA in definitive IST-naïve AA subjects.

The composition of the dataset from AUS01T (proportion of subjects usually associated with higher eltrombopag exposure like females, children, elderly, subjects with hepatic impairment, East/South-East Asian subjects) could also not explain this observation.

The summary of PK parameters at the 150 mg dose in these cohorts (and the pooled data) were presented during evaluation. After daily 150 mg doses, the PK of eltrombopag at steady-state was similar between subjects in Cohort 1 and Extension Cohort both for rate and for extent of absorption. Peak concentrations (Cmax) in plasma were achieved between 2 and 8 hours (Tmax) after the morning dose and the overall variability of parameters was moderate, in line with what was reported in previous clinical studies.

2.3.3. Pharmacodynamics

Mechanism of action

Eltrombopag is an oral TPO-receptor (TPO-R) agonist, which interacts with the transmembrane domain of the TPO-R on megakaryocytes and human bone marrow progenitor cells. Eltrombopag increases hematopoiesis by inducing proliferation and differentiation of early bone marrow progenitor cells. The multilineage effects of eltrombopag in subjects with aplastic anemia may be through stimulation of bone marrow progenitor cells, as suggested by some preclinical research.

Results on eltrombopag mechanism of action, ethnopharmacologic and paediatric differences in exposure were detailed in prior applications.

2.3.4. PK/PD

The small sample size and the restriction of PK and PD observations to a subset of subjects enrolled in Cohort 1 in Study AUS01T did not allow an extensive evaluation of PK/PD relationships. At Month 3, hematological response was observed at all quartiles of exposure measures with no particular trend. There was no apparent relationship between eltrombopag exposure and the occurrence of selected abnormal liver and renal function parameters at Month 3.

2.3.5. Discussion on clinical pharmacology

A clinical pharmacology program had already been conducted for eltrombopag and was detailed in prior applications. Current information on absorption, distribution, metabolism, excretion and drug-drug

interactions of eltrombopag is described in the approved SmPC and is considered adequate for the target population.

To assess the pharmacokinetics in SAA naïve patients, data from the AUS01T are used. This is a non-randomized, single-arm, single-center, Phase I/II study investigating the standard regimen of h-ATG and CsA, in combination with eltrombopag as experimental therapy in subjects with SAA who have not received prior definitive IST. The PK of eltrombopag was an exploratory objective of this study.

The study included 3 Cohorts that differed only by the treatment starting day, duration of eltrombopag and the addition of a CsA maintenance regimen. h-ATG was administered at a dose of 40 mg/kg. CsA dosing was based on body weight, except for obese subjects for whom the dose was based on the adjusted body weight that was calculated as the midpoint between the ideal weight and actual body weight. Total daily dose of CsA for subjects ≥ 12 years and <12 years was 6 mg/kg/day and 12 mg/kg/day, respectively. CsA dosing was adjusted to obtain a therapeutic trough level between 200 to 400 μg/L. Subjects received their starting dose of eltrombopag according to their age and ethnicity (East/South-East Asian or non-Asian). Eltrombopag 150 mg once daily was selected as the starting dose for non-Asian ≥12 year old subjects. Eltrombopag starting dose in East/South-East Asian subjects was 50% lower than those in non-Asians.

After the first cut-off (30-Sept-2016), only subjects enrolled in Cohort 1 who had received once daily eltrombopag for at least 7 days prior to the landmark month 3 visit (to be at PK steady-state with no recent dose interruptions) were included in the PK assessments. Twenty-one (21) subjects enrolled in Cohort I (AUST01) were evaluable for PK, 1 subject at the 100 mg dose, 1 subject at the 125 mg dose, and 19 subjects at the 150 mg dose. Three (3) out of 21 subjects were adolescents aged 12, 14, and 17 years (2 of them received 150 mg dose). There were no children between 2 and 11 years old included in the PK study and there were only two older than 12 years. There was no East/South-East Asian subject evaluable for the PK assessment.

The update cut-off (28-feb-2018) allowed assessment on PK parameters of eltrombopag in 33 subjects in Extension Cohort, of whom 1 subject received eltrombopag at 37.5 mg/day (South-East Asian, 10 years), 6 subjects 75 mg/day (3 non-Asians of 6 to 7 years and 3 South-East Asian >18 years), and the remaining 26 subjects at 150 mg/day. Results with the update cut-off (28-Feb-2018) showed similar results as those obtained during the original cut-off. Eltrombopag was absorbed with a peak plasma concentration occurring 2-8 hours after repeat oral administration. In the 45 subjects with PK at the dose 150 mg dose the geometric mean (geometric mean coefficient of variation - CV) Cmax was 40.1 μg/mL (45%), AUClast (equivalent to AUC0-24 post-dose, henceforth will be referred to as AUC) was 772 h.μg/mL (47%), and Ctrough was 29.4 μg/mL (62%). Overall variability of PK parameters at 150 mg was moderate, with geometric mean CV below 62% for all parameters.

In addition, subgroup analyses by dose-normalised (to 150 mg/day), gender, race, and by hematological response at Month 3 including subjects in Cohort 1 and Extension cohort was performed. The analysis by gender confirmed a trend of higher exposure in females and South-Asian subjects when compared to male subjects or other races (Cmax, Ctrough and AUClast were approximately 40 to 50% higher in female and South-East Asian subjects when compared to male subjects and to other races). For the other subgroup analyses, no notable difference between subgroups was observed.

Regarding PK results by age subgroup in a total of 50 non-Asian naïve SAA subjects, 3 of them were aged from 6 to 11 years and total of 8 and 39 subjects aged 12-17 years and >18 years were respectively included. These 50 subjects received from 75 to 150 mg/day of eltrombopag. When PK parameters were dose-normalised, a trend of higher exposure was observed in 6 to 11 years old subgroup when compared to older groups (Cmax, and AUClast in 6 to 11 years subjects were approximately 60-80% higher than in older age groups, whereas Ctrough are approximately 30% higher than in older age groups). PK results seen in 12-17 years subgroup and in adults could be considered similar. However, regarding adolescents

this assertion is based only on PK data from 8 patients which is considered not enough to assure PK behaviour in this age group. Also it must be taken into account that only 3 subjects aged from 6 to 11 years and no patients aged 2 to 5 were included in the PK assessment. Therefore, the CHMP consider PK in patients aged <12 years has not been well established.

In this respect, it is worth noting that according to the Paediatric Investigation Plan, an open-label, non-controlled, intra-patient dose-escalating trial to evaluate PK, safety, activity and acceptability/palatability of eltrombopag in children from 1 year to less than 18 years of age with SAA that is refractory, or relapsed after IST or with newly diagnosed in combination with IST is planned (Study identifier CETB115E2201). In this study, PK assessment will be the primary endpoint with a dose escalation schedule according to paediatric age. 20 paediatric patients on each group (relapsed/refractory and treatment naïve to IST) are planned to be included.

The PK results above described in SAA naïve patients (Study AUS01T) after the original cut-off (30-Sept-2016) were compared with PK data obtained in other indications currently authorised (i.e ITP, healthy subjects and CLD) from other studies (Matthys *et al* 201, Gibiansky *et al* 2011 and Farrell *et al* 2013). To enable comparisons between populations, the PK parameters obtained at 150 mg in Study AUS01T were adjusted to the theoretical dose for which empirical Bayes estimates for AUC and Cmax were calculated in the ITP and CLD publications (50 mg), under the assumption of PK linearity.

When considering a similar dose (by dose-normalising to 50 mg), exposure in definitive IST-naïve subjects with SAA from Study AUS01T (AUC for 150 mg dose=671 µh.h/ml; AUC for normalised 50 mg dose =224 µh.h/ml) was between 2- to 3- fold higher than exposure in healthy subjects (AUC for 150 mg dose=239) µh.h/ml,) and in subjects with ITP (AUC for 50 mg dose=99 µh.h/ml), whereas it was similar to the exposure in subjects with CLD (AUC for 50 mg dose=221 µh.h/ml). In addition and after the updated cut-off, the MAH provided exposure data by subgroup age in ITP and SAA naïve non-Asian patients. These results showed similar exposure to eltrombopag (AUC, Cmáx and Ctrough) between ITP adults and children aged 12-17 years. This exposure was approximately 2-fold in ITP younger patients (i.e. 11 years and 1-5 years). PK data in naïve SAA patients by age subgroup showed similar behaviour: the exposure was higher in >12 years old subgroup (including adults) in comparison to younger group (6-11 years old). No naïve SAA patients aged between 1-5 years were included in the PK analysis, therefore no conclusion can be drawn in this age group. Also it is important to consider that in the naïve SAA 6-11 years old group, only 3 patients were included for PK analysis which is not considered appropriate to adequately describe the PK behaviour.

In addition, and in the absence of East/South-east Asian subjects in the PK AUS01T study (cut-off 30-Sept-2016), a comparison with other studies was performed using PK data (Ctrough was used) from the 2 supportive Japanese studies in refractory aplastic anemia (Study E1201) and definitive IST-naïve aplastic anemia (Study E1202).

In Study E1201, the exposure to eltrombopag (AUC, Cmax) measured at steady-state was considered similar to the previously reported values in Japanese ITP subjects. No substantial difference was apparent in the PK of eltrombopag monotherapy when starting at 25 mg/day and adjusting according to the platelet count, comparing Japanese AA and ITP subjects. In Study E1202 trough concentrations increased with ascending dose from 25 to 75 mg. Regarding the results obtained for the comparison of SAA naïve patients in AUS01T vs. Japanese refractory AA population, steady-state Ctrough was used and similar results in median Ctrough were seen (Study AUS01T median Ctrough for normalised 75 mg dose=11.8 µg/ml [1.8-24.8]; Study E1201 median Ctrough for 75 mg dose=13.7 µg/ml [1.0-37.9]). In Study E1202, the comparison of eltrombopag exposure between definitive IST-naïve AA Japanese patients (Study E1202) to non-Asian origin (Study AUS01T), suggested that at the same dose, average exposure is approximately 2-fold higher in Japanese naïve patients (mean Ctrough for 75 mg dose in Japanese

subjects= 21.3 µg/mL [8.1-34.9]; mean Ctrough for normalised 75 mg dose in non-Asian subjects=11.8 µg/mL [1.8-24.8]).

Given all these results, no differences were found in the exposure to eltrombopag between naïve SAA patients and CLD patients. On the contrary, differences in exposure were found between treatment-naïve SAA patients and ITP. However, similar trend in exposure by age group were found between >12 years ITP and naïve-SAA patients vs <12 years ITP and naïve SAA patients.

At the same time differences were found between Japanese refractory and Japanese naïve patients (and therefore between Japanese naïve SAA and non-Asian naïve SAA patients). No justification has been provided for this finding. Considering that PK behaviour of eltrombopag could be different for all naïve and non-naïve patients, the MAH was asked to discuss the PK results observed in non-Asian naïve SAA patients compared with non-naïve SAA patients. No justification has been provided, at this time point. However we agree with the MAH that, despite the higher eltrombopag exposures observed in naïve SAA patients, the safety profile of eltrombopag at doses up to 150 mg/day in naive SAA in AUS01T Study was consistent with the established safety profile in the approved IPT, HCV and refractory SAA indications. In addition, dose adjustment rules based on platelet response and safety events of liver functions and thrombosis were proposed.

2.3.6. Conclusions on clinical pharmacology

The MAH provided updated PK data from AUS01T study in 50 non-Asian naïve SAA patients who received 75-150 mg/day of eltrombopag (cohort 1 and Extension cohort from study AUS01T). With this new PK data 12-17 years and >18 years subgroups are better represented (8 subjects and 39 subjects, respectively). According to PK results between these two age subgroups exposure to eltrombopag appears similar. Comparing eltrombopag exposure in >12 years naïve SAA patients with ITP patients, similar behaviour has been found. However, the PK profile in adolescents is still considered not well defined in this age group.

Regarding the PK results in younger subgroups a trend of higher exposure was observed in 6 to 11 years old subgroup when compared to older ones. However the number of patients in this age range included for this assessment, only three, is considered insufficient to characterise PK behaviour. In addition no patient from 2-5 years were included.

According to the PIP, the results of the planned trial proposed in paediatric patients (naïve and non-naïve SAA paediatric patients, CETB115E2201) would shed light on this issue.

2.4. Clinical efficacy

The efficacy evaluation of eltrombopag with standard IST for the treatment of SAA as a first-line therapy is predominantly based on data from 123 subjects (enrolled as of 30-Sept-2016) who have been exposed to treatment with eltrombopag added to horse anti-thymocyte globulin (h-ATG)+cyclosporine (CsA) in the pivotal Study AUS01T. The MAH updated these data with the responses during evaluation, using a new cut-off date (28-Feb-2018). With this new cut-off date, data are provided for 30 additional subjects (8 paediatrics and 22 adults) providing data for a total of 92 patients presented in the Cohort 3+extension, in which the treatment recommended by the MAH was given. Moreover, with this cut-off-date 41 additional subjects were evaluable at month 6 for the efficacy, resulting in a total of 87 subjects evaluable in cohort3+extension.

Efficacy data from 4 historical studies are also presented to assess the effect of adding eltrombopag to standard therapy of h-ATG+CsA; these include Scheinberg *et al* 2009, Scheinberg *et al* 2011, Tisdale *et al* 2000, and Rosenfeld *et al* 2003. In addition, efficacy results from Study E1202 and Boddu *et al* 2017 are provided to independently substantiate the results of the pivotal study (Table 17).

The key efficacy analyses are primarily based on complete response (CR) and overall response (OR) rates at the landmark month-6 assessment, for both the pivotal Study AUS01T and the individual studies included in the historical analysis for comparisons of eltrombopag with h-ATG+CsA to the historical arms h-ATG+CSA alone.

Table 17. Description of clinical efficacy studies

Publication (Study #)	Population/ No. of subjects efficacy)	Study description	Treatment regimen	Dose in arm of interest	Efficacy endpoints for comparison
			Pivotal Study		
Study AUS01T	Definitive IST-naïve SAA (N = 123): Cohort 1 (N=30) Cohort 2 (N=31) Cohort 3 (N=31) Extension Cohort 3 (N=31 and still recruiting)	Non-randomized, 3 cohorts	3 sequential cohorts: Cohort 1: h-ATG (Day 1-4) + CsA[1] (Day 1-Month 6) + Eltrombopag (Day 14-Month 6) Cohort 2: h-ATG (Day 1-4) + CsA[1] (Day 1-Month 6) + Eltrombopag (Day 14-Month 3) Cohort 3 + Extension: h-ATG (Day 1-4) + CsA[1] (Day 1-Month 6) +Eltrombopag (Day 1-Month 6) Maintenance CsA for responders from Month 6 to Month 24.	h-ATG (Day 1-4): 40 mg/kg/day CsA[5] (Day 1 to Month 6) starting dose: - Age ≥12 years: 6 mg/kg/day - Age <12 years: 12 mg/kg/day Eltrombopag (Day 1- Month 6): depends on age and ethnicity, maximum 150 mg/day	CR and OR rates at Month 6
			Historical Studies		
Scheinberg et al 2011 (06-H-0034)	Treatment-naïve subjects with SAA (N = 60)[3]	Randomized, parallel arms	h-ATG (Day 1-4) + CsA (Day 1-Month 6)[4] r-ATG (Day 1-5) + CsA (Day 1-Month 6)	h-ATG (Day 1-4): 40 mg/kg/day CsA[5] (Day 1-Month 6) starting dose: - Age ≥ 12 years: 10 mg/kg/day - Age <12 years: 15 mg/kg/day ORR at Month 6	CR and OR rate at Month 6
Scheinberg et al 2009 (03-H-0193)	Treatment-naïve subjects with SAA (N = 42)[3]	Randomized, parallel arms	h-ATG (Day 1-4) + CsA (Day 1-Month 6)[4] h-ATG (Day 1-4) + CsA (Day 1-Month 6) + Sirolimus (Day 1-Month 6)	h-ATG (Day 1-4): 40 mg/kg/day CsA[5] (Day 1 to Month 6) starting dose: - Age ≥ 12 years: 10 mg/kg/day - Age <12 years: 15 mg/kg/day	CR and OR rates at Month 6
Tisdale et al 2000 (97-H-0117)	Treatment-naïve subjects with SAA (N = 16)[3]	Randomized, parallel arms	h-ATG (Day 1-4) + CsA (Day 1-Month 6)[4] Cyclophosphamide (Day 1-4) + CsA (Day 1-Month 6)	h-ATG (Day 1-4): 40 mg/kg/day CsA[5] (Day 1- Month 6) starting dose: 12 mg/kg/day	CR and OR rates at Month 6
Rosenfeld et al 2003 (90-H-0146)	Treatment-naïve subjects with SAA (N = 122)	Single arm	h-ATG (D1-4) + CsA (D1-M6)[4]	h-ATG (Day 1-4): 40 mg/kg/day CsA[5] (Day 1-Month 6) starting dose: - Adults: 10 mg/kg/day - Children: 15 mg/kg/day	OR rate at Month 6

Publication (Study #)	Population/ No. of subjects efficacy)	Study description	Treatment regimen	Dose in arm of interest	Efficacy endpoints for comparison
			Independent Substantiation Studies		
Study E1202	ATG/ALG treatment-naïve subjects with MAA or SAA (N = 10, 3 MAA and 7 SAA)	Non-randomized, single arm	r-ATG (Day 1-5) + CsA[2] (Day 1-Month 6) + Eltrombopag (Day 15-Month 6)	r-ATG: 2.5 to 3.75 mg/kg/day CsA[5]: according to prescribing information; starting daily dose ~ 5 to 6 mg/kg Eltrombopag: 75 mg once daily initially; decreased by 25 mg every 2 weeks thereafter according to platelet count or hematologic response criteria[6]	CR and OR rates at Month 6
Boddu et al 2017 (and abstract **Kadia et al 2015**)	Treatment- naïve subjects with SAA (N=42)	Non-randomized, single arm	2 sequential cohorts: IST: h-ATG for 4 days, G-CSF (filgrastim or pegfilgrastim) up to 3 months, and CsA daily up to 6 months Eltrombopag + IST (h-ATG+CsA)	h-ATG 40 mg/kg/day (or 35 mg/kg/day for age ≥ 55 yrs) for 4 days, G-CSF (filgrastim or pegfilgrastim) up to 3 months, and CsA[5] (5mg/kg) daily up to 6 months Eltrombopag: starting dose of 50 mg/day increased by 50 mg every 2 weeks (150 mg daily max)	OR rate at 6 months

IST=immunosuppressive therapy, CsA= cyclosporine, ATG= anti-thymocyte globulin, ALG=anti-lymphocyte globulin, h-ATG =horse anti-thymocyte globulin, r-ATG =rabbit anti-thymocyte globulin, SAA=severe aplastic anemia, OR=overall response

[1]CsA continued at lower dose for 18 months in responders from Cohort 2 (after protocol amendment) and Cohort 3+Extension

[2]After Month 6, CsA was tapered or continued at the discretion of the Investigator

[3]Number of subjects enrolled in h-ATG+CsA treatment arm

[4]For historical studies, only the h-ATG+CsA treatment arm was included in the pooled analyses

[5]CsA dose in each study was determined by exposure levels

[6]Starting dose of 75 mg once daily was selected for children of 12 years up to adults of East and South-East Asian ethnicity due to ethno-pharmacologic differences in exposure

2.4.1. Dose response study

No dose finding studies have been performed in the clinical development of this product. The proposed posology for the first line indication in SAA is eltrombopag 150 mg once daily as the starting dose in patients older than 12 years of age, 75 mg once daily for children between 6 and 11 years of age, and

2.5 mg/kg once daily for children between 2 and 5 years of age in the non-Asian population. In addition, the starting dosing regimen must consider also the ethnicity given the PK differences observed. Further doses should be adjusted based on the subject's platelet counts and the observable safety (Table 18, 19 and 20).

Table 18. Starting dosing of eltrombopag according to age and ethnicity

Ethnicity/Age groups	Daily dose
Non-Asian	
≥ 12 years	150 mg
6-11 years	75 mg
2-5 years	2.5 mg/kg
East-Asian and South-East-Asian	
≥ 12 years	75 mg
6-11 years	37.5 mg
2-5 years	1.25 mg/kg

Table 19. Dose adjustment of eltrombopag on platelet count

Platelet Count	Dose adjustment
> $200x10^3$/µL (untransfused)	Eltrombopag dose should be decreased by 25 mg every 2 weeks to the lowest dose that maintains platelet count ≥ $50x10^3$/µL. In children under 12 years, the dose should be decreased by 12.5 mg.
> $400x10^3$/µL (untransfused)	Eltrombopag should be discontinued for 1 week. Once platelet count is < $200x10^3$/µL, reinitiate eltrombopag at a daily dose reduced by 25 mg (or 12.5 mg in children under 12 years).

Table 20. Recommended dose modification of eltrombopag for liver function abnormalities and thrombosis/embolism

Side effects	Dose adjustment
Liver function abnormalities	Increase in ALT > 6xULN during Days 1 to 14 Discontinue eltrombopag. Once ALT is < 5xULN, reinitiate eltrombopag at the same dose. Increase in ALT > 6xULN after reinitiating eltrombopag (and is not attributable to other inciting factors, e.g. serum sickness, sepsis, or azole antifungal agents): Monitor ALT at least every 3 to 4 days. If ALT remains > 6xULN on repeat blood tests: Discontinue eltrombopag. Once ALT is < 5xULN, reinitiate eltrombopag at a daily dose reduced by 25 mg from the previous dose. If ALT returns to > 6xULN on the reduced dose: Reduce the daily dose of eltrombopag by 25 mg until ALT is < 5xULN.
Thrombosis/ embolism	Deep vein thrombosis (other than a line-related upper extremity thrombosis), pulmonary embolus, TIA or stroke, myocardial infarction at any time while on eltrombopag: Discontinue eltrombopag but remain on h-ATG and CsA. If the platelet level is ≥ $50x10^3$/µL at the time of thrombosis, treatment with enoxaparin or another appropriate anticoagulant is recommended as clinically indicated until the platelet count drops < $20x10^3$/µL or a standard 3 to 6 months course of anticoagulation is completed.

A more detailed explanation about this issue was provided. The starting dose used in AUS01T study is based on results from refractory SAA study (AUS28T), exposure observed between paediatric and adult ITP patients *vs* paediatric SAA patients as well as PK/PD results and safety profile obtained from the AUS01T updated cut-off (28-Feb-2018).

- Results from refractory SAA study (AUS28T).

The eltrombopag dose scheme in the second line SAA pivotal Study AUS28T (also referred as Study ELT112523 or 09-H-0154) in subjects with refractory SAA, consisted of starting doses in non-Asians of 50 mg daily, to be adjusted in 25 mg increments every 2 weeks as necessary and up to a maximum dose of 150 mg daily to achieve the target platelet count ≥ 50,000/μL. Nearly all patients were successfully escalated to the 150 mg daily dose without any dose-limiting toxicity. Haematological responses were only observed while receiving the 150 mg daily dosing. Based on these observations, the NIH modified the dose algorithm in Study AUS01T for first line SAA, with dose adjustments for ethnic and age-related considerations.

Therefore the most effective dose used in AUS28T study (150 mg/day), adjusted for age (<12 years) and ethnicity (East/South-East Asian), was selected as starting dose of eltrombopag in AUS01T.

- Exposure between paediatric and adult ITP patients.

The proposed doses for paediatric subjects (i.e. 75 mg/day 2.5 mg/kg/day for patients aged 6-11 years and 2-5 years, respectively) are based on the pivotal Study AUS01T and on pooled PK analysis from Studies TRA108062 (PETIT) and TRA115450 (PETIT2) in paediatric ITP patients.

In studies TRA108062/PETIT and TRA115450/PETIT2, dose-normalised (DN) eltrombopag exposure (Cmax and AUC) in ITP patients at steady state was similar between paediatric patients in the 12-17 years group and adult patients. This data suggested the use of the same dosing strategy between SAA adult and 12-17 years old SAA patients (i.e. 150 mg in SAA patients ≥12 years) (see next Table 21 and Figure 4).

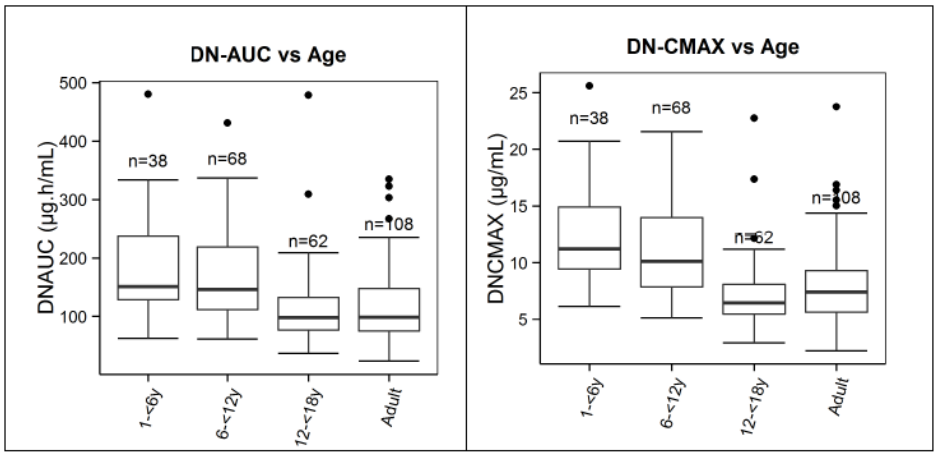
In younger ITP patients, from 1 to 11 years, plasma eltrombopag DN-AUCtau and DN-Cmax values were 60% higher than in patients ≥12 years of age, supporting a 2-fold lower eltrombopag starting dose in subjects of 1 to 11 years of age than in subjects ≥12 years (i.e. 75 mg in SAA patients 6-11 years). According to this rationale patients aged from 2- 5 years would be candidate to receive 75 mg/day of eltrombopag. Instead, a more conservative approach using a weight-based dosing strategy was considered in the younger group (2-5 years).

Table 21. Summary of dose normalised PK parameters for eltrombopag by subgroup in ITP patients.

Covariate	N	DN-AUCtau (µg.h/mL)	DN-Cmax (µg/mL)	DN-Ctrough (µg/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)
Age							
12-17 Years	62	103 (91.1, 116)	6.80 (6.17, 7.50)	2.43 (2.08, 2.85)	4.0 (2.0-6.0)	51.9 (48.4, 55.7)	0.49 (0.43, 0.55)
6-11 Years	68	153 (137, 170)	10.3 (9.42, 11.2)	3.55 (3.06, 4.11)	4.0 (2.0-6.0)	50.3 (47.4, 53.3)	0.33 (0.29, 0.36)
1-5 Years	38	162 (139, 187)	11.6 (10.4, 12.9)	3.48 (2.76, 4.40)	4.0 (2.0-4.0)	46.9 (42.9, 51.2)	0.22 (0.19, 0.25)
Adult	108	101 (91.4, 113)	7.03 (6.44, 7.68)	2.54 (2.21, 2.91)	4.0 (1.0-6.0)	44.0 (41.8, 46.3)	0.49 (0.44, 0.55)

Data presented as geometric mean (95% CI), except tmax presented as median (minimun, maximum)
DN: dose normalized to 50 mg
Source: Report 2013N181329_00 (TRA108062, TRA115450) submitted to NDA 207027 (SN 0000)

Figure 4. Plasma eltrombopag dose-normalized (to 50mg) AUC(0-tau) and Cmax by covariates in ITP patients.



Median (line inside box), Interquartile Range (IQR, box), 1.5x IQR (whiskers), outliers (points)
Source: Report 2013N181329_00 (TRA108062, TRA115450) submitted to NDA 207027 (SN 0000)

The popPK analysis in paediatric ITP patients showed that lower body weight was associated with lower plasma eltrombopag clearance and lower volume parameters, with estimated exponents for weight on clearance and volume parameters close to allometric values. Therefore, for patients in the younger group (2-5 years), a more conservative approach using a weight-based dosing strategy was considered. In Study TRA108062, review of the platelet count, safety and eltrombopag PK data in non-Asian ITP subjects between 1 and 5 years of age supported eltrombopag starting doses in SAA up to 2.5 mg/kg once daily. The latter, considering the 2- to 3-fold higher eltrombopag exposure (AUC) in SAA than ITP patient populations based on PK in adults, it provides the rationale for a safe and effective eltrombopag starting dose of 2.5 mg/kg in non-Asian first-line treatment of SAA subjects of 2 to 5 year.

- PK/PD results and safety profile obtained from the AUS01T updated cut-off (28-Feb-2018).

The PK of eltrombopag was an exploratory objective of Study AUS01T and only included in a sub-set of patients in Cohort 1 and the Extension Cohort. Table 19 presents a summary of dose-normalized eltrombopag PK parameters observed in Study AUS01T, by age group in non-East/South-East Asians, as of the 28-Feb-2018 cut-off date. PK parameter were normalized to a 150 mg dose in order to use all data available, including data collected in patients who may have received lower than the starting doses. No PK data were collected in patients aged 2 to 5 years (Table 22).

Table 22. Summary of dose-normalized PK parameters for eltrombopag by age group in non-East/South-East Asian SAA subjects.

	6-11 years N=3	12-17 years N=8	> 18 years N=39
DN-Cmax (µg/mL)	78.9 (21.5)	41.6 (37.7)	40.3 (46.0)
Tmax (h)	4 (3.92-4.08)	5.01 (4.00-6.00)	4.00 (1.92-8.00)
DN-AUClast (µg*h/mL)	1280 (32.4)	767 (42.5)	785 (48.1)
DN-Ctrough (µg/mL)	38.4 (47.7)	25.6 (51.9)	27.1 (56.5)

DN: Dose-normalized. Data are presented as Geo Means (CV% of Geo Means) except for Tmax, for which Median (MinMax) are presented. PK parameters in non-East/South-East Asians are presented normalized to a 150 mg dose.

In SAA patients between 12 and 18 years of age, dose-normalised eltrombopag exposure was similar to that observed in adults (≥18 years), similar to what was previously observed in paediatric ITP patients. In patients aged 6-11, exposure (AUC and Cmax) when dose normalised to the same dose as in adults (150 mg), was higher than in the older patients. In the 3 patients aged 6 to 11 years, dose-normalised Cmax and AUClast for eltrombopag are approximately 60-90% higher than in older age groups, whereas Ctrough is approximately 40-50% higher than in older age groups.

The Cmax, AUClast, and Ctrough normalised to the starting dose of 75 mg in patients in the 6 to 11 year age group were 39.5 µg/mL, 640 µg*h/mL, and 19.2 µg/mL respectively; these were similar or slightly lower (20-25%) than in older (≥12 years old) age groups.

Along AUS01T Study up to 51% of patients required temporary dose adjustment (cohort 3+extension cut-off 28-Feb 2018), being the main reason for this adjustment platelet count >200x10^3/µl (50.4%) (Table 23).

Table 23. Dose adjustments of eltrombopag - Safety set.

Cut-off date	30-Sep-2016				28-Feb-2018
	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=62 n (%)	Cohort 3 + Extension N=92 n (%)
Subjects with dose adjustments	**10 (33.3)**	**5 (16.1)**	**19 (61.3)**	**31 (50.0)**	**47 (51.1)**
Total number of dose adjustments	25	9	58	91	127
Reasons for dose adjustments[a]					
Platelet count > 200x10^3/µL	18 (72.0)	7 (77.8)	35 (60.3)	51 (56.0)	64 (50.4)
Toxicity	1 (4.0)	2 (22.2)	11 (19.0)	20 (22.0)	31 (24.4)
Adverse event	1 (4.0)	0	7 (12.1)	12 (13.2)	14 (11.0)
Subject compliance	2 (8.0)	0	5 (8.6)	8 (8.8)	12 (9.4)
Other reason	2 (8.0)	0	0	0	5 (3.9)
Platelet count > 400x10^3/µL	1 (4.0)	0	0	0	1 (0.8)

Only dose adjustments that occurred during the core treatment period of 3 months (for Cohort 2) or 6 months (all other cohorts) were included.
a. Percentage was based on total number of dose adjustments.

However, the majority of patients were receiving the same dose as recommended as starting dose at the time of month 6 assessment. In the subset of non-Asian ≥12 years old, expected to receive 150 mg/day, the last dose was still 150 mg for 72% of patients in Cohort 3+extension (cut-off 28-Feb-2018) (Table 24).

Table 24. Last dose of eltrombopag within 6 months, for Non-East or South-East Asians ≥12 years old - Safety set - cut-off 28-Feb-2018.

Eltrombopag dose	Cohort 1 N=28 n (%)	Cohort 2 N=28 n (%)	Cohort 3 N=30 n (%)	Cohort 3 + Extension N=75 n (%)
25 mg	2 (7.1)	0	3 (10.0)	6 (8.0)
50 mg	0	0	2 (6.7)	4 (5.3)
75 mg	1 (3.6)	1 (3.6)	1 (3.3)	1 (1.3)
100 mg	1 (3.6)	1 (3.6)	4 (13.3)	6 (8.0)
125 mg	3 (10.7)	0	1 (3.3)	4 (5.3)
150 mg	21 (75.0)	26 (92.9)	19 (63.3)	54 (72.0)

Pharmacokinetics in subjects with aplastic anemia updated AUS01T Study data

After the updated cut-off (28-feb-2018) new PK data from cohort 1 and cohort 3+extension in AUS01T Study was included for evaluation. This new cut-off allowed assessment in 33 additional subjects in the extension cohort. The analysis by gender confirmed that exposure (Cmax, Ctrough and AUClast) were approximately 40 to 50% higher in female and South-East Asian subjects when compared to male subjects and to other races.

The analysis by age 50 non-Asian patients who received 75-150 mg/day of eltrombopag were included. In the 3 subjects aged 6-11 years included after this new cut-off, eltrombopag dose-normalised Cmax and AUClast were approximately 60-80% higher than in older age groups, whereas Ctrough was approximately 30% higher than in older age groups (i.e >12 years). For the other subgroup analyses, no notable difference between subgroups was observed. This trend in exposure were similar to those observed in ITP patients when comparing >12 years vs <12 years old patients.

2.4.2. Main study

Study AUS01T (pivotal study)

Study AUS01T was a Phase I/II, non-randomized, single-arm, single-center study designed to evaluate the efficacy and safety of eltrombopag treatment, in combination with the regimen of h-ATG and CsA, in definitive immunosuppressive therapy-naïve subjects with severe aplastic anaemia (SAA).

Methods

Study participants

Eligibility and SAA inclusion criteria were based on the lowest hematological laboratory results obtained within 60 days prior to treatment initiation (pre-study hematological parameters), and all subjects included in the FAS met the hematological parameters criteria for SAA.

Inclusion Criteria

- Severe aplastic anemia characterized by Bone marrow cellularity < 30% (excluding lymphocytes)

AND at least two of the following:

    - Absolute neutrophil count < 500/ µL
    - Platelet count < 20,000/ µL
    - Absolute reticulocyte count < 60,000/ µL
- Age > 2 years old
- Weight > 12 kg

Exclusion criteria:

- Diagnosis of Fanconi anemia
- Evidence of a clonal disorder on cytogenetics performed within 12 weeks of study entry.
- Patients with super severe neutropenia (ANC < 200 /µL) will not be excluded initially if cytogenetics are not available or pending. If evidence of a clonal disorder consistent with myelodysplasia is later identified, the patient will go off study.
- Prior immunosuppressive therapy with any ATG, alemtuzumab, or high dose cyclophosphamide
- Subjects with a PNH clone size in granulocytes of > 50% by flow cytometric analysis
- SGOT or SGPT > 3 times the upper limit of normal
- Subjects with liver cirrhosis
- Hypersensitivity to eltrombopag or its components

- Infection not adequately responding to appropriate therapy
- Moribund status or concurrent hepatic, renal, cardiac, neurologic, pulmonary, infectious, or metabolic disease of such severity that it would preclude the patient's ability to tolerate protocol therapy, or that death within 7-10 days is likely
- Potential subjects with cancer who are on active chemotherapeutic treatment or who take drugs with hematological effects will not be eligible
- Current pregnancy, or unwillingness to take oral contraceptives or use a barrier method of birth control or practice abstinence to refrain from pregnancy if of childbearing potential during the course of this study
- Inability to understand the investigational nature of the study or to give informed consent

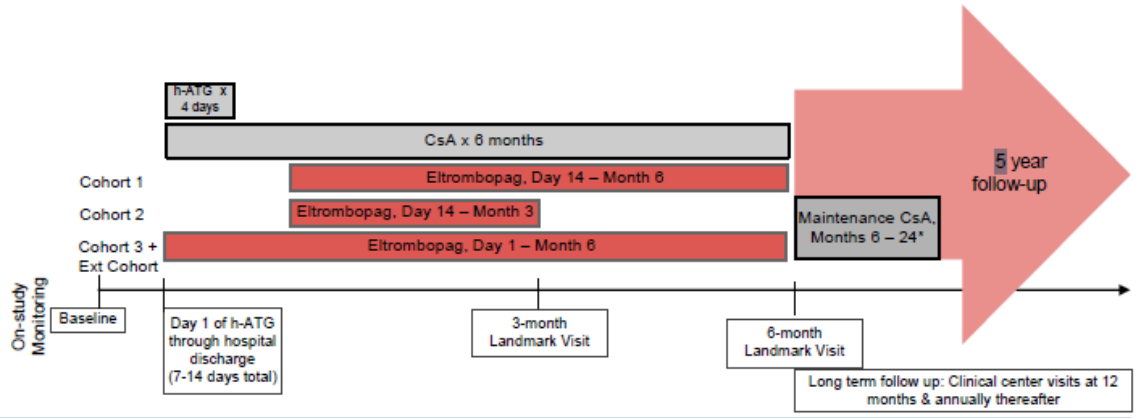
Treatments

The subjects were treated with immunosuppressive therapy, h-ATG + CsA, combined with eltrombopag as experimental therapy, see Figure 5. The cohorts differed by the starting day of eltrombopag, the duration of eltrombopag, and by the addition of a CsA maintenance regimen:

- Cohort 1 (N=31): h-ATG on Days 1-4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 6.
- Cohort 2 (N=31): h-ATG on Days 1-4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 3. Following amendment 15 to the protocol, responding subjects who did not relapse at month 6, received low dose of CsA (maintenance dose) from month 6 to month 24.
- Cohort 3 (N=31) and Extension Cohort (N=31 at data cut-off 30-Sept-2016 recruitment was still ongoing): All 3 drugs started concurrently on Day 1: h-ATG on Days 1-4, CsA and eltrombopag from Day 1 to month 6. Responding subjects received low dose of CsA (maintenance dose) from month 6 to month 24. Between 30-Septembre-2016 and 28-February-2018, eight additional paediatric patients and 22 additional adult subjects were enrolled in the Extension Cohort: 25 who met the Month 6 assessment or withdrew earlier and 5 subjects who had not yet reach this assessment and were still receiving the study treatment with eltrombopag. Additionally, 15 subjects who were still receiving the study treatment with eltrombopag, and 1 subject who had stopped eltrombopag but was still on study, had not yet reached the Month 6 assessment at the original cut-off are included in this analysis. There are a total of 41 additional subjects now evaluable at Month 6 (or who withdrew earlier). All 46 subjects (30 newly recruited, and 16 newly evaluable for the Month 6 assessment) were enrolled in the Extension Cohort.

All subjects were followed at the NHLBI at month 3 and month 6 visits (the landmark visits). Subsequent follow-up visits at the NHLBI were scheduled at month 12 and then annually for up to 5 years. The subjects were also followed between landmark visits by their referral physicians at their discretion.

Figure 5. Study design



*Following amendment 15 to the protocol (starting with Subject 46 in Cohort 2) responders received maintenance CsA up to month 24. In all cohorts, therapeutic doses of CsA could be re-started in subjects who had evidence of relapse after month 6. Eltrombopag could be restarted in subjects who had evidence of relapse after month 3 in Cohort 2 and after month 6 in all other cohorts.

Study participation was considered complete after 5 years, unless the subject had died, voluntarily withdrawn, or had a protocol-specified event for which the study drug administration was discontinued at the discretion of the Principal Investigator.

The treatment phase with CsA + eltrombopag was 6 months, with CsA maintenance from Month 6-24, with the possibility of re-initiation of CsA + eltrombopag at therapeutic dose in the case of relapse.

Objectives

Primary objective:

- To evaluate the safety and activity profile of h-ATG/CsA/eltrombopag in treatment naïve SAA.

Secondary objectives:

- To evaluate hematological response at 3, 6 and 12 months and yearly thereafter
- To evaluate relapse
- To evaluate clonal evolution to PNH, clonal chromosomal population in bone marrow, myelodysplasia by morphology, or acute leukemia
- To evaluate overall survival
- To evaluate health-related quality of life (HRQL)
- To evaluate hematological response of relapsed subjects that re-start treatment
- To evaluate the effect of a 2 mg/kg/day CsA dose starting Month 6 for 18 months until month 24 on the rate of relapse of subjects deemed responders at Month 6

Outcomes/endpoints

Primary endpoint: Toxicity profile in the 6 months following h-ATG/CsA/eltrombopag, Complete response (CR) rate at 6 months following h-ATG + CsA + eltrombopag, defined as (all 3 were to be met):

• Absolute neutrophil count $>1\times10^3$/ µL

• Platelet count $>100\times10^3$/ µL

• Hgb>10 g/dL

For each cohort, the rate of CR was calculated as the number of subjects who achieved a CR at 6 months, divided by the total number of subjects enrolled into that cohort who had reached the 6-month landmark or had withdrawn earlier for any reason, including non-evaluable subjects. The two-sided 95% confidence interval (CI) of the CR rate was computed based on the exact method of (Clopper & Pearson, 1934).

Secondary endpoints:

- CR rates at 3 and 12 months and yearly thereafter up to 5 years
- Overall response (OR: CR or PR) rates at 3, 6 , 12 months and yearly thereafter up to 5 years
- Duration of CR
- Duration of OR
- Overall survival (OS)
- Relapse/duration of response
- Change from baseline to post-baseline assessments in PROMIS Global Health, Sleep Disturbance, Applied Cognition-Abilities, Anxiety and Depression scores
- Change from baseline to post-baseline assessments in FACT- Anemia, Thrombocytopenia and Neutropenia scores

The primary analysis of complete hematological response rate at month 6 was based on the investigator assessment of response. However, improvement in blood counts following administration of other therapies such as growth factors or transfusions (including re-introduction of eltrombopag after month 3 and prior to month 6 for Cohort 2) were not considered as fulfilling the response criteria. Subjects were considered non-responders if they received the following therapies:

- Platelets transfusions: 7 days preceding the assessment of platelet count
- Packed red blood cell transfusions: 14 days preceding the assessment of hemoglobin
- Growth factors: 21 days preceding the assessment of response

A complete response was defined as hematological parameters meeting all the following 3 criteria on 2 consecutive serial blood count measurements at least one week apart:

- Absolute neutrophil count > 1000/μL
- Platelet count > 100x103/μL
- Hemoglobin > 10 g/dL

Sample size

Past experience with h-ATG/CsA suggests that the CR probability at 6 months for previously untreated subjects given this regimen is approximately 10% to 12%. It was hypothesised that the actual CR probability using this treatment would reach 30% or more and a CR probability of 10% or less would warrant terminating the treatment on this subject population.

The sample size was determined using 2-Stage Minimax Design of Simon, since it required a smaller total number of subjects (N=31) compared to 2-Stage Optimal Design (N=34). At first stage in Cohort 1, 24 subjects were planned to be accrued and to test the null hypothesis, and the null hypothesis was accepted (i.e. the treatment had to be terminated) if no more than 2 subjects demonstrated a CR to the

treatment within 6 months. If 3 or more subjects had a CR to the treatment within 6 months at the first stage, an additional 7 subjects was accrued.

Once accrual to Cohort 1 was completed it was proposed to treat another cohort (Cohort 2) of 33 subjects, and once accrual to Cohort 2 was completed it was proposed to treat another Cohort (Cohort 3) of 31 subjects. Of note, the protocol was amended to increase Cohort 2 sample size from 31 to 33 subjects was submitted on 23-Oct-2014 while amendment to add Cohort 3 was being reviewed. Ultimately, only 31 subjects were enrolled in Cohort 2 as the Cohort 3 amendment was approved prior to enrol the 2 additional subjects in Cohort 2.

An Extension to Cohort 3 of at least up to 55 subjects will improve precision of exploratory analysis of secondary endpoints. However, this data was not used for the primary analysis of Cohort 3.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

Sensitivity and supportive analyses were performed to assess the overall robustness of the primary efficacy results. Sensitivity analyses included repeating the primary efficacy analysis using the per protocol set (PPS) and using a more stringent definition of CR (ANC ≥ 1500/μL, platelet count ≥ 150×10^3/μL, hemoglobin ≥ 12g/dL). The supportive analysis included a subgroup analysis of CR rate at 6-months by age (<18 years, 18-64 years, ≥ 65 years), gender, race, GPI negative neutrophils level (≤ 50% vs. > 50%), and severity of aplastic anemia.

Results

Participant flow

Study AUS01T (data cut-off of 30-Sep-2016) enrolled a total 123 subjects, and all of them received eltrombopag with h-ATG+CsA for the FAS. From the FAS, 30 subjects were included in Cohort 1, 31 subjects in each of Cohort 2 and Cohort 3, and 31 subjects in the Extension to Cohort 3. At the update cut-off (28-Feb-2018), 30 additional subjects (8 paediatrics and 22 adults) were recruited, including 25 who met the Month 6 assessment or withdrew earlier, and 5 subjects who had not yet reached this assessment and were still receiving the study treatment with eltrombopag. Additionally, 15 subjects who were still receiving the study treatment with eltrombopag, and 1 subject who had stopped eltrombopag but was still on study, had not yet reached the Month 6 assessment at the original cut-off are included in this analysis. There were in all 41 additional subjects now evaluable at Month 6 (or who withdrew earlier). All 46 subjects (30 newly recruited, and 16 newly evaluable for the Month 6 assessment) were enrolled in the Extension Cohort, and are presented for analysis. Longer follow-up of Study AUS01T and further evidence of the efficacy and safety of eltrombopag added to standard immunosuppressive therapy (IST) in IST-naïve severe aplastic anemia (SAA) subjects is provided. Overall median (min-max) follow-up now extends to 61, 47, 33 and 22 months in Cohort 1, 2, 3 and combined Cohort 3 + Extension Cohort, respectively.

During the first cut-off period the majority of subjects (60.2%) were Caucasian (White).

Recruitment

Recruitment was not randomized between the different cohorts.

Study initiation date: 02-Jul-2012 (first subject first visit). The study is still ongoing.

Conduct of the study

The study was conducted according to the ethical principles of the Declaration of Helsinki. Informed consent was obtained from each subject in writing before commencement of the treatment.

The study protocol was amended 25 times prior to data cut-off (30 Sept-2016). The main protocol amendments were the following:

- To increase the accrual ceiling to 31 subjects from 25 subjects
- To remove the following exclusion criterion: Subjects with a PNH clone size in granulocytes of > 50% by flow cytometric analysis.
- To add a second cohort of 31 subjects (Cohort 2) and then increase to 33 subjects.
- Modify the eligibility criteria to clarify which lab results will be used to determine eligibility.
- Adding a 3rd cohort of 31 subjects with a modified treatment schedule
- Adding an Extension cohort of at least 26 subjects who will receive treatment as dictated in Cohort 3.

Baseline data

Disease characteristics were reflective of a population with advanced disease at baseline. In each cohort, approximately one-third of the subjects were diagnosed with very severe aplastic anemia (ANC < 200/μL), and three subjects in total had glucose phosphate isomerase (GPI) negative neutrophil >50% at baseline (an actionable level for treatment of PNH) (Table 25). Demographic characteristics were unchanged at the update cut-off (Table 25-2).

Table 25. Demographics at Baseline – FAS (cut-off 30-Sept-2016)

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3 + Extension N=62	All subjects N=123
Age (years)					
Mean (SD)	39.7 (18.94)	33.8 (18.65)	36.2 (21.90)	34.4 (22.11)	35.5 (20.51)
Median	39.0	28.0	29.0	26.5	30.0
Min–Max	12–72	3–68	11–82	5–82	3–82
Age category (years) - n (%)					
< 18	5 (16.7)	6 (19.4)	8 (25.8)	18 (29.0)	29 (23.6)
2 - 5	0	1 (3.2)	0	1 (1.6)	2 (1.6)
6 - 11	0	1 (3.2)	1 (3.2)	7 (11.3)	8 (6.5)
12 - 17	5 (16.7)	4 (12.9)	7 (22.6)	10 (16.1)	19 (15.4)
18 - 64	20 (66.7)	23 (74.2)	18 (58.1)	34 (54.8)	77 (62.6)
≥ 65	5 (16.7)	2 (6.5)	5 (16.1)	10 (16.1)	17 (13.8)
Sex - n (%)					
Female	14 (46.7)	14 (45.2)	14 (45.2)	31 (50.0)	59 (48.0)
Male	16 (53.3)	17 (54.8)	17 (54.8)	31 (50.0)	64 (52.0)
Race - n (%)					
White	16 (53.3)	19 (61.3)	23 (74.2)	39 (62.9)	74 (60.2)
Black or African American	6 (20.0)	7 (22.6)	4 (12.9)	9 (14.5)	22 (17.9)
Other[a]	3 (10.0)	0	3 (9.7)	6 (9.7)	9 (7.3)
East or South-East Asian	2 (6.7)	1 (3.2)	0	4 (6.5)	7 (5.7)
Non East or South-East Asian	1 (3.3)	3 (9.7)	1 (3.2)	1 (1.6)	5 (4.1)
Unknown	2 (6.7)	1 (3.2)	0	3 (4.8)	6 (4.9)
Ethnicity – n (%)					
Hispanic/Latino	5 (16.7)	2 (6.5)	9 (29.0)	13 (21.0)	20 (16.3)
Not Hispanic/ Latino	25 (83.3)	29 (93.5)	22 (71.0)	49 (79.0)	103 (83.7)
Weight (kg)					
Mean (SD)	72.3 (16.7)	75.2 (27.3)	70.2 (18.2)	67.6 (23.2)	70.7 (23.0)
Median	69.0	76.9	67.3	66.8	69.9
Min-Max	47.3-115.8	13.9-126.6	36.8-105.2	16.6-142.9	13.9-142.9
Height (cm)					
Mean (SD)	168.2 (10.4)	165.9 (18.1)	169.1 (9.4)	164.3 (17.5)	165.6 (16.2)
Median	168.9	167.5	170.0	167.4	167.6
Min-Max	141.3-193.5	97.7-190.2	140.0-187.0	114.9-198.2	97.7-198.2

a. Other: multiple or American Indian or Alaska Native.
Source: Table 14.1-2.2

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3 + Extension N=62	All subjects N=123
Platelet count (10^3/µL)					
n	30	31	31	59	120
Mean (SD)	11.0 (7.69)	7.6 (3.83)	9.8 (6.27)	10.1 (6.79)	9.7 (6.49)
Median	10.0	8.0	9.0	9.0	9.0
Min - Max	2 - 37	1 - 14	1 - 27	1 - 40	1 - 40
Absolute neutrophil count (10^3/µL)					
n	30	31	31	60	121
Mean	0.405 (0.404)	0.339 (0.246)	0.359 (0.358)	0.335 (0.372)	0.353 (0.351)
Median	0.28	0.33	0.31	0.25	0.27
Min - Max	0.00 - 1.38	0.00 - 0.90	0.00 - 1.81	0.00 - 1.93	0.00 - 1.93
Absolute reticulocyte count (10^3/µL)					
n	30	31	31	60	121
Mean (SD)	23.2 (16.66)	19.4 (14.90)	28.1 (17.93)	27.3 (18.86)	24.3 (17.57)
Median	22.5	15.0	24.0	23.0	20.0
Mini - Maximum	2 - 52	2 - 53	2 - 60	2 - 86	2 - 86

Due to incorrect units, results for Subject 117 were not included in this summary table.

Table 25-2. Demographic characteristics (cut-off 28-02-2018).

Cutoff date	30-Sep-2016 Cohort 3 + Extension N=62	28-Feb-2018 Cohort 3 + Extension N=92
Age (years)		
Mean (SD)	34.4 (22.11)	35.0 (22.10)
Median	26.5	28.0
Min–Max	5–82	5-82
Age category (years) - n (%)		
< 18	18 (29.0)	26 (28.3)
2 - 5	1 (1.6)	1 (1.1)
6 - 11	7 (11.3)	11 (12.0)
12 - 17	10 (16.1)	14 (15.2)
18 - 64	34 (54.8)	51 (55.4)
≥ 65	10 (16.1)	15 (16.3)
Sex - n (%)		
Female	31 (50.0)	50 (54.3)
Male	31 (50.0)	42 (45.7)
Race - n (%)		
White	39 (62.9)	57 (62.0)
Black or African American	9 (14.5)	16 (17.4)
Other[a]	6 (9.7)	6 (6.5)
East or South-East Asian	4 (6.5)	6 (6.5)
Unknown	3 (4.8)	5 (5.4)[b]
Non East or South-East Asian	1 (1.6)	2 (2.2)
Ethnicity – n (%)		
Not Hispanic/ Latino	49 (79.0)	74 (80.4)
Hispanic/Latino	13 (21.0)	18 (19.6)
Weight (kg)		
Mean (SD)	67.6 (23.2)	67.8 (22.9)
Median	66.8	66.1
Min-Max	16.6-142.9	16.5-142.9
Height (cm)		
Mean (SD)	164.3 (17.5)	163.5 (16.5)
Median	167.4	165.8
Cutoff date	**30-Sep-2016** **Cohort 3 + Extension** **N=62**	**28-Feb-2018** **Cohort 3 + Extension** **N=92**
Min-Max	114.9-198.2	114.9-198.2

a. Other: multiple or American Indian or Alaska Native.
b. Subject AUS01T-133 was 20 years old Asian female but the exact origin was missing and thus was reported under "Unknown" race. However, she started eltrombopag at a dose of 75 mg/day suggesting that she was East or South-East Asian.

Cutoff date	30-Sep-2016 Cohort 3 + Extension N=62	28-Feb-2018 Cohort 3 + Extension N=92
Platelet count (10^3/µL)		
Mean (SD)	10.1 (6.79)	9.3 (6.44)
Median	9.0	8.0
Min-Max	1-40	0-40
Absolute neutrophil count (10^3/µL)		
Mean (SD)	0.335 (0.372)	0.351 (0.368)
Median	0.25	0.27
Min-Max	0.00-1.93	0.00-1.93
Absolute reticulocyte count (10^3/µL)		
Mean (SD)	27.3 (18.86)	27.0 (19.70)
Median	23.0	21.0
Min-Max	2-86	2.0-97.1

Numbers analysed

As of the data cut-off date of 30-Sep-2016, the eltrombopag post-treatment follow-up was still ongoing in 61.3% subjects. Results from this primary efficacy analysis of the study are the key efficacy data to support the proposed indication. The MAH has updated these data expanding the cut-off date to 28-Feb-2018. Providing data for 30 additional subjects (8 paediatrics and 22 adults) leading to a total of 92 patients data presented in the Cohort 3+extension, which is the treatment recommended by the MAH. Moreover, with this cut-off-date 41 additional subjects were evaluable at month 6 for the efficacy, leading to a total of 87 subjects evaluable in Cohort 3+extension.

Study AUS01T consisted of 3 consecutive cohorts of subjects, Cohort 1, 2, and 3, and an extension to the third cohort (where enrollment continues) to which subjects were sequentially enrolled. After the 28-Feb-2018 cut-off-date the efficacy population, derived from the Full Analysis Set (FAS), comprised 153 subjects in Study AUS01T with the target indication who received at least 1 dose of study drug. The median duration of exposure to eltrombopag was 183 days in Cohort 3 + Extension (h-ATG (Day 1-4) + CsA (Day 1-Month 6)) + eltrombopag (Day 1-Month 6).

Outcomes and estimation

Primary efficacy analysis: complete response at month 6

The study met its primary efficacy objective for each cohort. The null hypothesis of complete response rate ≤10% was rejected as ≥7 CRs were observed at month 6 assessment among the 31 subjects in each cohort.

The study met its primary efficacy objective for the 3 cohorts that used a Simon two-stage design, with complete hematological response was observed at the month 6 landmark visit in 33.3% and 25.8% of subjects in Cohort 1 and 2, respectively, and in over half of the subjects in Cohort 3 (58.1%). There was no primary efficacy objective specific to the Extension Cohort, with the exception of the interest in collecting additional safety and efficacy within the target regimen. Complete hematological response at month 6 was observed in 24 (52.2%) subjects in combined Cohort 3 + Extension Cohort.

Between 30-Sep-2016 and 28-Feb-2018 in the Extension Cohort, 41 additional subjects had reached the Month 6 visit or withdrew earlier. The proportion of complete responses at Month 6 in the combined Cohort 3 + Extension Cohort for the new period was reported at 43.7% (95% CI: 33.1-54.7) (Table 26).

Table 26. Primary endpoint: complete hematological response rate at month 6-FAS (including cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016				28-Feb-2018
	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3 + Extension N=62	Cohort 3 + Extension N=92
Subjects who reached Month 6 visit or withdrew earlier	30	31	31	46	87
Complete response - n (%)	10 (33.3)	8 (25.8)	18 (58.1)	24 (52.2)	38 (43.7)
95% CI	17.3, 52.8	11.9, 44.6	39.1, 75.5	36.9, 67.1	33.1, 54.7

All cohorts received eltrombopag up to Month 6 visit, except in Cohort 2 where subjects stopped eltrombopag at Month 3.
The denominator for % calculation of CR was the number of subjects in the cohort who reached the Month 6 visit or withdrew earlier.
The 95% CI were computed based on the exact method of Clopper-Pearson.

Supportive, sensitivity and subgroup analyses

Complete response at month 6 on per-protocol set (PPS)

The PPS analysis (including only subjects with sufficient exposure to the study treatment and without major protocol deviations) on complete hematological response at month 6 was consistent with the primary analysis on the FAS.(Table 27 cut-off 30-Sept-2016 and Table 27-2 cut-off 28-Feb-2018).

Table 27. Complete hematological response rate at month 6-PPS (cut-off 30-Sept-2016)

	Cohort 1 N=30	Cohort 2 N=30	Cohort 3 N=31	Cohort 3 + Extension N=58
Subjects who reached the 6-month visit or withdrew earlier	**30**	**30**	**31**	**46**
Complete Response - n (%)	10 (33.3)	8 (26.7)	18 (58.1)	24 (52.2)
95% CI	17.3, 52.8	12.3, 45.9	39.1, 75.5	36.9, 67.1

The denominator for % calculation of CR was the number of subjects in the treatment group who reached the 6-month visit or withdrew earlier.
The 95% CI were computed based on the exact method of Clopper-Pearson.

Table 27-2. Complete hematological response rate at month 6-PPS (cut-off 28-Feb-2018).

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Table 14.2-1.2u (Page 1 of 1)
Complete response at Month 6 assessment by cohort
Per Protocol Set

	Cohort 1 N=30		Cohort 2 N=30		Cohort 3 N=31		Cohort 3 + Extension N=88	
	n (%)	<95% CI>	n (%)	<95% CI>	n (%)	<95% CI>	n (%)	<95% CI>
Total, n	30		30		31		87	
Complete Response (CR)	10 (33.3)	(17.3, 52.8)	8 (26.7)	(12.3, 45.9)	18 (58.1)	(39.1, 75.5)	38 (43.7)	(33.1, 54.7)

- N: The total number of patients in the treatment group.
- 'Total, n' is the number of patients in the treatment group who reached this timepoint or withdrew earlier. It is denominator for percentage (%) calculation.
- The 95% CI were computed based on the exact method of Clopper-Pearson.

Analysis on hematological responses defined as normalization of parameters

A sensitivity analysis was also performed using a more stringent definition for complete response, taken as complete normalisation of hematological parameters, on 2 consecutive serial blood count measurements at least one week apart:

- ANC ≥ 1500/μL
- Platelet count ≥ 150x103/μL
- Hemoglobin ≥ 12 g/dL (female) or ≥ 13 g/dL (male)

Table 28. Hematological response defined as normalisation of parameters at month 6 - FAS

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3 + Extension N=62
Subjects who reached the 6-month visit or withdrew earlier	**30**	**31**	**31**	**46**
Complete Response (normalized) - n (%)	2 (6.7)	1 (3.2)	2 (6.5)	2 (4.3)
95% CI	0.8, 22.1	0.1, 16.7	0.8, 21.4	0.5, 14.8

The denominator for % calculation was the number of subjects in the treatment group who reached the 6-month visit or withdrew earlier.
The 95% CI were computed based on the exact method of Clopper-Pearson.

According to new cut-off period, no haematological response defined as normalisation of parameters have been provided.

Subgroup analysis

Table 29. Complete response at month 6 by subgroup-FAS (cut-off 30-Sept-2016).

	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3 + Extension N=62	
Subjects who reached the 6-month visit or withdrew earlier	30		31		31		46	
	n[a]	**n (%) - 95%CI**	**n[a]**	**n (%) - 95%CI**	**n[a]**	**n (%) - 95%CI**	**n[a]**	**n (%) - 95%CI**
Age, year								
< 18	**5**	1 (20.0) - 0.5,71.6	**6**	3 (50.0) - 11.8,88.2	**8**	5 (62.5) - 24.5,91.5	**12**	5 (41.7) - 15.2,72.3
2-5	**0**	0	**1**	0	**0**	0	**0**	0
6-11	**0**	0	**1**	0	**1**	0	**4**	0
12-17	**5**	1 (20.0)	**4**	3 (75.0)	**7**	5 (71.4)	**8**	5 (62.5)
18-64	**20**	7 (35.0) - 15.4,59.2	**23**	5 (21.7) - 7.5,43.7	**18**	10 (55.6) - 30.8,78.5	**27**	16 (59.3) - 38.8,77.6
≥ 65	**5**	2 (40.0) - 5.3,85.3	**2**	0 - 0.0,84.2	**5**	3 (60.0) - 14.7,94.7	**7**	3 (42.9) - 9.9,81.6
Gender								
Male	**16**	5 (31.3) - 11.0,58.7	**17**	4 (23.5) - 6.8,49.9	**17**	10 (58.8) - 32.9,81.6	**24**	13 (54.2) - 32.8,74.4
Female	**14**	5 (35.7) - 12.8,64.9	**14**	4 (28.6) - 8.4,58.1	**14**	8 (57.1) - 28.9,82.3	**22**	11 (50.0) - 28.2,71.8
Race								
White	**16**	8 (50.0) - 24.7,75.3	**19**	5 (26.3) - 9.1,51.2	**23**	15 (65.2) - 42.7,83.6	**30**	18 (60.0) - 40.6,77.3
African American	**6**	0 - 0.0,45.9	**7**	2 (28.6) - 3.7,71.0	**4**	1 (25.0) - 0.6,80.6	**7**	3 (42.9) - 9.9,81.6
Asian	**3**	1 (33.3) - 0.8,90.6	**4**	1 (25.0) - 0.6,80.6	**1**	0 - 0.0,97.5	**3**	1 (33.3) - 0.8,90.6
Other	**5**	1 (20.0) - 0.5,71.6	**1**	0 - 0.0,97.5	**3**	2 (66.7) - 9.4,99.2	**6**	2 (33.3) - 4.3,77.7
Severity of aplastic anemia								
Severe	**19**	4 (21.1) - 6.1,45.6	**19**	5 (26.3) - 9.1, 51.2	**22**	13 (59.1) - 36.4,79.3	**31**	17 (54.8) - 36.0,72.7
Very severe	**11**	6 (54.5) - 23.4,83.3	**12**	3 (25.0) - 5.5,57.2	**9**	5 (55.6) - 21.2,86.3	**15**	7 (46.7) - 21.3,73.4

Table 29-2. Complete response at month 6 by subgroup-FAS (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016 Cohort 3 + Extension N=62		28-Feb-2018 Cohort 3 + Extension N=92	
Subjects who reached Month 6 or withdrew earlier	46		87	
	n total[a]	n (%) - 95%CI	n total[a]	n (%) - 95%CI
Age, year				
< 18	**12**	5 (41.7) - 15.2,72.3	**25**	7 (28.0) – 12.1,49.4
2-5	0	0	1	0
6-11	4	0	11	1 (9.1)
12-17	8	5 (62.5)	13	6 (46.2)
18-64	**27**	16 (59.3) - 38.8,77.6	**47**	26 (55.3) - 40.1,69.8
≥ 65	**7**	3 (42.9) - 9.9,81.6	**15**	5 (33.3) - 11.8,61.6
Gender				
Male	**24**	13 (54.2) - 32.8,74.4	**39**	19 (48.7) - 32.4,65.2
Female	**22**	11 (50.0) - 28.2,71.8	**48**	19 (39.6) - 25.8,54.7
Severity of aplastic anemia[c]				
Severe	**27**	17 (63.0) – 42.4,80.6	**48**	25 (52.1) - 37.2,66.7
Very severe	**19**	7 (36.8) – 16.3, 61.6	**39**	13 (33.3) - 19.1,50.2

a. n is the number of subjects who reached the Month 6 timepoint or withdrew earlier in each subgroup category. It is the denominator for % calculation.
The 95% CI were computed based on the exact method of Clopper-Pearson.
b. Asian (non E/SE Asian), East Asian, South East Asian are reported under 'Asian' subgroup. American Indian or Alaska Native subjects are reported under 'Other' category
c. In the original cut off 30-Sept-2016 the severity of aplastic anemia was derived from baseline instead of the protocol defined pre-study time point. This table show results after correction for the pre-study parameters in the 30-Sep-2016 cutoff.

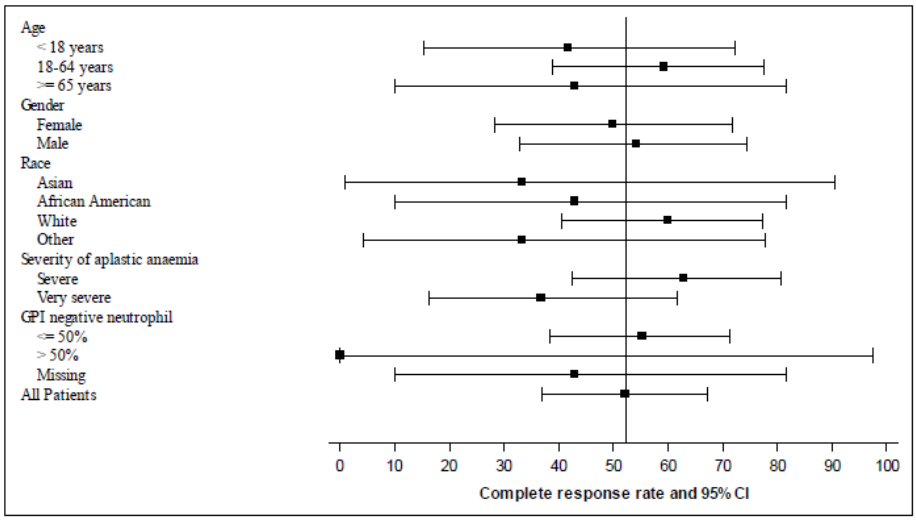
As stated before, a reduction in complete response rates in Cohort 3 + Extension between both cut-offs was seen when results from the update was considered (52.2% vs 43.7%) and also with results obtained in Cohort 3 where complete response was reached in 58.1% of patients. Regarding results by subgroups differences in complete response between some of these subgroups were observed but the number of subjects concerned was too small to draw any conclusion (i.e. age). Differences were also observed between gender with 48.7% of complete responders in male vs. 39.6% in female subjects. An ad hoc logistic regression investigating the prognostic factors associated with complete response was carried out and included age, gender, pre-study platelet, neutrophil and reticulocytes counts as well as the severity of the disease. According to the MAH analysis, the severity of the disease and absolute neutrophil count emerged as the only significant prognostic factors.

Based on these prognostic factors identified by the MAH, complete response along Cohort 3 + extension (cut-off 28-Feb-2018) was almost 20% higher in the subgroup of severe aplastic anemia (sAA) when compared with the subgroup of very severe aplastic anemia (vsAA) (52.1% and 33.3%, respectively). Differences in complete response between subgroups of sAA and vsAA along Cohort 3 + extension (cut-off 30-Sept-2016) were around 25% (63.0% and 36.8%, respectively). However, these results seemed lower (around 3.5%) for Cohort 3 where 59.1% and 55.6% of patients with sAA and vsAA reached complete response. A higher proportion of patients with vsAA were included in Cohort 3 + extension for both cut-offs in relation to Cohort 3 (29%, 48%, 55% for Cohort 3, Cohort 3 + extension cut-off 30-Sept-2016 and cut-off 28-Feb-2018, respectively).

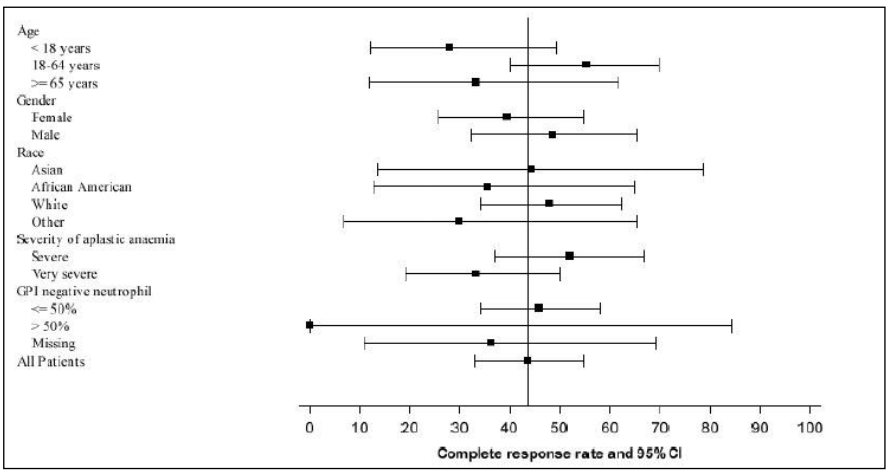
Complete response at month 6 is also presented by subgroups in figures 6-9 (both cut-offs) for all cohorts

Figures 6-9. Forest plot of CR rate at month 6 with 95% CI for subgroups-FAS.

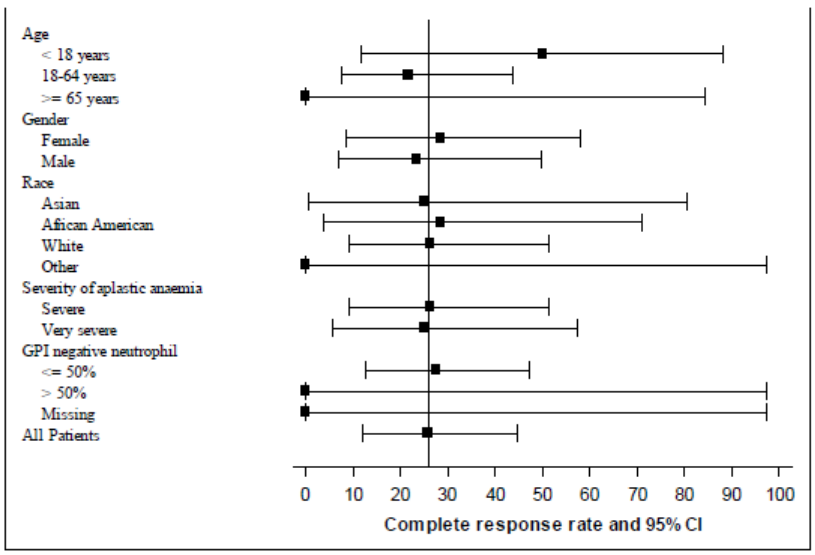
Combined Cohort 3 + extension (cut-off date 30-Sept-2016)

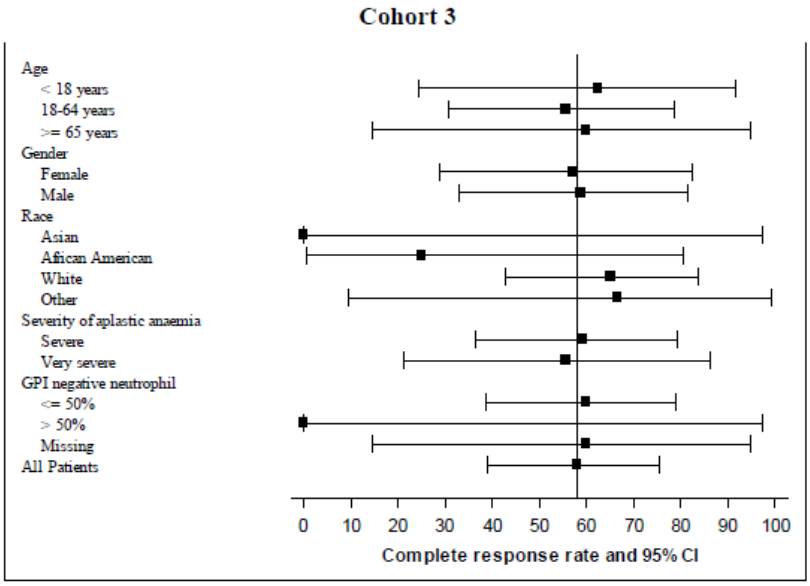


Combined Cohort 3 + extension (cut-off date 28-Feb-2018)



Cohort 2





Complete response results by age subgroup and severity of the disease in Cohort 3 + extension (cut-off 28-Feb-2018) have been provided (Table 30).

Table 30. Complete response at month 6 by severity of aplastic anemia and age subgroup in Cohort 3 + extension (28-Feb-2018).

Cutoff date	28-Feb-2018			
	Cohort 3 + Extension N=92			
Severity of aplastic anemia at baseline	Severe N=51		Very Severe N=41	
Subjects who reached Month 6 or withdrew earlier	48		39	
	n total[a]	n (%)	n total[a]	n (%)
Age, year				
< 18	11	4 (36.4)	14	3 (21.4)
2-5	0	0	1	0
6-11	4	0	7	1 (14.3)
12-17	7	4 (57.1)	6	2 (33.3)
18-64	31	20 (64.5)	16	6 (37.5)
≥ 65	6	1 (16.7)	9	4 (44.4)

a. n total is the number of subjects who reached the Month 6 timepoint or withdrew earlier in each subgroup category. It is the denominator for % calculation.

Secondary efficacy results

Subjects were enrolled sequentially into cohorts i.e. once enrollment into a given cohort was completed, enrollment into the next cohort started. Therefore, the follow-up of subjects in a given cohort was approximately 1 year longer than the follow-up of subjects in the next cohort (e.g. 1.5 year more for Cohort 1 as compared to Cohort 2). At the original 30-Sept-2016 cut-off, none of the subjects in Cohort 3 had yet reached 2 year assessment, and none of the subjects in the Extension Cohort had yet reached 1 year assessment. Therefore the data beyond month 6 were not yet mature enough for an evaluation of the long-term efficacy. With the update cut-off (28-Sept-2018), in the combined Cohort 3 + extension 14 subjects had not yet reached the 1 year assessment (or withdrew earlier), including 5 subjects who had not yet reached month 6 and were still receiving eltrombopag (all in the extension cohort). Efficacy by assessment time such as hematological response by assessment time, duration of response, maintenance of response or overall survival are presented cumulative as of the update cut-off and are not compared with the data at the original cut-off.

Hematological response by assessment time

In Cohort 3, all subjects had already reached the Year 2 assessment (or withdrew earlier). In this cohort, the rate of complete responders was relatively stable and above 50% at all time points from Month 6 to Year 2. There was an incidence of relapse + withdrawal of 25.8% at Year 1 and 35.5% at Year 2. For this period, Cohort 3 compares favorably against Cohorts 1 and 2, that had lower complete response rates (always below 24% in Cohort 1 and below 42% in Cohort 2) and higher rates of withdrawal + relapse (70.0% and 38.7%, respectively in Cohorts 1 and 2 at Year 1, and 73.3% and 45.2%, respectively in Cohorts 1 and 2 at Year 2). Beyond Year 2, the results should be interpreted with caution as in Cohort 3 only 17 subjects over 31 (55%) had yet reached Year 3 (or withdrew earlier) (Table 31).

Table 31. Hematological responses by assessment time - FAS (cumulative as of 28-Feb-2018).

	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3 + Extension N=92	
Response	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Month 3 , Total n	**30**		**31**		**31**		**88**	
Overall Response	23 (76.7)	57.7, 90.1	24 (77.4)	58.9, 90.4	27 (87.1)	70.2, 96.4	66 (75.0)	64.6, 83.6
Complete Response	5 (16.7)	5.6, 34.7	7 (22.6)	9.6, 41.1	15 (48.4)	30.2, 66.9	24 (27.3)	18.3, 37.8
Month 6 , Total n	**30**		**31**		**31**		**87**	
Overall Response	24 (80.0)	61.4, 92.3	27 (87.1)	70.2, 96.4	29 (93.5)	78.6, 99.2	69 (79.3)	69.3, 87.3
Complete Response	10 (33.3)	17.3, 52.8	8 (25.8)	11.9, 44.6	18 (58.1)	39.1, 75.5	38 (43.7)	33.1, 54.7
Year 1 , Total n	**30**		**31**		**31**		**78**	
Overall Response	9 (30.0)	14.7, 49.4	18 (58.1)	39.1, 75.5	23 (74.2)	55.4, 88.1	44 (56.4)	44.7, 67.6
Complete Response	5 (16.7)	5.6, 34.7	10 (32.3)	16.7, 51.4	16 (51.6)	33.1, 69.8	30 (38.5)	27.7, 50.2
Year 2 , Total n	**30**		**31**		**31**		**62**	
Overall Response	8 (26.7)	12.3, 45.9	17 (54.8)	36.0, 72.7	20 (64.5)	45.4, 80.8	24 (38.7)	26.6, 51.9
Complete Response	7 (23.3)	9.9, 42.3	13 (41.9)	24.5, 60.9	17 (54.8)	36.0, 72.7	19 (30.6)	19.6, 43.7
Year 3 , Total n	**30**		**31**		**17**		**44**	
Overall Response	7 (23.3)	9.9, 42.3	10 (32.3)	16.7, 51.4	2 (11.8)	1.5, 36.4	2 (4.5)	0.6, 15.5
Complete Response	5 (16.7)	5.6, 34.7	8 (25.8)	11.9, 44.6	2 (11.8)	1.5, 36.4	2 (4.5)	0.6, 15.5
Year 4 , Total n	**30**		**22**		**14**		**41**	
Overall Response	7 (23.3)	9.9, 42.3	3 (13.6)	2.9, 34.9	0	0.0, 23.2	0	0.0, 8.6
Complete Response	6 (20.0)	7.7, 38.6	2 (9.1)	1.1, 29.2	0	0.0, 23.2	0	0.0, 8.6
	Cohort 1 N=30		**Cohort 2 N=31**		**Cohort 3 N=31**		**Cohort 3 + Extension N=92**	
Response	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Year 5 , Total n	**27**		**19**		**14**		**41**	
Overall Response	4 (14.8)	4.2, 33.7	0	0.0, 17.6	0	0.0, 23.2	0	0.0, 8.6
Complete Response	3 (11.1)	2.4, 29.2	0	0.0, 17.6	0	0.0, 23.2	0	0.0, 8.6

Overall Response = Complete or Partial Response
'Total n' is the number of subjects in the treatment group who reached this timepoint or withdrew earlier. It is the denominator for percentage (%) calculation. The 95% CI were computed based on the exact method of Clopper-Pearson.

Some subjects who were partial responders at Month 6 became complete responder at a later assessment. Although a confirmatory sample was not required from Year 1 onward, this improvement was due to a continuous increase of blood counts in most patients. Respectively 3 (10.0%), 10 (32.3%) and 8 (9.2%) subjects in Cohort 1, Cohort 2 and combined Cohort 3 + Extension Cohort improved their response after Month 6. Subjects in combined Cohort 3 + Extension Cohort had shorter follow-up and higher complete response rate at Month 6 which could explain the lower proportion of subjects who improved their response after Month 6. Several pediatric subjects, 3 in Cohort 2 (3 years, 7 years and 16 years); 2 Subjects in combined Cohort 3 + Extension Cohort (5 years and 11 years) with very severe aplastic anemia at baseline reached a complete response for the first time at Year 1 or later. 2 other pediatric subjects, with severe aplastic anemia, one in Cohort 1 (17 years) and another in combined Cohort 3 + Extension Cohort (14 years) reached also a complete response at Year 1 or later (Table 32).

Table 32. Improvement in hematological response after month 6-FAS (cumulative as of 28-Feb-2018).

	Subject AUS01T-ID	Age (years)	Severity of aplastic anemia	Month 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Cohort 1	006	17	Severe	PR	PR	CR	CR	CR	CR	CR
	012	39	Severe	PR	PR	PR	CR	CR	CR	CR
	024	26	Severe	PR	PR	PR	CR	CR	CR	-
Cohort 2	038	16	Very Severe	PR	PR	PR	PR	CR	-	-
	043	33	Very Severe	PR	PR	PR	CR	CR	PR	-
	045	21	Severe	NR	PR	CR	CR	Relapse	-	--
	048	21	Severe	PR	PR	CR	CR	CR	-	-
	049	3	Very Severe	PR	PR	CR	CR	CR	-	-
	050	7	Very Severe	PR	PR	CR	CR	Relapse	-	-
	052	31	Severe	CR	PR	PR	CR	CR	-	-
	057	25	Severe	CR	PR	CR	CR	CR	-	-
	058	20	Severe	PR	PR	PR	PR	CR	-	-
	060	51	Severe	PR	PR	PR	CR	CR	-	-
Cohort 3	064	25	Severe	PR	PR	CR	CR	CR	-	-
	072	29	Severe	PR	PR	PR	CR	-	-	-
	073	56	Severe	PR	PR	PR	CR	-	-	-
	081	11	Very Severe	PR	PR	PR	CR	-	-	-
	085	22	Very Severe	NR	PR	CR	CR	-	-	-
Extension Cohort	114	5	Very Severe	PR	PR	CR	-	-	-	-
	130	14	Severe	PR	PR	CR	-	-	-	-
	131	50	Severe	CR	PR	CR	-	-	-	-

CR: complete response, NR: no response, PR: partial response.
Severe aplastic anemia: absolute neutrophil count < 500/µL and either platelet count < $20x10^3$/µL, absolute reticulocyte count < $60x10^3$/µL or both),
Very severe aplastic anemia: absolute neutrophil count < 200 µL and either platelet count < $20x10^3$/µL, absolute reticulocyte count < $60x10^3$/µL or both)

Duration of response

- *Duration of complete response*

As planned per protocol, none of the subjects in Cohort 1 and only approximately half of the responding subjects in Cohort 2 received a maintenance dose of CsA beyond the month 6 landmark visit.

In Cohorts 2 and 3, the relapse-free (95% CI) probability estimate at 18 months after complete response was first observed compared favorably (80.2% and 79.7%, respectively) to Cohort 1 (53.8%) (Table 33). Results for longer time should be interpreted with caution, as not all responders in Cohort 3 were on study long enough to have been followed more than 18 months after response.

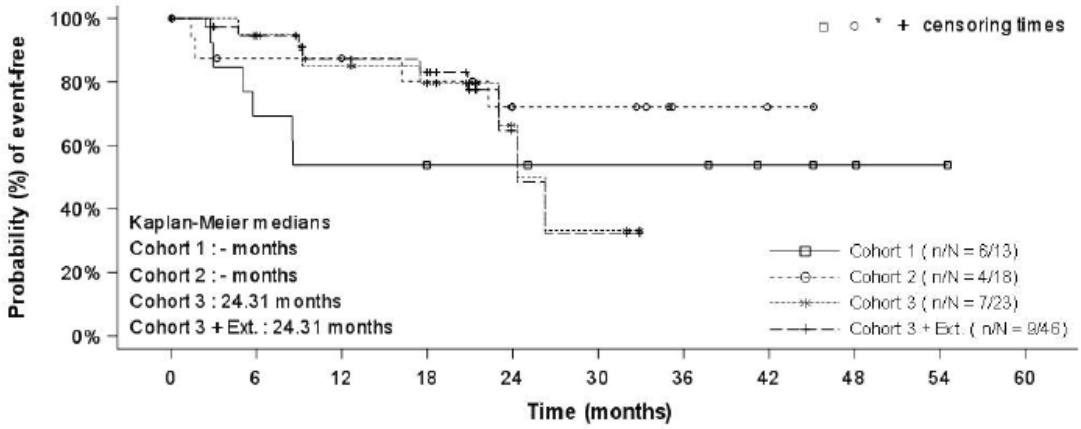
Table 33. Duration of complete response in subjects who responded at anytime FAS (cumulative as of 28-Feb-2018).

	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=92 n (%)
Complete responder at any time	**13 (43.3)**	**18 (58.1)**	**23 (74.2)**	**46 (50.0)**
Relapsed	6 (46.2)	4 (22.2)	7 (30.4)	9 (19.6)
Still responding	7 (53.8)	14 (77.8)	16 (69.6)	37 (80.4)
follow up ongoing	3 (23.1)	12 (66.7)	16 (69.6)	36 (78.3)
discontinued the study	4 (30.8)	2 (11.1)	0	1 (2.2)
Duration of complete response (months) - Percentiles (95% CI)				
25th	5.7 (2.8,NE)	22.3 (1.4,NE)	23.0 (4.7,26.3)	23.0 (9.0,26.3)
50th	NE (5.1, NE)	NE (22.3, NE)	24.3 (23.0, NE)	24.3 (23.0, NE)
Relapse-free probability estimates - % (95% CI)				
6 months	69.2 (37.3,87.2)	87.5 (58.6,96.7)	95.0 (69.5,99.3)	94.6 (80.0,98.6)
12 months	53.8 (24.8,76.0)	87.5 (58.6,96.7)	85.0 (60.4,94.9)	87.3 (69.2,95.1)
18 months	53.8 (24.8,76.0)	80.2 (50.1,93.2)	79.7 (54.5,91.9)	83.1 (63.5,92.8)

The denominator for % calculation is the number of complete responder at any time.
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
% Relapse-free probability is the estimated probability that a subject will remain relapse-free up to the specified time point. Estimates are obtained from the KM survival estimates; Greenwood formula is used for confidence intervals of KM estimates.
NE = Not estimable.

In Cohort 1, almost half of complete responders relapsed within 1 year whereas in other cohorts only 20% relapsed within 1.5 years, (Figure 10).

Figure 10. Kaplan-Meier plot of duration of CR in subjects who responded at any time-FAS (cumulative as of 28-Feb-2018).



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60
Cohort 1	13	9	7	6	6	5	5	3	2	1	0
Cohort 2	18	13	12	11	6	6	2	1	0		
Cohort 3	23	19	17	14	4	2	0				
Cohort 3 + Ext.	46	33	22	18	4	2	0				

'n/N' are the total number of events / total number of patients in that group.

- *Duration of overall response*

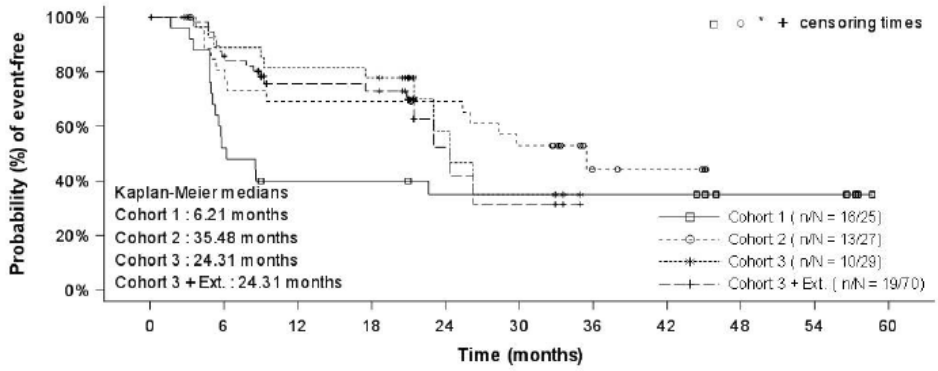
For overall (complete + partial) responders the relapse-free (95% CI) probability at 18-month was 40.0 (21.3,58.1), 69.2 (47.8,83.3), 77.8 (57.1,89.3), 72.9 (58.1,83.2) for Cohort 1, Cohort 2, Cohort 3 and combined Cohort 3 + Extension Cohort, respectively, (Table 34 and Figure 11).

Table 34. Duration of OR in subjects who responded at any time- Overall responders from FAS (cumulative as of 28-Feb-2018).

	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=92 n (%)
Overall responder at any time	**25 (83.3)**	**27 (87.0)**	**29 (93.5)**	**70 (76.1)**
Died	1 (4.0)	1 (3.7)	0	0
Relapsed	15 (60.0)	12 (44.4)	10 (34.5)	19 (27.1)
Still responding	9 (36.0)	14 (51.9)	19 (65.5)	51 (72.9)
follow up ongoing	3 (12.0)	12 (44.4)	17 (58.6)	46 (65.7)
discontinued the study	6 (24.0)	2 (7.4)	2 (6.9)	5 (7.1)
Duration of overall response (months) – Percentiles (95% CI)				
25th	5.0 (1.7,5.7)	6.2 (4.4,28.3)	21.4 (4.7,24.3)	17.5 (5.8,23.0)
50th	6.2 (5.1, NE)	35.5 (9.5, NE)	24.3 (21.4, NE)	24.3 (21.4, NE)
Relapse-free - Probability estimates (95% CI)				
6 months	52.0 (31.2,69.2)	80.8 (59.8,91.5)	88.9 (69.4,96.3)	85.7 (73.5,92.6)
12 months	40.0 (21.3,58.1)	69.2 (47.8,83.3)	81.5 (61.1,91.8)	75.7 (61.6,85.2)
18 months	40.0 (21.3,58.1)	69.2 (47.8,83.3)	77.8 (57.1,89.3)	72.9 (58.1,83.2)

Percentiles with 95% CIs was calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). % Relapse-free probability was the estimated probability that a subject will remain relapse-free up to the specified time point. % Relapse-free probability estimates were obtained from the KM survival estimates; Greenwood formula is used for confidence intervals of KM estimates.
NE = Not estimable.

Figure 11. Kaplan-Meier plot of duration of OR in subjects who responded at any time - FAS (cumulative as of 28-Feb-2018).



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60
Cohort 1	25	13	9	9	7	7	7	7	4	4	0
Cohort 2	27	21	18	18	17	13	4	3	0		
Cohort 3	29	24	22	21	5	3	0				
Cohort 3 + Ext.	70	48	27	26	5	3	0				

n/N' are the total number of events / total number of patients in that group

Maintenance of response

- *Effect of CsA maintenance dose on duration of overall response*

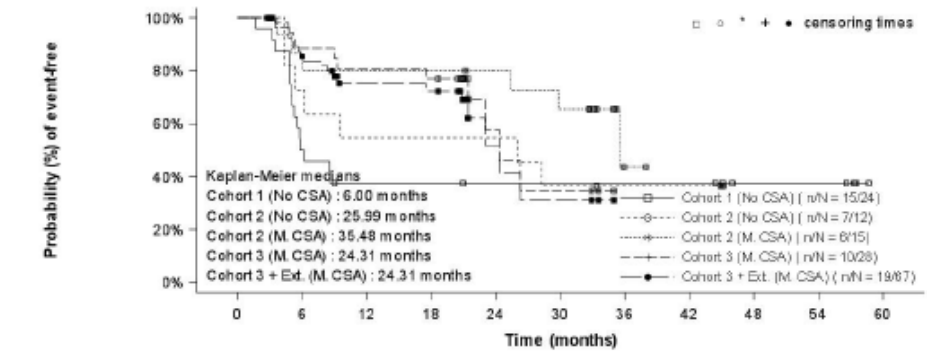
The addition of a maintenance dose of CsA from Month 6 to Month 24 was implemented with protocol amendment 15 in subjects who were responders at Month 6. It started with Subject AUS01T-046 in Cohort 2 and continued with all subjects enrolled thereafter. In Cohort 2, responders who used maintenance dose of CsA (approximately half of subjects enrolled) showed a longer median duration of overall response of 35.5 months vs. 26.0 months for subjects who did not in this cohort, and a better relapse-free probability estimate at 1.5 years (80.0% vs 54.5%), (Table 35 and figure 12). In Cohort 1 where no subject used maintenance CsA, a lower rate of relapse-free probabilities and a shorter median duration of overall response was also observed when compared with cohorts that used maintenance CsA. The addition of maintenance CsA (low dose) was associated with a prolonged duration of response.

Table 35. Duration of OR by use of maintenance dose of CsA - Overall responders at month 6 from FAS (cumulative as of 28-Feb-2018).

	Cohort 1	Cohort 2		Cohort 3	Cohort 3 + Extension
Maintenance CsA	**No**	**No**	**Yes**	**Yes**	**Yes**
	N=24 n (%)	**N=12 n (%)**	**N=15 n (%)**	**N=28 n (%)**	**N=67 n (%)**
Relapsed	15 (62.5)	6 (50.0)	6 (40.0)	10 (35.7)	19 (28.4)
Still responding	9 (37.5)	5 (41.7)	9 (60.0)	18 (64.3)	48 (71.6)
follow-up ongoing	3 (12.5)	4 (33.3)	8 (53.3)	16 (57.1)	45 (67.2)
discontinued the study	6 (25.0)	1 (8.3)	1 (6.7)	2 (7.1)	3 (4.5)
Duration of overall response (months) – Percentiles (95% CI)					
25th	4.9 (1.7, 5.6)	5.3 (4.4, 26.0)	25.4 (3.7, NE)	21.4 (4.7, 24.3)	17.5 (5.8, 23.0)
50th	6.0 (5.0, NE)	26.0 (4.4, NE)	35.5 (6.1, NE)	24.3 (21.4, NE)	24.3 (21.4, NE)
Relapse-free probability estimates (95% CI)					
6 months	50.0 (29.1, 67.8)	72.7 (37.1, 90.3)	86.7 (56.4, 96.5)	88.5 (68.4, 96.1)	85.5 (73.0, 92.4)
12 months	37.5 (19.0, 56.0)	54.5 (22.9, 78.0)	80.0 (50.0, 93.1)	80.8 (59.8, 91.5)	75.2 (60.9, 84.9)
18 months	37.5 (19.0, 56.0)	54.5 (22.9, 78.0)	80.0 (50.0, 93.1)	76.9 (55.7, 88.9)	72.3 (57.3, 82.8)

Maintenance CSA: maintenance dose (2 mg/kg/day) of CsA from Month 6 to month 24 in subjects who were responders at Month 6 assessment.
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). % Relapse-free probability estimate is the estimated probability that a subject will remain relapse-free up to the specified time point. % relapse-free probability estimates are obtained from the KM survival estimates; Greenwood formula is used for CIs of KM estimates.
NE: not estimable

Figure 12. Kaplan-Meier plot of duration of OR by use of maintenance CsA- Overall responders at month 6 from FAS (cumulative as of 28-Feb-2018).



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60
Cohort 1 (No CSA)	24	12	8	8	7	7	7	7	4	4	0
Cohort 2 (No CSA)	12	8	6	6	6	4	3	3	0		
Cohort 2 (M. CSA)	15	13	12	12	11	9	1	0			
Cohort 3 (M. CSA)	28	23	21	20	5	3	0				
Cohort 3 + Ext. (M. CSA)	67	47	26	25	5	3	0				

'n/N' are the total number of events / total number of subjects in that group.

Overall survival

In the combined Cohort 3 + Extension Cohort, 3 subjects died leading to a probability of survival at 2 years of 96% (Table 36 and Figure 13). This is similar to what was reported in the most recent historical studies of IST alone, see (Scheinberg et al 2009) (Scheinberg et al 2011), but higher than the 70% survival observed at 2 years in the study reported by (Rosenfeld et al 2003).

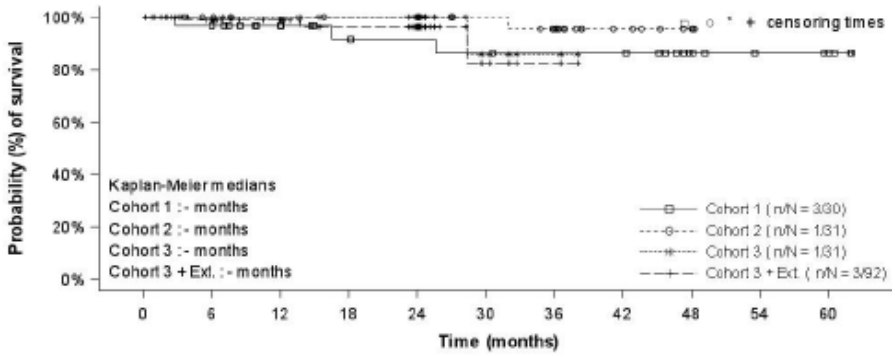
Table 36. Overal survival by cohort- FAS (cumulative as of 28-Feb-2018).

	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=92 n (%)
Number of patients				
Died	3 (10.0)	1 (3.2)	1 (3.2)	3 (3.3)
Alive	27 (90.0)	30 (96.8)	30 (96.8)	89 (96.7)
Follow up ongoing	7 (23.3)	20 (64.5)	20 (64.5)	63 (68.5)
Discontinued the study	20 (66.7)	10 (32.3)	10 (32.3)	26 (28.3)

	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=92 n (%)
Survival probability estimates <(<95%> CI)>				
6 months	96.7 (78.6, 99.5)	100.0 (NE, NE)	100.0 (NE, NE)	98.8 (91.6, 99.8)
12 months	96.7 (78.6, 99.5)	100.0 (NE, NE)	100.0 (NE, NE)	98.8 (91.6, 99.8)
18 months	91.6 (69.4, 97.9)	100.0 (NE, NE)	100.0 (NE, NE)	96.2 (84.6, 99.1)
24 months	91.6 (69.4, 97.9)	100.0 (NE, NE)	100.0 (NE, NE)	96.2 (84.6, 99.1)
30 months	86.2 (62.2, 95.5)	100.0 (NE, NE)	85.7 (33.4, 97.9)	82.5 (38.6, 96.2)
36 months	86.2 (62.2, 95.5)	95.5 (71.9, 99.3)	85.7 (33.4, 97.9)	82.5 (38.6, 96.2)
48 months	86.2 (62.2, 95.5)	95.5 (71.9, 99.3)	NE	NE
60 months	86.2 (62.2, 95.5)	NE	NE	NE

- Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
- % survival probability estimate is the estimated probability that a patient will be alive up to the specified time point.
- % survival probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
- NE = Not estimable.

Figure 13. Kaplan-Meier plot of overall survival – FAS (cumulative as of 28-Feb-2018).



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60
Cohort 1	30	29	22	18	17	16	15	15	9	6	5
Cohort 2	31	29	27	26	26	22	18	8	4	0	
Cohort 3	31	30	28	26	22	5	2	0			
Cohort 3 + Ext.	92	77	48	37	30	5	2	0			

'n/N' are the total number of events / total number of subjects in that group.

Subject-reported outcomes

Updated subject-reported outcomes have not been provided. The one´s described below are data from 30-Sept-2016 cut-off.

PROMIS scores

Self-reported health outcomes PROMIS Global Physical (GPH) and Mental (GMH) Health, sleep disturbance, anxiety, depression and applied cognitive abilities were secondary endpoints. For analysis and ease of interpretation, scores are converted into T-scores where a score of 50 represents the mean for the US population with a standard deviation of 10. A higher score represents more of the concept being measured e.g. a person who has a score of 60 for the GPH or GMH scales is one standard deviation better than the general population. Therefore, on the GPH and GMH, higher scores represent better

quality-of-life outcomes whereas on the symptom scales, a higher score represents a worse outcome e.g. more sleep disturbance, more anxiety and/or more depression.

A change of 10 points on each PROMIS subscale is equal to one standard deviation difference from the population mean; according to the MAH this value may be useful for interpretation of clinical relevance where minimally important differences (MID) have not been established. For 3 subscales, published MIDs are available: Sleep disturbance MID=7.4 (Purvis 2017); anxiety MID=4.5 (Yost 2011); and depression MID=4.5 (Yost 2011).

At Baseline, mean T-scores on the GPH ranged between 43.5 and 44.6 in the 3 cohorts.

FACT scores

According to the MAH data from Health related quality of life Functional Assessment of Cancer Therapy assessment (FACT) (Wagner et al 2008) showed clinically mean improvements over time on the 3 symptom specific FACT scales among groups of subjects who responded to eltrombopag treatment.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of Efficacy for trial AUS01T

Title: Eltrombopag added to standard immunosuppression in treatment-naïve severe aplastic anemia			
Study identifier	CETB115AUS01T		
Design	Phase I/II - Non-randomized, single-arm, single-center, pilot study investigating the standard regimen of horse antithymocyte globulin (h-ATG) and cyclosporine (CsA), in combination with eltrombopag as experimental therapy in subjects with SAA who have not received prior definitive immunosuppressive therapy (IST).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months of treatment with eltrombopag not applicable Extension Cohort - from month 6 to month 24	
Hypothesis	Exploratory: rate of complete responder (CR) at month 6 $\leqslant$ 10%		
Treatments groups	Cohort 1		h- ATG on Days 1 - 4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 6. n=30
	Cohort 2		h- ATG on Days 1 - 4 + CsA from Day 1 to month 6 + eltrombopag from Day 14 to month 3. Following amendment 15 to the protocol, responding subjects who did not relapse at month 6 received maintenance dose of CsAfrom month6 to month 24. n=31
	Cohort 3 and Extension Cohort		All 3 drugs started concurrently on Day 1: h-ATG on Days 1-4, + CsA and eltrombopag from Day 1 to month 6. Responding subjects received low dose of CsA (maintenance dose) from month 6 to month 24. Cohort 3 n=31, Cohort 3 + Extension n=92 (first cut-off included 62 patients)
Endpoints and definitions	Primary endpoint	CR	Complete response rate at 6 months following h-ATG/CsA/eltrombopag. defined as (all 3 were to be met): Absolute neutrophil count >1×10^3/ µL; Platelet count >100×10^3/ µL, Hb>10 g/dL
	Secondary endpoints	Complete response rates at 3 and 12 months and yearly thereafter	
		Overall response rates at 3, 6, 12 months and yearly thereafter up to 60 months	
		Duration of complete response	
		Duration of overall response	
		Time to first occurrence of clonal evolution	

		Overall survival
		Change from Baseline to post-Baseline assessments in PROMIS Global Health
		Sleep Disturbance
		Applied Cognition-Abilities
		Anxiety and Depression scores
		Change from Baseline to post-Baseline assessments in FACT-Anemia
		Thrombocytopenia and Neutropenia scores
		Duration of response in subjects responding at month 6
Database lock	First cut-off 30 September 2016 (updated February 2018)	

Results and Analysis

Analysis description	**Primary Analysis**					
Analysis population and time point description	Per Protocol set (PPS): subset of subjects in the FAS without any major protocol deviation and who have completed a minimum exposure requirement.					
Descriptive statistics and estimate variability	30-September-2016					28-Feb-2018
	Treatment group	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	Cohort 3 + extension N=62	Cohort 3 + extension N=92
	Number of subjects who reached Month 6 visit of withdrew earlier	30	31	31	46	87
	Complete Response, n (%)	10 (33.3)	8 (25.8)	18 (58.1)	24 (52.2)	38 (43.7)
	95% CI	17.3, 52.8	11.9, 44.6	39.1, 75.5	36.9, 67.1	33.1, 54.7
Notes	For each cohort, the rate of CR was calculated as the number of subjects who achieved a CR at month 6 landmark, divided by the total number of subjects enrolled into that cohort who had reached the month 6 landmark or had withdrew earlier for any reason and including non-evaluable subjects.					

Supportive studies

Instead of performing a direct comparison and in order to assess the effect of the addition of eltrombopag to standard therapy the MAH retrieved efficacy data from 4 historical studies. For this retrieval, a search in PubMed was made using specified search criteria (i.e. (((aplastic anemia[Title]) OR aplastic anaemia[Title]) AND clinical trials) AND ("2001/01/01"[Date - Publication] : "2016/09/23"[Date - Publication])).

All studies reported within a time period of approximately 15 years, 1-Jan-2001 to 23-Sept-2016, were considered for inclusion, in addition to studies prior to 1-Jan-2001 if they were mentioned in AUS01T study protocol as potential historical controls.

As the search continued during the preparation of the dossier, a later update included publications issued from 2016/09/23 to 2017/12/31 which resulted in 5 additional publications, including (Townsley *et al* 2017) publication reporting results from AUS01T study.

In summary, a total of 71 publications excluding (Townsley *et al* 2017) (the subject of this dossier) were considered for further investigation. These trials were evaluated for inclusion using the following criteria:

1. IST-naïve patients included in the trial,

2. IST consisting of h-ATG+CsA for at least one arm,

3. Definition of complete and/or overall responses based on similar criteria than AUS01T and response rate at month 6 reported,

4. IST regimen comparable to AUS01T in terms of doses and durations

Only studies that met all the criteria above were included as historical controls. This selection resulted in 3 studies (Rosenfeld *et al* 2003, Scheinberg *et al* 2009 and Scheinberg *et al* 2011). A fourth study mentioned in the protocol and published earlier (Tisdale *et al* 2000) met the above criteria and was added to the pool of historical control studies. All 4 studies were coincidentally conducted at the NIH, the same institution conducting AUS01T.

For completeness, a literature search of studies published before 2001 did not show any other study that meet the criteria except the Tisdale *et al* 2000 mentioned above and the Rosenfeld *et al* 1995 of which an updated version published in 2003 is already used as a historical control study. Furthermore, data obtained from NIH individual subject data from the 2 most recent studies (Scheinberg *et al* 2009 and Scheinberg *et al* 2011), including demographic data and baseline blood counts that defined the severity of the disease (age, gender, platelet count, neutrophil count and reticulocyte count).

Historical studies

Study population

The historical studies reported in Scheinberg *et al* 2011, Scheinberg *et al* 2009, Tisdale *et al* 2000, and Rosenfeld *et al* 2003 all enrolled subjects with SAA who were also treatment-naïve; however, the Scheinberg *et al* 2011 and Rosenfeld *et al* 2003 studies only used treatment with h-ATG+CsA. The Scheinberg *et al* 2009 study and the Tisdale *et al* 2000 study had 2 treatment arms with treatment arm using h-ATG+CsA as comparison. The populations of interest in these historical studies are the arms using the IST treatment regimen alone (specifically h-ATG+CsA arms), as they are used for comparison to the pivotal Study AUS01T with h-ATG+CsA + eltrombopag.

Demographic and other subject characteristics

A comparison of key demographics and other baseline characteristics is presented for the h-ATG+CsA arm of the historical studies and Study AUS01T (Cohort 3+Extension) in table 38 (cut-off 30-Sept-2018).

Subjects in each of the 4 historical studies had SAA similar to Study AUS01T, as determined by individual study inclusion criteria. All historical studies had paediatric subjects as in Study AUS01T, except for Tisdale *et al* 2000 with only adults participating.

Some demographic information was unavailable in each of the historical study publications.

Table 38. Subject demographics and baseline characteristics in the h-ATG+CsA arms of historical studies and Study AUS01T (cohort 3+extension) (cut-off 30-Sept-2016).

Baseline variable	Scheinberg et al 2011 (h-ATG+CsA) N=60	Scheinberg et al 2009 (h-ATG+CsA) N=42	Tisdale et al 2000 (h-ATG+CsA) N=16	Rosenfeld et al 2003 (h-ATG+CsA) N=122	Study AUS01T (Cohort 3 + extension) N=62
Age (years)					
Mean (SD)	NA	NA	NA	NA	34.4 (22.11)
Median	37.4 (2.7)[1]	25	47.5	35	26.5
Min–Max	2–77	4–78	18–67	NA[2]	5–82
Age category (years) - n (%)					
<18	12 (20.0)	NA	NA	31 (25.4)	18 (29.0)
18 – 64	NA	NA	NA	NA	34 (54.8)
≥ 65	NA	NA	NA	NA	10 (16.1)
Sex - n (%)					
Female	26 (43)	19 (45)	NA	61 (50)	31 (50.0)
Male	34 (57)	23 (55)	NA	61 (50)	31 (50.0)
Etiology - n (%)					
Idiopathic	58 (97)	40 (95)	NA	84 (69)	NA
Post-hepatitis	2 (3)	2 (5)	NA	12 (10)	NA
Other	0	0	NA	26 (21)	NA
Cell counts – median					
ARC (10^3/µL)	22.1 (2.584)[1]	14.6	22.4	NA	23.0
ALC (10^3/µL)	1.291 (0.071)[1]	1.422	NA	NA	NA
ANC (10^3/µL)	0.41 (0.05)[1]	0.28	0.40	NA	0.25
<200 (10^3/µL) - n (%)	23 (38)	12 (29)	2 (13)	48 (39)	20 (32.3)
Platelet count (10^3/µL)	16.3 (4.689)[1]	7.0	13.5	NA	9.0

A detailed pediatric age ranged included in historical studies used for the comparison with pivotal study was requested to the MAH. Table 39 presents the age distribution from patients in the h-ATG+CsA arm for the historical control studies and from patients with efficacy data at month 6 for Study AUS01T using the cut-off date of 28-Feb-2018. Except the Tisdale *et al* 2000 study which enrolled only adult patients, the proportion of paediatric patients is similar in each of the historical studies and Study AUS01T. The age range in Table 38 was for all patients enrolled in both treatment arms in Scheinberg 2011 (i.e. over the 60+60 patients studied) and Scheinberg 2009 (i.e. in the 42+35 patients studied), whereas it was limited to only patients treated with h-ATG+CsA alone in Table 39.

Table 39. Age in the h-ATG+CsA arms of historical studies and Study AUS01T (Cohort 3+extension) (cut-off 28-Feb-2018).

	Historical studies using h-ATG + CsA				Study AUS01T (Cohort 3 + extension)	
Baseline variable	**Scheinberg et al 2011 N=60[1]**	**Scheinberg et al 2009 N=42[1]**	**Tisdale et al 2000 N=16**	**Rosenfeld et al 2003 N=122**	**30-Sep-2016 cut-off N=46[2]**	**28-Feb-2018 cut-off N=87[2]**
Age (years)						
Mean (SD)	37.0 (20.93)	31.4 (19.26)	NA[5]	NA[5]	35.1 (21.76)	35.2 (22.53)
Median	35.5	25.0	47.5	35	28.0	27.0
Min–Max	5-76.0	9-78	18–67	NA[5]	6-82	5-82
Age category, years - n (%)						
<18	12 (20.0)	11 (26.2)	0	31 (25.4)	12 (26.1)	25 (28.7)
18 – 64	41 (68.3)	28 (66.7)	NA[5]	NA[5]	27 (58.7)	47 (54.0)
≥ 65	7 (15.2)	3 (7.1)	NA[5]	NA[5]	7 (15.2)	15 (17.2)

[1] Results obtained from subjects data provided by NIH for the comparison to historical control using subject-level data.
[2] eltrombopag + h-ATG+CsA. The number of subjects who reached the month 6 time point or withdrew earlier.
[5] NA=Not applicable; information was unavailable and not presented in the publication.

Subject disposition

Limited information was available on disposition for the 4 historical studies based on their publications.

In Scheinberg *et al* 2011, a total of 120 consecutive subjects, 2 to 77 years of age, were randomly assigned to h-ATG+CsA or r-ATG+CsA (60 in each group). In the h-ATG+CsA arm, 1 subject had early evolution, and 59 subjects were evaluable at 3 months. Following this, 1 subject discontinued the study due to progressive disease, and 58 subjects were evaluable at 6 months.

In Scheinberg *et al* 2009, 77 consecutive subjects with SAA (42 in the h-ATG+CsA arm; 35 in the h-ATG+CsA + sirolimus arm) received an initial course of treatment. In total, 8 subjects died; 5 were in the h-ATG+CsA arm.

Thirty-one subjects were enrolled into the study Tisdale *et al* 2000. Sixteen subjects were assigned h-ATG+CsA, and 15 were assigned cyclophosphamide+CsA. The study was terminated prematurely after 3 early deaths occurred in the cyclophosphamide arm within 6 weeks of the start of treatment. At a median follow-up of 667 days, 4 deaths had occurred (3 in the cyclophosphamide arm and 1 in the h-ATG arm due to refractory pseudomonal sepsis on Day 151).

In Rosenfeld *et al* 2003, a cohort of 122 subjects (31≤18 years and 91>18 years) with SAA were enrolled into the single-arm study to receive h-ATG+CsA. Sixteen patients (13%) died prior to their 3-month evaluation (mainly due to fungal infection).

Compliance

No information on compliance was available in Scheinberg *et al* 2011, Scheinberg *et al* 2009, Tisdale *et al* 2000, and Rosenfeld *et al* 2003.

Treatment exposure

No information, or very limited information, on treatment exposure was available in Scheinberg *et al* 2011, Scheinberg *et al* 2009, Tisdale *et al* 2000, and Rosenfeld *et al* 2003.

In Scheinberg *et al* 2011, the median follow-up was 839 days (28 months) (range: 2 to 1852 days) for all subjects and 891 days (30 months) (range: 185 to 1852 days) for surviving subjects. In Rosenfeld et al 2003, the median follow-up at the time of the 6-month analysis was 7.2 years.

Efficacy results in historical studies and comparison of Study AUS01T with historical efficacy data

Complete response rate and overall response rate

Indirect comparisons of CR results at month 6 from Study AUS01T (eltrombopag + h-ATG+CsA) to historical data (h-ATG+CsA alone) were performed for subject-level data (using propensity score matching and IPTW propensity score methods) and study summary-level data (using frequentist fixed effect, frequentist random effects, and Bayesian MAP methods). For CR, 3 historical studies were used for the comparison using study summary-level data, and 2 for the subject-level data.

Complete response rates as presented by the MAH according to results obtained by Scheinberg *et al* 2011, Scheinberg *et al* 2009 and Tisdale *et al* 2000 for the h-ATG+CsA arms were 11.7%, 7.1%, and 12.5% at 3 months, with improved responses at 6 months of 20.0%, 11.9%, and 25.0%, respectively (Table 40). However, results from Scheinberg 2011 provided by the MAH are based on data from NIH, not available in publications selected according to bibliographic search proposed and therefore impossible for our part to review. Results from Tisdale 2000 provided by the MAH differ from the one available in the publication where only rough efficacy results can be extracted from a graph available in the publication (around 35% of patients, not 25% as stated by the Applicant, reached CR). Complete response rates for historical study Rosenfeld *et al* 2003 were not provided in the publications.

Overall response rates as presented by the MAH according to results obtained by Scheinberg *et al* 2011, Scheinberg *et al* 2009, Tisdale *et al* 2000 and Rosenfeld *et al* 2003 for the h-ATG+CsA arms were at 6 months of 68.3%, 61.9%, 56.30% and 61.5% respectively (Table 40).

Table 40. Complete response rates in historical control studies and Study AUS01T (cut-off 28-Feb-2018).

	h-ATG + CsA arm from historical studies				Eltrombopag + h-ATG + CsA from Study AUS01T	
	(Scheinberg et al 2011) N=60	(Scheinberg et al 2009) N=42	(Tisdale et al 2000) N=16	(Rosenfeld et al 2003) N=122	Cohort 3 + Extension (N=92)	Treatment effect[1] (95% CI)
Benefit						
CR rate at Month 6 - n (%)	12 (20.0)[2]	5 (11.9)	4 (25.0)[3]	NA	38 (43.7)[4]	26.9 (14.6, 39.3) 28.4 (13.0, 43.7) 27.1 (11.7, 42.5)
OR rate at Month 6 – n (%)	41 (68.3)	26 (61.9)	9 (56.3)	75 (61.5)	69 (79.3)[4]	16.3 (5.8, 26.7) 10.4 (-3.4, 24.3) 9.9 (-2.4, 22.1)
Relapse-free estimate for CR	NA	NA	NA	NA	At 6 months: 95%	ND
Relapse-free estimate for OR	At 3 years: 72%	At 3 years: 75%	NA	At 5 years: 65%	At 6 months: 86%	ND
Key risks						
Incidence of clonal evolution	At 3 years: 21%	At 3 years: 9%	NA	At 3 years: 6%[5]	At 1 year: 9%	ND
ALT or AST > 3xULN and TBIL > 2x ULN[6] – n (%)	NA	NA	NA	NA	26 (28.3)	ND
Rash[7] – n (%)	NA	NA	NA	NA	7 (7.6)	ND

CR=Complete response, OR= overall (complete + partial) response, NA=Not available, ND=Not done
[1] Treatment effect [(eltrombopag + IST) – IST alone] obtained from fixed effects model using study level data when available, propensity score matching and IPTW propensity score using subject-level data from the 2 Scheinberg studies, and presented in this order.
[2] Derived from subject level data provided by NIH for the meta-analysis using subject level data
[3] The original publication reported higher percentages based on evaluable subjects only
[4]. The denominator for the calculation of percentage is the number of subjects (87) who reached Month 6 landmark visit or withdrew earlier.
[5]. Cumulative incidence estimated from the Kaplan-Meier curve provided in (Rosenfeld et al 2003) publication
[6]. Using ALT/AST and total bilirubin results obtained from sample collected within maximum 30 days of each other
[7]. Combines the following preferred terms: rash and rash maculopapular

The overall treatment effect (i.e. difference from the CR between historical and AUS01T Study) as shown in table 40 is between 26.9% and 28.4%, depending on the method for the comparison performed. In addition, overall the treatment effect measured as OR (i.e. difference from the OR between historical and AUS01T Study) as shown in table 40 is between 9.9% and 16.3%, depending on the method for the comparison performed.

In the comparison with the historical studies, no responses rates (CR or OR) by age range have been provided.

Duration of response

In the historical studies, the duration of response is represented by the incidence of relapse. In Scheinberg *et al* 2009, the incidence of relapse at 3 years was 25% for the h-ATG+CsA arm, with 6 subjects relapsing. Four of these subjects had completed the CsA taper, and two had relapsed during tapering.

In the h-ATG+CsA arm of Scheinberg *et al* 2011, the incidence of relapse at 3 years (calculated with the use of Kaplan-Meier estimates) was 28% (95% CI: 9 to 43). For the subjects receiving h-ATG+CsA in Rosenfeld *et al* 2003, the cumulative incidence of relapse among responders was approximately 35% at 5 years. In this study, age, sex, delay between diagnosis and protocol entry, ANC prior to treatment, or presumed etiology were not associated with relapse. Qualitative blood counts at 3 months were also not associated with relapse.

Overall survival

The 3-year OS for subjects in the h-ATG+CsA taper arm in Scheinberg *et al* 2009 was 90%. After a median follow-up of 42 months, the median survival had not been reached in either treatment arm. In total, eight subjects died; five were in the h-ATG+CsA arm and three in the h-ATG+CsA+sirolimus arm. Three died from infectious complications, two died from transplant-related complications, one died of heart failure, one died in a car accident, and one died at home of unknown causes.

In Scheinberg *et al* 2011, the OS rate at 3 years was 96% (95% CI: 90 to 100) in the h-ATG+CsA arm (vs. 76%, 95% CI: 61 to 95 in the r-ATG arm, p=0.04). Of the four deaths in the h-ATG arm, one each resulted from intracranial hemorrhage, sepsis, and lung cancer, and one occurred after stem cell transplantation.

In Tisdale *et al* 2000, at median follow-up of 667 days, one death had occurred in the ATG group due to refractory pseudomonal sepsis on Day 151 (three deaths occurred in the cyclophosphamide arm). However, the OS comparison did not reach significance (p=0.26).

Clonal evolution

In Scheinberg *et al* 2009, four subjects in the h-ATG+CsA arm of this study showed evidence of clonal evolution (3 to monosomy 7 and 1 with complex cytogenetics). Of the 3 subjects who evolved to monosomy 7, 1 had died, 1 developed leukemia, and 1 was receiving only supportive care.

In Scheinberg *et al* 2011, the cumulative incidence of clonal evolution at 3 years (in all subjects, those with and without a response) was 21% (95% CI: 7 to 33) in the h-ATG+CsA arm. Among the 60 subjects treated with h-ATG+CsA, 1 each had deletion 3, deletion 5q, deletion 13q, deletion 20q, and leukemia, and 4 had monosomy 7.

Survival after clonal evolution in Rosenfeld *et al* 2003 was poor, as over 60% of subjects who had evolved (all with monosomy 7), had died within 3 years of the event. An assessment of evolution on survival using a Cox regression model with a time-varying covariate, showed that subjects who had evolved were at seven times the risk of death compared with those who had not evolved (p<0.001).

Independent substantiation studies

Study E1202

Results from [Study E1202] independently provide further data on the efficacy of the addition of eltrombopag to IST in treatment-naïve subjects with MAA or SAA. In this study, the addition of eltrombopag to r-ATG+CsA demonstrated that this treatment is an improvement over r-ATG+CsA alone. Although Scheinberg *et al* 2011 confirmed that the hematological response rate in SAA subjects with h-ATG was significantly higher than with r-ATG (68% vs. 37% at 6 months, p<0.001), the addition of eltrombopag to r-ATG+CsA in Study E1202 still showed improvement in response in subjects with SAA compared to r-ATG+CsA alone in Scheinberg *et al* 2011 at 6 months (57% vs. 37%, respectively).

The median duration of eltrombopag was 168.5 days (range, 125 to 172 days). Ten subjects were enrolled and received eltrombopag. The median age was 55.5 years, and 7 of the subjects were female. All subjects were Asian (Japanese heritage). The median time since diagnosis of AA was 0.59 months. At baseline, the severity of AA was moderate or moderately severe (Stage II or III) in 3 subjects and severe

or very severe (Stage IV or V) in 7 subjects (including 4 subjects with Stage V). Six subjects were transfused with red blood cells (RBCs) within 8 weeks before starting r-ATG+CsA and 8 were transfused with platelets within 4 weeks before starting r-ATG+CsA.

Median baseline values for platelets, hemoglobin, neutrophils, and reticulocytes were 14.3×103/μL, 77.5 g/L, 0.26×103/μL, and 10×103/μL, respectively.

The primary efficacy endpoint was the ORR (CR and PR rates) at 6 months after the start of treatment (Week 26). The ORR at Week 26 was 70.0% (7 of 10), with no CRs. The ORR was 100% (3 of 3) in subjects with non-severe AA and 57.1% (4 of 7) in subjects with SAA. In comparison, in Scheinberg *et al* 2011, the ORR in a similar population at 6 months treated with r-ATG+CsA alone was 37%. The ORR at Week 52 was 60.0% (6 of 10); all responses in 6 subjects were PRs.

Of 7 partial responders at Week 26, 6 maintained PR until Week 52 despite interruption of eltrombopag after entering the Extension part according to the dose adjustment criteria. The remaining 1 responder had a relapse by Week 52 assessment. No delayed responses occurred, as subjects who had not responded by Week 26 did not respond in subsequent weeks.

At baseline, 6 of 10 subjects were RBC transfusion dependent. Of the 6 subjects, 4 had been RBC transfusion independent at least for 8 weeks after initiation of treatment with r-ATG+CsA until Week 52. The 4 subjects became independent by Week 26 assessment, and 3 of them maintained independence until the clinical data cut-off for Week 52 analysis. The other 1 subject restarted RBC transfusion due to lack of efficacy during the Extension part. Four subjects were independent of RBC transfusion at baseline but required RBC transfusion after initiating the r-ATG+CsA therapy. Thereafter, they became independent of RBC transfusion by the Week 26 assessment. Of 4 subjects, 3 had been independent until the clinical data cut-off for Week 52 analysis. The other 1 subject achieved PR at Week 26 assessment but subsequently needed RBC transfusion.

At baseline, 8 of 10 subjects were platelet transfusion dependent. Of the 8 subjects, 5 had been independent of platelet transfusion at least for 4 weeks after initiation of treatment with r-ATG+CsA until Week 52. Of these 5 subjects, 4 were platelet transfusion independent at Week 52 assessment. In the remaining 1 subject, platelet transfusion was required after entering the Extension part. Two subjects who were platelet transfusion independent at baseline were transfusion independent at Week 52 assessment. For subjects who entered the Extension part, the median platelet counts, hemoglobin, neutrophil counts, and reticulocyte counts were stable after Week 26 assessment, though hematologic values had a great variability. No deaths were reported during the study.

According to the MAH the results indicated improvement with the addition of eltrombopag to r-ATG+CsA for subjects with moderate or more severe AA who had not received prior ATG+CsA-based IST.

Boddu *et al* 2017/Kadia *et al* 2015

Results from Boddu *et al* 2017 (and in Kadia *et al* 2015) independently provide further data on the efficacy of the addition of eltrombopag to IST in treatment-naïve subjects. The single-arm, Phase-II study in subjects with severe and non-severe AA, presented in Boddu *et al* 2017 (and Kadia *et al* 2015), evaluated 2 sequential cohorts of interest (of the 5 total cohorts):

1. h-ATG+CsA (plus prednisone/granulocyte colony stimulating factor (G-CSF)) alone

2. eltrombopag + h-ATG+CsA (plus prednisone/G-CSF)

A total of 95 treatment-naïve AA (63 severe or very severe and 32 non severe AA) subjects were enrolled; 75 out the 95 subjects were treated with ATG-based IST regimen and 62 had evaluable response at a minimum of 3-month post-IST. ORRs were 74% (46/62); best attained response at any time was a CR in 32 (70%), and PR in 14 (30%). Boddu *et al.* 2017 did not specify how many evaluable

subjects were assigned to the above arms. Kadia *et al* 2015 indicated that 17 and 14 evaluable, treatment-naïve SAA subjects were treated with IST alone and eltrombopag + IST respectively; 10 (59%) and 11 (79%) responded to IST alone and Eltrombopag + IST, at any time during the study and 4 (24%) and 3 (21%) had a complete response. Kadia *et al.* 2015 concluded that despite including older pts and those with significantly lower blood counts, the cohort receiving eltrombopag had a higher ORR than IST alone, albeit with a longer time to response.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

No formal dose finding study has been performed. Instead, a rationale has been provided based on results from the refractory SAA study (AUS28T), the exposure observed between paediatric and adult ITP patients vs. paediatric SAA patients, as well as the PK/PD results and safety profile obtained from the AUS01T updated cut-off (28-Feb-2018).

In AUS28T Study where subjects with refractory SAA were included, haematological responses were only observed while receiving 150 mg/day of eltrombopag, adjusted for age (<12 years) and ethnicity (East/South-East Asian). Almost all patients reached this maximum dose and, therefore, it was considered the most effective dose.

The exposure to eltrombopag for paediatric and adult ITP patients, based on results from PETIT and PETIT 2 studies, showed that the exposure after dose-normalised PK parameters for adults and 12-17 years old patients was similar which supports the use of the same dosing for both age groups (i.e. 150 mg/day in patients >12 years old). On the contrary, dose-normalised PK parameters in children aged 1-5 years and 6-11 years resulted in similar exposures but higher (approximately 2-fold) compared to children aged 12-17 years. This would support the use of 75 mg/day as the initial dose in these age groups. In addition, popPK analysis in ITP paediatric patients in the younger group (2-5 years) showed that a lower body weight was associated with lower clearance and volume parameters. Therefore, a more conservative approach using a weight-based dosing strategy was proposed for this age group.

PK/PD results and safety profile obtained from the AUS01T updated cut-off (28-Feb-2018) were considered. With these new data 33 additional patients from the extension cohort were included compared to the original 19 patients in the initial cut-off (30-Sept-2016). These new data included overall 50 patients: 39 patients aged >18 years, 8 patients aged 12-17 years and only 3 patients aged 6-11 years. No patient aged 2-5 years or Asian patients were included in this assessment. Data revealed that dose-normalised PK parameters in adults and 12-17 years subgroups were comparable showing similar exposure data. In addition and similar to what has been described in ITP pediatric patients, the exposure to eltrombopag observed in 6-11 years old subgroup SAA naïve patients was approximately double than the exposure described for >12 years SAA naïve patients.

In addition, in AUS01T Study, where the majority of patients (72%) at the updated cut-off in the extension cohort were receiving 150 mg/day of eltrombopag, the safety profile was consistent with the expected safety of eltrombopag in the approved chronic ITP, HCV and refractory SAA indications.

Although the MAH's rationale to explain the initial dose used in pivotal trial is acceptable, the PK profile in patients aged <18 years cannot be considered established due to the low number of children available. Concerns about the appropriateness of the dose used in paediatric patients (i.e. <18 years old) are raised.

Pivotal trial: Study AUS01T

Efficacy of eltrombopag in the claimed indication is based on study AUS01T a phase I/II, non-randomized, single-arm, single-center study designed to evaluate the efficacy and safety of eltrombopag in combination with h-ATG and CsA in definitive immunosuppressive therapy-naïve subjects with SAA. This study, still ongoing, is an investigator-sponsored study conducted by the Haematology Branch of the National Heart, Lung and Blood Institute/National Institutes of Health (NHLBI/NIH) and supported by Novartis.

The trial was designed in an adaptive way that is commonly used in phase I/II single arm trials to assess response rate at an interim time point and allow early termination of a cohort if efficacy is not shown. This is acceptable in early steps of development where dose response and the best regimen are being studied. However, this study has been submitted as the pivotal evidence for efficacy in the new indication. Although it is acknowledged that conducting a randomized controlled trial in this setting could be challenging, the inclusion of standard treatment as a comparator would have been crucial to assess the contribution of eltrombopag in naïve SAA patients.

It is worth mentioning that there is an ongoing study comparing hATG+CsA vs hATG+CsA+Eltrombopag for SAA (Study RACE) sponsored by European Group for Blood and Marrow Transplantation with Novartis and Pfizer as collaborators. Differences between both studies, mainly in terms of treatment regimen and CsA maintenance dosing, have been pointed out by the MAH. According to this, in RACE study treatment regimen is similar to the one used in Cohort 1 and 2 from AUS01T study, where efficacy results were lower compared to Cohort 3. Also, maintenance treatment with CsA is not employed in RACE study. In addition, assessment of efficacy in RACE study is limited to 3 months. However, even when a conclusive comparison of the results between both trials is not possible, the RACE study does demonstrate that performing a randomized controlled trial in this setting (SAA patients) is feasible. Results from this study would have been considered supportive for this application; however the results are not yet available.

As previously mentioned, study AUS01T consisted of 3 consecutive cohorts of subjects, Cohort 1, 2, and 3, and an extension to the third cohort (where enrolment continues) to which subjects were sequentially enrolled. There are 3 sequential cohorts:

- Cohort 1: h-ATG (Day 1-4) + CsA (Day 1-Month 6) + eltrombopag (Day 14-Month 6)
- Cohort 2: h-ATG (Day 1-4) + CsA (Day 1-Month 6) + eltrombopag (Day 14-Month 3)
- Cohort 3 + Extension: h-ATG (Day 1-4) + CsA (Day 1-Month 6) + eltrombopag (Day 1-Month 6)

The extension cohort was included to recruit more subjects with the same dosing regimen as Cohort 3, and collect more data for the analysis of the secondary endpoints within the target regimen. In Cohort 2 (starting with subject 46) and all of Cohort 3 and Extension, low-dose maintenance CsA was administered to subjects who achieved a hematologic response at 6 months.

The primary endpoint was Complete response (CR) rate at 6 months following h-ATG+CsA+eltrombopag, defined as (all 3 were to be met):

- Absolute neutrophil count >1×103/ µL
- Platelet count >100×103/ µL
- Hgb>10 g/dL

The secondary endpoints were mainly aimed at assessing CR at 3, 12 months and yearly thereafter up to 5 years, overall response at 3, 6, 12 months and yearly thereafter up to 5 years, duration of CR and OR, overall survival, relapse/duration of response and HRQoL.

The primary and secondary endpoints are considered acceptable for the assessment of the treatment in SAA. A complete response would allow reducing the risk of life-threatening complications such as recurrent infections due to neutropenia, bleeding episodes due to thrombocypopenia and fatigue due to anemia. Considering that eltrombopag induces proliferation and differentiation of early bone marrow progenitor cells its action is expected to have effects on multi-lineage blood cells and mainly in platelets. Therefore, the addition of eltrombopag to standard therapy should be accompanied by a decline in transfusions requirements. Among all the affected cell lines, platelet deficiency is considered to be at the highest risk since it could not only generate longer hospitalizations but also life threatening bleedings.

Efficacy data and additional analyses

The pivotal study included 153 treatment-naïve patients with SAA. Thirty patients were included in cohort 1, 31 in cohort 2 and 3 and 92 in the cohort 3+extension (cut-off 28-Feb-2018). Previous efficacy results were reported at the original cut-off 30-Sept-2016 when 62 patients were included in the cohort 3 + extension. The MAH has confirmed that inherited causes were excluded from the study AUS01T.

- Primary endpoint: Complete response (CR) at Month 6

CR at month 6 was observed in 10 (33.3%), 8 (25.8%) and 18 (58.1%) subjects in cohort 1, cohort 2 and cohort 3, respectively (FAS population). However, at the updated cut-off, 38 subjects (43.7%) in the pooled cohort 3 + extension cohort achieved a CR compared to the data at the original cut-off (52.2%) showing to some extent worse result. The MAH links this reduction in efficacy with the inclusion of more very severe AA patients (vSAA) in the updated cohort 3 + extension (44,6%) compared to those included in cohort 3 (35.5%) and in cohort 3 + extension at the original cut-off (43.5%). However, in the updated cohort (February 2018) 20 and 21 new patients with vSAA and SAA, respectively, were included and CR was maintained in vSAA patients (36% in the original cut-off and 33% in the updated cut-off) while it was reduced in SAA patients (63% in the original cut-off and 52% in the updated cut-off). These data suggest that reduction in global CR (43.7%) could have not been influenced by the severity of the disease but by the higher number of patients assessed, bringing the efficacy results closer to reality.

Improvement in blood counts is of little relevance if this not translated into clinical outcomes (e.g., reduction in the number of transfusions). The MAH states that they do not have the complete information regarding the transfusions even when legislation regarding transfusions compels blood transfusion centres/hospitals to record every transfusion done including information about the receptors (i.e. type and date of transfusion as well as patient identification). The MAH argued about the association between improvement in cytopenias and survival outcome (Rosenfeld *et al* 2003). In this publication the authors concluded that there is a relationship between platelet or reticulocytes achievements $\geq 50x10^3/\mu l$ and better survival, in relation to platelet or reticulocytes achievements $<50x10^3/\mu l$ in survivors/responder at three months. Also, the MAH has provided data of improvements in transfusion-free interval and on the correlation between CR and longer relapse-free survival when eltrombopag is added to SOC. However, at the time being, we cannot relate changes in transfusion requirements with the addition of eltrombopag to SOC, in the absence of a compared study. Therefore, the CHMP consider that the lack of a comparator in the pivotal study will continue to be the main unresolved issue.

There were important differences in CR rate between Cohort 1 and 3 (33.3% *vs.* 58.1% of CR at month 6, respectively). The MAH states that since demographic characteristics between the cohorts were similar the differences in efficacy can be attributed to the difference in duration of eltrombopag treatment. However, the difference was not so large, 14 days in the administration of eltrombopag between both cohorts. Moreover, the differences in efficacy among cohorts are reduced when higher number of patients are treated (updated cut-off results): 43.7% of CR at month 6 versus 58.1% (i.e. a difference of approximately 10% between both cohorts) probably bringing the efficacy results closer to reality.

There were also differences between the proportion of children included in cohort 1 vs. cohort 3 (16.7% vs. 25.8% respectively) which could have an impact on the efficacy results. However, the number of children included in Cohort 1 was too low it is difficult to draw any conclusion about the impact of children on efficacy or the relationship between age and efficacy.

- Secondary endpoints: Overall response (CR or PR)

More than 75% of subjects of the whole population achieved an OR (PR or CR) at month 3 (76.7%, 77.4%, 87.1%, 79.6% and 75.0% for Cohort 1, 2, 3, 3+extension original and updated cut-off, respectively) and improved at month 6 (80%, 87.1%, 93.5%, 84.8% and 79.3% for Cohort 1, 2, 3, 3+extension original and updated cut-off, respectively). It seems, again, that the response decreases as more patients are included in the cohorts.

- Secondary endpoints: Duration of the effect

In patients from Cohort 1 who did not received CsA maintenance treatment beyond month 6 the CR dropped from 33.3% at month 6 to 16.7% at month 12. On the contrary, in patients from Cohort 2 who did receive CsA as maintenance treatment, CR improved from 25.8% at month 6 to 32.3% at month 12. Moreover, for Cohort 2, relapse-free probability estimates for overall response was 72.7% *vs.* 86.7% at month 6 for patients who did not received and received CsA as maintenance treatment, respectively, and 54.5% *vs.* 80.0% at month 12 for patients who did not received and received CsA as maintenance treatment, respectively.

Subjects from Cohort 3, at the updated time, had reached the 2 year assessment (or withdrew earlier). In this cohort CR was relatively stable and above 50% at all time points from month 6 to year 2. These results show favorable results for cohort 3 compared with the cohorts 1 and 2. However, for Cohort 3 and 3+extension (updated cut-off 28-Feb-2018) the results beyond month 6 have to be read with caution since 14 patients have not yet reached 1 year assessment, including 5 subjects who had not yet reached month 6 and were still receiving eltrombopag. Furthermore, the maintenance treatment with CsA may have played a role in the response beyond month 6. In fact, in Cohort 3 and Cohort 3 + extension (updated cut-off) 8 patients who had partial response at month 6 improved their response after this time point when they did not received eltrombopag any longer and, on the contrary, were on CsA. Therefore, the real benefit of addition eltrombopag to IST in the long-term scenario is questionable.

Moreover, taking into account that AA is an immune mediated disease and considering the mechanism of action of eltrombopag (inductor of proliferation and differentiation of progenitor cells in the bone marrow (mainly platelets)) and timoglobulin/CsA (immunomodulators), it seems more plausible that the administration of hATG as well as the long term use of CsA are related to this long-term effect.

- Secondary endpoints: Overall survival (OS)

Regarding OS, results at 2 years reported by survival probability estimates were 96% in cohort 3 + extension. However, definite results of OS are still pending.

No efficacy data are available for r-ATG. The fact that in some European countries only r-ATG is available could have potentially an impact on the efficacy results. The MAH was asked to discuss this point but this issue remains as an uncertainty.

- Subgroup analysis

Subgroup analysis by age, gender, race and severity of the disease have been provided. For most of the subgroups numbers are too small as to reach any sound conclusion. As children are included in the claimed indication, efficacy assessment by age group deserves further discussion. At cut-off 28 Feb 2018 and focusing on cohort 3+ extension original and updated cut-off in which the posology selected for the

proposed indication was used, only 25 children were included, 1 (2-5 years old), 11 (6-11 years old) and 13 (12-17 years old).

In the subgroup of 12-17 years of age CR was observed in 71.4%, 62.5 % and 46.2% of patients in cohort 3, cohort 3 + extension original and updated cut-off, respectively. It is observed that only 6 out of 13 achieved CR. In addition, the number of children aged 2 to 11 years included in the main study (n=12) was very limited and a complete response was only seen in one of them.

As previously mentioned, the MAH attributed the worse efficacy results in the paediatric population to the severity of the disease (defined by ANC >200/mcl or <200/mcl for SAA and vSAA, respectively), even though the use of G-CSF was permitted during the AUS01T Study. In this sense 57.1% of patients <12 years included in cohort 3+ extension suffered from very severe disease in comparison to 42.8% of patients aged >12 years. However, the poorer efficacy attributed by the MAH to the severity of the disease contradicts the results obtained by Führer *et al* 2005, where a higher CR was observed in children with vSAA treated with IST + G-CSF compared to children with SAA (68% vs 45%, respectively) concluding that the more severe disease stage at diagnosis the more favourable outcome. As a general rule, a higher response rate and survival is expected in the paediatric population compared to adults due to the fact that children have a higher stem-cell reserve. However, results of AUS01T study do not go in this direction. In the limited number of children aged 2 to 11 years included (n=12) CR was seen in only one of them. It should be also considered that children are not included in the currently approved indication (refractory SAA) that it is limited to adults. Based on this, the MAH had proposed during the evaluation to restrict the initial indication to paediatric patients 12-17 years of age to reflect the following indication wording:

'*Revolade is indicated for the first-line treatment of acquired Severe Aplastic Anaemia in combination with standard immunosuppressive therapy in adult and paediatric patients aged 12 years and above who are not eligible for a haematopoietic stem cell transplant at the time of diagnosis'*.

Supportive efficacy data and comparison with AUS01T results

Supportive efficacy data from other clinical studies in AA were included in the dossier. Study E1202 evaluated eltrombopag in combination with r-ATG + CsA in treatment naïve Japanese subjects with moderate AA or SAA. The study conducted by Boddu *et al* (2017) was carried out at the MD Anderson Cancer Center and evaluated h-ATG + CsA in combination with eltrombopag in treatment-naïve subjects diagnosed with AA. This data has been used by the MAH for further substantiation from a non-NIH center. However, no comparisons with the pivotal study were done as the design and the results of this study were available only as a publication and only limited information is available.

Data from the pivotal study are compared with historical studies in which patients were treated with h-ATG + CsA in SAA. The search strategy for the selection of historical studies has been justified by the MAH, as requested. The retrieval included the publications by Scheinberg *et al* 2009, Scheinberg *et al* 2011, Tisdale *et al* 2000, and Rosenfeld *et al* 2003. From an efficacy point of view, only these historical studies are considered relevant as supportive information.

However, the limitations of using historical controls are well-known and they can be considered as reliable as an internal control. The impact on the results of known and unknown prognostic factors for treatment-naïve SSA patients cannot be controlled in the absence of a randomized clinical trial. In addition, the limited number of patients in study AUS01T could have substantial influence on the point estimates of the populations by chance, i.e. there is a higher risk that the point estimates could substantially deviate from the "true" parameter. In fact, with the updated cut-off (28-Feb-2018) when a more patients were included compared to the original cut-off, a reduction in the efficacy results measured as CR have been revealed.

The comparisons have been done between historical studies and the cohort 3+extension. The aim of this cohort was to increase the number of subjects with the same dosing regimen as Cohort 3 and to collect more data for the analysis of the secondary endpoints within the proposed regimen. It is relevant to highlight that only part of the whole population studied in each historical study (i.e. groups receiving h-ATG + CsA) has taken into account for comparison. The age range reported originally for Scheinberg 2009 and Scheinberg 2011 was for all patients enrolled in both treatment arms in Scheinberg 2009 (77 [42+35] patients) and in Scheinberg 2011 (120 [60+60] patients). For the comparison, only those patients randomized to h-ATG+CsA, i.e., 42 and 60 patients, respectively were used.

The study by Scheinberg *et al* 2009 included 77 patients with SAA of 4-78 years of age but the selected cohort (h-ATG+CsA) included only 42 patients. The MAH clarified that, for the selected cohort used in the comparison, patients between 9-78 years were included and of those 26.2%, 66.7% and 7.1% were <18 years, 18-64 years and ≥64 years, respectively. However, the age range distribution of patients younger than 18 years it is not provided in the publication.

The study by Scheinberg *et al* 2011 included 120 patients from 2 to 77 years of age who were assigned to hATG or rATG (60 in each group). For the selected cohort used in the comparison, patients between 5-76 years were included. However, the number of children aged from 2-5, 6-11 and 12-17 years is not specified in the paper either.

Tisdale's *et al* study included 31 patients with an age range between 18-67 years and, therefore, no children were included. Only 16 who received ATG + CsA were included in the comparison.

The study by Rosenfeld *et al* included 122 patients receiving h-ATG+CsA, 31 of whom were <18 years but the age range data, again, is not included in the publication.

The MAH has compared the definition of haematological responses of study AUST01 with those used in the mentioned publications. However, it must be taken into account that for one of these historical studies (Rosenfeld *et al* 2003) CR results were not available. In the other three, the definition of CR was the same as the one used in AUS01T study. However, data provided on CR for Scheinberg *et al* 2011 (CR 20%) and Tisdale *et al* 2000 (CR 25%) are not provided in the published papers. Only rough efficacy results from Tisdale *et al* 2000 study can be extracted from a graph available in the publication. The MAH states that efficacy results from both studies were obtained from NIH, but this is not confirmed by any document. Therefore, only one historical study (Scheinberg 2009) with 42 patients included (31 of them were adults) could be considered as acceptable for comparison. Nevertheless, there are shortcomings and limitations in the comparisons with historical controls and that mainly refer to the bias derived from the lack of randomisation. Moreover, in principle, one arm studies could be considered acceptable if comparative trials are unfeasible, e.g., due to the impossibility to recruit patients because of the rarity of the disease. This does not seem to be the case here as one comparative trial sponsored by EBMT with the collaboration of Novartis is currently ongoing (RACE study).

Comparison of this study (Scheinberg *et al* 2009) with AUS01T shows that CR of eltrombopag + IST was 28.4% higher than that of IST alone. However, in this comparison paediatric population is also included (11/42 subjects) and, again, the age range distribution of patients younger than 18 years is not provided in the publication making it unfeasible to compare efficacy results of patients aged 12-17 years between both studies.

Bearing in mind the following limitations:

- the absence of a comparative study (eltrombopag + IST vs. IST). The submitted data (study NIH AUS01T) do not allow a reliable and valid assessment of the efficacy and safety of Revolade as first line treatment of severe aplastic anaemia on top of IST due to the lack of a robust comparison against the established treatment. The indirect comparison with historical data cannot overcome this deficiency. The

results of the ongoing study RACE may provide supportive efficacy and safety data versus standard of care in these patients.

- that the historical studies potentially acceptable included only 42 patients.

Data provided suggest some treatment effect of eltrombopag on top of IST as a first line treatment in adults in terms of CR. However, the lack of a comparator in the pivotal study is the crucial unresolved issue that prevents from reaching a positive conclusion on the benefit/risk ratio of Revolade as the first line treatment of SAA patients.

2.4.4. Conclusions on the clinical efficacy

This extension of the indication is based on a single and non-comparative trial in which treatment-naïve patients with SAA were included (results from the study AUS01T) showed that CR, the primary endpoint, was observed in 33.3%, 25.8% and 58.1% of subjects in cohort 1, cohort 2 and cohort 3, respectively, (FAS population) at month 6 of treatment. When cohort 3 and the extension cohort were pooled (cut-off 28 feb-2018) CR was observed in 43.7% of patients at month 6.

In the absence of an internal comparator arm in study AUT01 the MAH has provided some comparisons with historical controls. Only one study where CR was clearly provided, was considered valid for this purpose. This comparison suggests greater efficacy for the combination of eltrombopag and h-ATG+CsA than for h-ATG+CsA alone in terms of CR at month 6. However, there are uncertainties related to the inherent limitations of the historical controls and the impossibility to assure that all prognostic factors that can have an impact on the results have been controlled in the absence of randomization.

Data on maintenance of the effect show better response in patients treated with CsA beyond Month 6 (when eltrombopag treatment was terminated) compared to those not treated with CsA suggesting that CsA may play a relevant role in the response of patients beyond month 6.

No data on clinical efficacy apart from the haematological response has been provided. Transfusion data, that could show clinical benefit beyond haematological response, was not considered as an endpoint in AUS01T study so they were not collected in a systematic way. The lack of these data is of concern. Nonetheless, the main question remains: whether any beneficial effects observed in study AUS01T can be explained by the addition of eltrombopag due to the lack of comparison.

Unfortunately, the study design does not allow either the identification of patient populations who can benefit of the addition of eltrombopag to IST as first line treatment.

Data in children are particularly limited to conclude on efficacy and safety in this subpopulation. Efficacy in adolescents cannot be sufficiently demonstrated either. Furthermore, even if the efficacy and safety of adding Revolade to IST in SAA adult patients were considered demonstrated the indication would need additional refinement and be restricted to adults unsuitable for haematopoietic stem cell transplantation.

Overall, the role of eltrombopag in first-line therapy of naive SAA patients needs to be further elucidated as it cannot be concluded based on the data provided.

2.5. Clinical safety

Introduction

Eltrombopag has been investigated in multiple clinical development programs since 2004 by the initial sponsor, GlaxoSmithKline (GSK). GSK was the original Marketing Authorization Holder (MAH) until 2015 when Novartis acquired eltrombopag. The MAH transfer from GSK to Novartis is still ongoing or has been completed in the countries where the product is approved (dates and status vary per country).

The cumulative post-marketing exposure worldwide from the first launch until June 2017 is 106,493 subject-years [PSUR version 10-dated 22-Nov- 2017]. Hepatotoxicity, thromboembolic events, post-therapy reoccurrence of thrombocytopenia, renal tubular toxicity, hematological malignancies and cytogenetic abnormalities are adverse events of special interest (AESIs). Cytogenetic abnormalities, although considered as AESI, were considered as part of the underlying disease and therefore not reported as AEs by the Principal Investigator and were analysed separately. Eltrombopag is currently approved in over 45 countries for the treatment of subjects with SAA who are refractory to other treatments.

A serious complication of aplastic anemia (AA) is its evolution to clonal hematologic diseases such as MDS and leukaemia, which is usually associated with the appearance of a cytogenetic abnormality in bone marrow cells. The actuarial risk for this complication has been estimated in other studies at around 15% at 5 years. Conversion from normal to abnormal karyotype occurs at a constant rate after initial diagnosis, with about 50% of cases developing within the first 30 months (Maciejewski *et al* 2002). Clonal evolution involving chromosome 7 abnormalities is frequently observed in SAA, mostly in refractory subjects, who fare as poorly as in primary MDS, with a high rate of conversion to acute leukaemia. However, cytogenetic abnormalities are not necessarily associated with a bad outcome or a change in symptoms or diagnosis of malignancy, but can be associated with dysplastic changes in bone marrow and development of MDS (Maciejewski *et al* 2002). It was previously assumed that the presence of an abnormal cytogenetic clone indicated a diagnosis of MDS and not AA. However it is now evident that abnormal cytogenetic clones (such as del (13q), trisomy 8 and others), which may be transient, are present in up to 12% of subjects with otherwise typical AA at diagnosis (Gupta *et al* 2006, Afable *et al* 2011b). Although monosomy 7 may indicate the likelihood of MDS in children, in adults monosomy 7 can also be seen in AA. Evolution of abnormal cytogenetic clones may arise during the course of the disease, and the appearance of a new cytogenetic abnormality may provide evidence of clonal evolution. Interestingly, malignant clonal evolution is rare in complete responders of IST. This safety review is based on the results of Study AUS01T which evaluated the safety and efficacy of eltrombopag in combination with h-ATG and CsA in subjects with SAA who had not received prior definitive IST. Additionally, the safety data from this single-arm study is put into perspective against two Novartis studies conducted in Japan, Study E1201 and Study E1202 and historical studies in subjects treated with h-ATG and CsA. Additional supportive safety data from the refractory studies for cytogenetic abnormalities are provided from Study US28T and Study US18T. The list of these studies and publications (Tisdale *et al* (2000), Rosenfeld *et al* (2003), Scheinberg *et al* (2009) and Scheinberg *et al* (2011)) and their contribution to the safety analysis is provided in table 41.

Table 41. Studies contributing to safety data in SAA.

	Type of study and contribution to the dossier	Subjects and Treatment	Safety endpoints presented in the SCS	Cut-off date
Pivotal study: h-ATG +CsA in combination with eltrombopag in definitive immunosuppressive therapy-naïve subjects with SAA				
[Study AUS01T]	Safety data from treatment-naïve subjects with SAA	N = 123[a] h-ATG + CsA + eltrombopag up to 150 mg/day[b]	AEs, SAEs, hematology, blood chemistry, vital signs, physical condition, ECG, and clonal evolution	30-Sep-2016
Supportive studies				
r-ATG +CsA in combination with eltrombopag in treatment-naïve subjects with MAA or SAA				
[Study E1202]	Supportive safety data from treatment-naïve Japanese MAA or SAA subjects;	N=10 (7 SAA and 3 MAA) r-ATG + CsA + eltrombopag 75 mg/day[b]	AEs, SAEs, hematology, blood chemistry, vital signs, physical condition, ECG, and cytogenetic abnormalities.	Jan-2017
Eltrombopag alone in treatment-refractory subjects with MAA or SAA				
[Study E1201]	Supportive safety data from refractory Japanese MAA or SAA subjects	N=21 (15 MAA and 6 SAA) Eltrombopag 100 mg/day[b]	AEs, SAEs, hematology, blood chemistry, vital signs, physical condition, ECG, and cytogenetic abnormalities.	Mar-2016
Eltrombopag alone in treatment-refractory subjects with SAA				
[Study US28T]	Supportive safety data on the development of cytogenetic abnormalities from NIH-sponsored trial in refractory SAA subjects	N=43 Eltrombopag 150 mg/day	Cytogenetic abnormality	May-2014
[Study US18T]	Supportive safety data on the development of cytogenetic abnormalities from NIH-sponsored trial in refractory SAA subjects	N=40 Eltrombopag 150 mg/day[b]	Cytogenetic abnormality	Jan-2015
Literature reports of relevant historical studies: h-ATG + CsA alone in subjects with SAA				
[Scheinberg et al (2011)]	Historical safety data for h-ATG + CsA alone in subjects with SAA	N=60[c] h-ATG + CsA	SAEs and clonal evolution	Jul-2010
[Scheinberg et al (2009)]	Historical safety data for h-ATG + CsA alone in subjects with SAA	N=42[c] h-ATG + CsA	SAEs and clonal evolution	Nov-2005
[Tisdale et al (2000)]	Historical safety data for h-ATG + CsA alone in subjects with SAA	N=16 h-ATG + CsA	Limited safety; clonal evolution	Mar-2000
[Rosenfeld et al (2003)]	Historical safety data for h-ATG + CsA alone in subjects with SAA	N=122 h-ATG + CsA	Limited safety; clonal evolution	Jan-1998

[a] 124 subjects were enrolled as of the cut-off date but one subject did not receive eltrombopag

[b] 150 = approved refractory dose and dose given in Study AUS01T. Asian subjects received 50% of maximum dose of eltrombopag due to known ethnic difference in PK (2-fold higher exposure in Asians observed across indications).

[c] Number of subjects enrolled in h-ATG+CsA treatment arm

h-ATG: horse anti-thymocyte globulin, r-ATG: rabbit anti-thymocyte globulin, CsA: cyclosporine A, MAA: moderate aplastic anemia, SAA: severe aplastic anemia.

Patient exposure

Exposure in Study AUS01T

Exposure to eltrombopag was planned from Day 14 to Month 6 (168 days) in Cohort 1, from Day 14 to Month 3 (77 days) in Cohort 2 and from Day 1 to Month 6 (182 days) in Cohort 3 and Extension Cohort. Exposure to h-ATG was planned from Day 1 to Day 4 (4 days) for all cohorts. The therapeutic dose of CsA was planned from Day 1 to Month 6 (182 days) for all cohorts. The maintenance dose of CsA was planned from Month 6 to Month 24 (540 days) for subjects enrolled in the study from protocol amendment 15 in

Cohort 2 (starting with Subject 46) and in Cohort 3 and Extension Cohort for subjects who were responders at Month 6.

h-ATG was administered at a dose of 40 mg/kg. CsA dosing was based on body weight, except for obese subjects. Total daily dose of CsA for subjects ≥ 12 years and <12 years was 6 mg/kg/day and 12 mg/kg/day, respectively. For obese subjects, the CsA dose was based on the adjusted body weight. CsA dosing was adjusted to obtain a therapeutic trough level between 200 to 400 µg/L. Subjects received a starting dose of eltrombopag according to age and ethnicity. Eltrombopag 150 mg once daily was selected as the starting dose for non-Asian subjects who were ≥ 12 years old. The median exposure to h-ATG in all cohorts was 4 days (range: 3-8 days).

The median exposures to a therapeutic dose of CsA in Cohort 1, 2, 3, and combined Cohort 3+Extension Cohort were 187 days (range: 44-196 days), 185 days (range: 111-197 days), 186 days (range: 40-195 days), and 183 days (range: 3-224 days), respectively. The median exposures to a maintenance dose of CsA in Cohort 2, Cohort 3, and combined Cohort 3 + Extension Cohort were 547 days (range: 13-739 days), 203 days (range: 29-488 days), and 167 days (range: 12-488 days), respectively.

The exposure to eltrombopag is presented in table 42. The exposure in Cohort 2 was lower than other cohorts as subjects' exposure to eltrombopag stopped at Month 3 per protocol. Of note, 15 of 31 subjects in the Extension Cohort were ongoing on eltrombopag and a therapeutic dose of CsA at the data cut-off date (30-Sep-2016). In addition the updated exposure to study treatment (as of 28-Feb-2018) is only presented for the combined Cohort 3 + extension cohort (table 42-2).

Maintenance dose of CsA was ongoing at the original cut-off date (30-Sep-2016) in subjects who had started at Month 6 (starting with Subject AUS01T-042 in Cohort 2) and had not withdrew from the study, or had not reached Month 24. Therefore, the updated exposure to maintenance dose of CsA is presented for all cohorts (except for Cohort 1 and for the subjects in Cohort 2 who never used maintenance dose of CsA).

Table 42. Exposure to eltrombopag (Study AUS01T) (cut-off 30-Sept-2016).

	Cohort 1 N=30	Cohort 2[a] N=31	Cohort 3 + Extension Cohort N=62
Duration of exposure (days)			
Mean (SD)	144.4 (48.02)	79.4 (9.90)	137.8 (61.51)
Median (min-max)	170.0 (38-183)	83.0 (32-94)	180.0 (3-195)
Total subject-year exposure	11.57	6.72	23.38
Dose intensity (%)			
Mean (SD)	97.05 (8.866)	98.37 (4.460)	93.46 (10.205)
Median (min-max)	100.0 (72.9-118.3)	100.0 (81.9-100.7)	99.20 (60.5-100)

A subject is counted in only one duration range, per treatment.
a. Subjects enrolled in Cohort 2 stopped eltrombopag at month 3.

Table 42-2. Exposure to eltrombopag (Study AUS01T) (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016 Cohort 3 + Extension[a] N=62	28-Feb-2018 Cohort 3 + Extension[b] N=92
Exposure (days)		
Mean (SD)	137.8 (61.51)	155.8 (53.83)
Median	180.0	183.0
Min-Max	3-195	6-204
Exposure categories - n (%)		
≤ 6 weeks	7 (11.3)	6 (6.5)
> 6 - ≤ 12 weeks	8 (12.9)	9 (9.8)
> 12 - ≤ 18 weeks	7 (11.3)	6 (6.5)
> 18 - ≤ 24 weeks	7 (11.3)	7 (7.6)
> 24 weeks	33 (53.2)	64 (69.6)
Relative dose intensity (%)		
Mean (SD)	93.46 (10.205)	93.36 (10.153)
Median	99.20	98.93
Q1-Q3	90.83-100	91.56-100
Min-Max	60.5-100	60.5-100
Relative dose intensity categories - n (%)		
≤ 75%	4 (6.5)	6 (6.5)
> 75 – 90%	10 (16.1)	15 (16.3)
> 90 - 110%	48 (77.4)	71 (77.2)
> 110%	0	0

a. 15 of 31 subjects in the Extension Cohort were receiving eltrombopag but had not yet reached Month 6 landmark visit at data cutoff (30-Sep-2016).
b. 5 of 61 subjects in the Extension Cohort were receiving eltrombopag but had not yet reached Month 6 landmark visit at data cutoff (28-Feb-2018)
Relative dose intensity = 100*[(Cumulative dose/Duration of exposure)/(Planned dose intensity)].

Relative dose intensity for exposure to eltrombopag, to h-ATG and to therapeutic dose of CsA was similar to what was observed at original cut-off, see Table 43, Table 44 and Table 45, respectively.

Table 43. Exposure to h-ATG (Study AUS01T) (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016 Cohort 3 + Extension N=62	28-Feb-2018 Cohort 3 + Extension N=92
Exposure (days)		
Mean (SD)	4.0 (0.18)	4.0 (0.38)
Median	4.0	4.0
Min-Max	3-5	1-5
Relative dose intensity (%)		
Mean (SD)	100.09 (2.187)	99.13 (5.216)
Median	100.06	100.06
Q1-Q3	99.80-101.04	99.68-100.75
Min-Max	85.8-103.9	66.0-103.9
Relative dose intensity categories - n (%)		
≤ 75%	0	1 (1.1)
> 75 - 90%	1 (1.6)	3 (3.3)
> 90 - 110%	61 (98.4)	88 (95.7)
> 110%	0	0

Planned dose intensity is based on weight at study entry = 40 mg/kg
Relative dose intensity = 100*[(Cumulative dose/Duration of exposure)/(Planned dose intensity)].

Table 44. Exposure to therapeutic dose of CsA (Study AUS01T) (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016	28-Feb-2018
	Cohort 3 + Extension N=62	Cohort 3 + Extension N=92
Exposure to therapeutic dose (days)		
Mean (SD)	151.0 (58.91)	168.2 (46.83)
Median	183	186.0
Min-Max	3-224	6-224
Relative dose intensity (%)		
Mean (SD)	97.79 (37.098)	93.82 (32.870)
Median	98.66	92.55
Q1-Q3	78.08-119.86	70.38-118.22
Min-Max	20.5-190.6	20.5-190.6
Relative dose intensity categories - n (%)		
≤ 75%	15 (24.2)	30 (32.6)
> 75 - 90%	10 (16.1)	13 (14.1)
> 90 - 110%	17 (27.4)	22 (23.9)
> 110%	20 (32.3)	27 (29.3)

Therapeutic dose is defined as the dose planned from Day 1 to Month 6
Planned therapeutic dose intensity is based on age and weight at study entry: < 12 years=12 mg/kg; ≥ 12 years=6 mg/kg
Relative dose intensity = 100*[(Cumulative dose/Duration of exposure)/(Planned dose intensity)].

Mean and median exposure to maintenance dose of CsA increased as expected with longer time on study, see Table 36-5.

Table 45. Exposure to maintenance dose of CsA (Study AUS01T) (cut-off 28-Feb-2018).

Cutoff date	28-Feb-2018		
	Cohort 2 N=31	Cohort 3 N=31	Cohort 3 + Extension N= 92
Number of subjects who were exposed to maintenance CsA	**15**	**28**	**67**
Mean (SD)	505.7 (249.54)	420.8 (206.30)	334.5 (210.69)
Median	561.0	543.5	387.0
Min-Max	13-891	29-610	22-646
Relative dose intensity (%)			
Mean (SD)	100.60 (30.331)	104.44 (17.630)	106.94 (16.350)
Median	100.94	107.96	107.94
Q1-Q3	90.20-110.06	96.54-115.99	98.81-116.82
Min-Max	42.2-179.9	31.3-125.6	31.3-161.9
Relative dose intensity categories - n (%)			
≤ 75%	2 (6.5)	1 (3.2)	1 (1.1)
> 75 - 90%	1 (3.2)	2 (6.5)	7 (7.6)
> 90 - 110%	8 (25.8)	12 (38.7)	28 (30.4)
> 110%	4 (12.9)	13 (41.9)	31 (33.7)

Maintenance dose is defined as the reduced dose planned from Month 6 to Year 2 for subjects responder who were enrolled in Cohort 2 under protocol amendment #15 (starting with Subject AUS01T-046), in Cohort 3 and in Extension Cohort. The maintenance dose intensity is based on weight at Month 6 (2 mg/kg).
Relative dose intensity = 100*[(Cumulative dose/Duration of exposure)/(Planned dose intensity)].

Dose adjustments of eltrombopag

The incidences and reasons for eltrombopag dose adjustment in combined Cohort 3 + Extension Cohort were similar to what was observed at the original cut-off (Table 46).

Table 46. Dose adjustments of eltrombopag- Safety set.

Cut-off date	30-Sep-2016				28-Feb-2018
	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=62 n (%)	Cohort 3 + Extension N=92 n (%)
Subjects with dose adjustments	**10 (33.3)**	**5 (16.1)**	**19 (61.3)**	**31 (50.0)**	**47 (51.1)**
Total number of dose adjustments	25	9	58	91	127
Reasons for dose adjustments[a]					
Platelet count > $200x10^3/\mu L$	18 (72.0)	7 (77.8)	35 (60.3)	51 (56.0)	64 (50.4)
Toxicity	1 (4.0)	2 (22.2)	11 (19.0)	20 (22.0)	31 (24.4)
Adverse event	1 (4.0)	0	7 (12.1)	12 (13.2)	14 (11.0)
Subject compliance	2 (8.0)	0	5 (8.6)	8 (8.8)	12 (9.4)
Other reason	2 (8.0)	0	0	0	5 (3.9)
Platelet count > $400x10^3/\mu L$	1 (4.0)	0	0	0	1 (0.8)

Only dose adjustments that occurred during the core treatment period of 3 months (for Cohort 2) or 6 months (all other cohorts) were included.
a. Percentage was based on total number of dose adjustments.

Exposure in Study E1202

In the safety population of 10 subjects, the median treatment duration of eltrombopag including days of interruptions was 344.5 days (range: 125 to 355 days) as of the clinical cut-off date. The median average dose of eltrombopag including days of interruptions was 49.8 mg/day (range: 27 to 75 mg/day).

The median duration of CsA was 365.0 days (range: 287 to 416 days). The median average dose of CsA was 135.5 mg/day (range: 82 to 276 mg/day).

Exposure in Study E1201

In the safety population of 21 subjects, the median treatment duration of eltrombopag was 189.0 days with a maximum duration of 371 days as of the clinical cut-off date. The average daily dose was <100 mg for all subjects. Almost all subjects (20/21) received the maximum dose of eltrombopag (100 mg/day) as per protocol-specified dose escalation, except one subject who discontinued eltrombopag due to hepatic function abnormal.

Post-marketing exposure

Estimates of the cumulative subject exposure based upon actual exposure data from completed and ongoing clinical trials until 30-Sep-2017 was 4463 subjects. The post marketing exposure data based on daily dose of 12.5 mg, 25 mg, 50 mg or 75 mg tablets, brings the cumulative exposure to 106,493 patient years worldwide, from the first launch until June 2017.

Subjects disposition

Study AUS01T

At the data cut-off 30-Sept-2016, all cohorts had completed their enrolment, except the Extension Cohort. A total of 124 subjects were enrolled in the study and 123 received eltrombopag, one subject (Subject 11) was misdiagnosed at Baseline (had AML and not SAA), the subject received h-ATG (4 days) and CsA (2 weeks) but did not start eltrombopag. Of the 123 subjects, 108 subjects completed treatment with eltrombopag. Post-eltrombopag treatment follow-up is ongoing in more than half (61.3%) of the 108 subjects who completed treatment with eltrombopag.

Between 30-Sept-2016 and 28-Feb-2018 in the extension cohort, 30 additional subjects had received treatment with eltrombopag, of whom 5 subjects had not yet reached the month 6 landmark visit (or withdrew earlier). In the combined Cohort 3 + extension cohort, 64 subjects (69,6%) had completed the 6-month treatment with eltrombopag as per protocol. Primary reasons to end eltrombopag and percentage of subjects who ended are presented in table 37.

Table 47. Subject disposition in Study AUS01T (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016				28-Feb-2018			
	Cohort 1 N=31 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=62 n (%)	Cohort 1 N=31 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=92 n (%)
Subject enrolled								
Treated with eltrombopag	30 (96.8)	31 (100)	31 (100)	62 (100)	30 (96.8)	31 (100)	31 (100)	92 (100.0)
Not treated with eltrombopag	1 (3.2)[a]	0	0	0	1 (3.2)[a]	0	0	0
Subject treated with eltrombopag								
End of treatment with eltrombopag	30 (96.8)	31 (100)	31 (100)	47 (75.8)	30 (96.8)	31 (100)	31 (100)	87 (94.6)
Treatment with eltrombopag ongoing	0	0	0	15 (24.2)[b]	0	0	0	5 (5.4)[b]
Primary reason to end eltrombopag								
Completed per protocol	19 (61.3)	27 (87.1)	23 (74.2)	32 (51.6)	19 (61.3)	27 (87.1)	23 (74.2)	64 (69.6)
Platelet count > $400x10^3/\mu L$	3 (9.7)	1 (3.2)	4 (12.9)	5 (8.1)	3 (9.7)	1 (3.2)	4 (12.9)	6 (6.5)
Platelet count > $200x10^3/\mu L$	3 (9.7)	0	2 (6.5)	4 (6.5)	3 (9.7)	0	2 (6.5)	5 (5.4)
Adverse event	0	1 (3.2)	1 (3.2)	4 (6.5)	0	1 (3.2)	1 (3.2)	4 (4.3)
Clonal evolution	2 (6.5)	0	1 (3.2)	1 (1.6)	2 (6.5)	0	1 (3.2)	3 (3.3)
Investigator decision	1 (3.2)	0	0	0	1 (3.2)	0	0	3 (3.3)
Subject decision	1 (3.2)	1 (3.2)	0	1 (1.6)	1 (3.2)	1 (3.2)	0	2 (2.2)
Death	1 (3.2)	0	0	0	1 (3.2)	0	0	0
Protocol deviation	0	1 (3.2)	0	0	0	1 (3.2)	0	0
Subject status after end of eltrombopag treatment								
Post-eltrombopag follow-up ongoing[c]	16 (51.6)	23 (74.2)	26 (83.9)	37 (59.7)	7 (22.6)	20 (64.5)	20 (64.5)	58 (63.0)
Completion/ withdrawal from study	14 (45.2)	8 (25.8)	5 (16.1)	10 (16.1)	23 (74.2)	11 (35.5)	11 (35.5)	29 (31.5)

Study E1202

At the data cut-off date, 6 of 10 subjects (60%) were still receiving eltrombopag: 3 subjects had discontinued for lack of efficacy and one subject had reached protocol defined withdrawal criteria. Four subjects had discontinued study treatment by the Week 52 assessment: 2 had completed the follow-up assessment and had been withdrawn, the other 2 were undergoing the follow-up assessment at the data cut-off date, and their participation in the study was considered as ongoing. Therefore, a total of 8 (80%) subjects were ongoing as of the clinical data cut-off date for the Week 52 analysis.

Study E1201

Twenty one subjects were enrolled in the study: 16 (76.2%) completed Week 26 assessment, of which 10 (47.6%) entered the extension part of the study. Of these, 8 subjects (38.1%) were still receiving study treatment and 2 had discontinued due to lack of efficacy or withdrawal of consent after Week 26.

Adverse events

Safety assessments consisted of collecting AEs, SAEs, with their severity and relationship to study drug. Safety assessment included regular monitoring of haematology, blood chemistry and assessments of vital signs, physical condition, electrocardiogram (ECG).

For Study AUS01T, AE summaries included all AEs occurring during the on-treatment period and reported in the database. The following AE summaries were produced by cohort for AEs occurring during the on-

treatment period (defined as the time interval between the date of first administration of study treatment and up to 30 days after the date of last administration of study drug, excluding the maintenance treatment of CsA); overview of AEs, AEs by system organ class and preferred term, summarised by maximum common terminology criteria for adverse events grade, relationship to study drug (AEs with missing, unlikely, possible, probable or definite attribution to investigational product), seriousness (SAEs and non-SAEs), leading to treatment discontinuation (AEs with therapy discontinued), leading to any study treatment dose interruption/adjustment (AEs with action taken either dose reduced, therapy interruption or both) and leading to fatal outcome.

Furthermore, AEs occurring during the on-treatment period were summarised by cohort and subgroup defined by age overall (<18 years, 18-64 years, ≥65 years) and in paediatric subjects (2-5 years, 6-11 years, 12-17 years), gender and race.

Further AE summaries were provided for safety data collected during the first 13-days and during the first 3-months of treatment and presented for Cohorts 1 and 2 combined and Cohorts 3 and Extension combined.

Only AEs that occurred during the on treatment period (AEs that occur on or within the 30 days after last dose of eltrombopag treatment) were included in this SCS.

In view of the underlying illness, subjects entered the study with abnormally low blood counts considered as a grade 3 or more commonly grade 4 toxicity and required frequent platelet and/or red cell transfusions. Thus grade 3-4 hematologic laboratory values including thrombocytopenia, platelet-transfusion dependence, anemia, red cell transfusion dependence, neutropenia, lymphopenia, or leukopenia, were not recorded as AEs for this study. The hematologic laboratory values were collected in the subject's source documents, but these abnormalities were not reported or recorded as AEs.

In addition, the non-hematologic AEs were captured as described below:

CsA, h-ATG, and eltrombopag are approved drugs with known toxicity profiles; any observed or volunteered AEs already listed on the package insert were not reported in the database or to the IRB unless the AE was:

- previously unknown (not listed in the prescribing information)
- more severe than on package insert
- met the criteria of an SAE.

Cohorts 1 and 2: during first week of h-ATG administration, only events that resulted in clinical action (i.e. dose reduction/discontinuation, prolongation of hospitalisation, etc.) were recorded in database.

Cohorts 3 and Extension: from start of h-ATG to 14 days post-treatment:

Grade 3 and 4 AEs that result in clinical action (i.e. dose reduction/discontinuation, prolongation of hospitalization, etc.) and AEs not attributed to h-ATG were recorded in database.

Grade 3 and 4 LFTs were recorded in the medical records. Grade 3 and 4 LFTs that persisted at grade 3 or 4 for greater than 5 days were recorded in the database and reported as AEs.

Grade 1 events listed as expected in the protocol, consent forms, or other applicable protocol documentation were captured in the medical records but not reported as AE in the database.

An Overview of the AEs and deaths in Study AUS01T is presented in table 48. In the combined Cohort 3 + Extension Cohort (cut-off 28-Feb-2018), the incidences of AEs related to eltrombopag, of grades 3/4 AEs, and of SAEs increased by approximately 10%, compared to the incidences observed at the original cutoff (from 61.3% to 70.7%) (Table 48-2). This increase can be explained by a higher number of

subjects exposed to the full 6-month of eltrombopag at the update cutoff. 5.4% (5/92) subjects were on-treatment at this update cutoff, while 24.2% (15/62) subjects were still on-treatment with eltrombopag at the original cut-off and so had not yet reached the Month 6 assessment. No increase in AEs leading to treatment discontinuation was observed. 4 additional deaths were recorded at the update cut-off, all occurred during the follow-up, and none was related to the study treatment.

Table 48. Overview of the AEs and deaths in Study AUS01T (cut-off 30-Sept-2016)

	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 N=31		Cohort 3 + Extension N=62	
	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)
All AEs	19 (63.3)	16 (53.3)	21 (67.7)	18 (58.1)	25 (80.6)	21 (67.7)	47 (75.8)	39 (62.9)
Related to eltrombopag	13 (43.3)	9 (30.0)	13 (41.9)	11 (35.5)	22 (71.0)	18 (58.1)	38 (61.3)	32 (51.6)
SAEs	13 (43.3)	12 (40.0)	12 (38.7)	12 (38.7)	13 (41.9)	11 (35.5)	26 (41.9)	22 (35.5)
Related to eltrombopag	6 (20.0)	6 (20.0)	8 (25.8)	8 (25.8)	7 (22.6)	5 (16.1)	13 (21.0)	10 (16.1)
AEs leading to treatment discontinuation	1 (3.3)	1 (3.3)	1 (3.2)	1 (3.2)	1 (3.2)	0	4 (6.5)	3 (4.8)
AEs requiring dose interruption/ adjustment	1 (3.3)	1 (3.3)	1 (3.2)	1 (3.2)	9 (29.0)	9 (29.0)	15 (24.2)	15 (24.2)
All deaths	3 (10.0)	-	0	-	0	-	0	-
On-treatment deaths	1 (3.3)	-	0	-	0	-	0	-

All deaths include those occurring at any time after first dose of study drug. On-treatment deaths include those occurring on or within 30 days after last dose of study treatment (excluding maintenance treatment). Per CTCAE definition, death is a grade 5 event.

Table 48-2. Overview of the AEs in Study AUS01T (cut-off 28-Feb-2018)

Cutoff date	30-Sep-2016*		28-Feb-2018	
	Cohort 3 + Extension N=62 n (%)		Cohort 3 + Extension N=92 n (%)	
	All grades	Grade 3/4/5	All grades	Grade 3/4/5
All AEs	**47 (75.8)**	**39 (62.9)**	**72 (78.3)**	**59 (64.1)**
AEs related to eltrombopag	38 (61.3)	32 (51.6)	65 (70.7)	54 (58.7)
SAEs	26 (41.9)	22 (35.5)	46 (50.0)	40 (43.5)
SAEs related to eltrombopag	13 (21.0)	10 (16.1)	31 (33.7)	25 (27.2)
AEs leading to treatment discontinuation	4 (6.5)	3 (4.8)	4 (4.3)	3 (3.3)
AEs requiring dose interruption or adjustment	15 (24.2)	15 (24.2)	28 (30.4)	27 (29.3)

* Result in Cohort 3 + Extension as of 30-Sep-2016 cutoff were not revised following the queries described in Section 2.5.2.

An Overview of the AEs and deaths in Studies E1202 and E1201 are presented in table 49 and 50.

Table 49. AEs and deaths in Study E1202

	Eltrombopag+ATG/CsA N=10 n (%)
Number of subjects with an adverse event	10 (100)
Number of subjects with an adverse event related to any study treatment	8 (80.0)
Number of subjects with an adverse event related to eltrombopag	5 (50.0)
Number of subjects with an adverse event related to CsA	8 (80.0)
Number of subjects with an adverse event leading to withdrawal from eltrombopag	1 (10.0)
Number of subjects with an adverse event leading to dose reduction or dose interruption of eltrombopag	3 (30.0)
Number of subjects with a serious adverse event	2 (20.0)
Number of subjects with a fatal adverse event	0

AEs occurring from the day of the first administration of ATG until 30 days after the last administration of eltrombopag were reported.

Table 50. AEs and deaths in Study E1201

	Eltrombopag N=21 n (%)
Number of subjects with an adverse event	21 (100)
Number of subjects with a serious adverse event	4 (19.0)
Number of subjects with a fatal adverse event	0
Number of subjects with a drug-related adverse event	12 (57.1)
Number of subjects with an adverse event leading to withdrawal from study drug	1 (4.8)
Number of subjects with an adverse event leading to dose reduction or dose interruption of study drug on treatment	5 (23.8)
Number of subjects with a serious adverse event leading to withdrawal from study drug	0

AEs occurring from the day of the first administration of ATG until 30 days after the last administration of eltrombopag were reported.

Common adverse events in Study AUS01T

System Organ Class

Most frequently occurring (at least ≥ 20% in a Cohort 1, Cohort 2 or combined Cohort 3 + Extension Cohort) AEs by system organ classes (SOCs) were during cut-off 30-Sept-2016:

- Gastrointestinal disorders: 20%, 6.5% and 14.5% in Cohort 1, Cohort 2 and in combined Cohort 3 + Extension Cohort, respectively
- Infections and infestations: 30.0%, 32.3% and 29.0% in Cohort 1, Cohort 2 and in combined Cohort 3 + Extension Cohort, respectively
- Investigations: 20.0%, 25.8% and 37.1% in Cohort 1, Cohort 2 and in combined Cohort 3 + Extension Cohort, respectively

In the combined Cohort 3 + Extension Cohort during cut-off 28-Feb-2018, changes in the frequencies of AEs were observed in some SOCs as compared to the original cut-off (such as an increased by 9.0% in infections) (Table 51). However, the AEs which were reported did not suggest a change in the safety profile.

Table 51. AEs by primary SOC- Safety set (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016*	28-Feb-2018
	Cohort 3 + Extension N=62 n (%)	Cohort 3 + Extension N=92 n (%)
All AEs	**47 (75.8)**	**72 (78.3)**
Investigations	23 (37.1)	38 (41.3)
Infections and infestations	18 (29.0)	35 (38.0)
Gastrointestinal disorders	9 (14.5)	18 (19.6)
Skin and subcutaneous tissue disorders	11 (17.7)	16 (17.4)
Blood and lymphatic system disorders	10 (16.1)	15 (16.3)
Immune system disorders	6 (9.7)	9 (9.8)
Respiratory, thoracic and mediastinal disorders	4 (6.5)	8 (8.7)
Nervous system disorders	2 (3.2)	7 (7.6)
Vascular disorders	3 (4.8)	7 (7.6)
Eye disorders	4 (6.5)	6 (6.5)
Metabolism and nutrition disorders	4 (6.5)	5 (5.4)
Injury, poisoning and procedural complications	3 (4.8)	5 (5.4)
Hepatobiliary disorders	4 (6.5)[a]	3 (3.3)
Renal and urinary disorders	2 (3.2)	3 (3.3)
Reproductive system and breast disorders	2 (3.2)	3 (3.3)
Cardiac disorders	0	2 (2.2)
Ear and labyrinth disorders	2 (3.2)	2 (2.2)
Psychiatric disorders	1 (1.6)	2 (2.2)
General disorders and administration site conditions	0	1 (1.1)
Musculoskeletal and connective tissue disorders	1 (1.6)	1 (1.1)
Surgical and medical procedures	1 (1.6)	1 (1.1)

* Result in Cohort 3 + Extension as of 30-Sep-2016 cutoff were not revised following the queries described in Section 2.5.2.
a. At the original analysis, an event ocular icterus was recorded in Subject AUS01T-065 in the SOC "hepatobiliary disorders", but has since been revised to the SOC "eye disorder".
Primary system organ classes are sorted by descending frequency in "Cohort 3 + Extension - 28-Feb-2018".

Preferred terms

The AEs observed were consistent with the known safety profile of eltrombopag and/or h-ATG and CsA in the SAA setting. Serum sickness was reported during the first 13 days, and was considered as "unlikely" related to or "unrelated" to eltrombopag by the principal investigator.

AEs were generally manageable and reversible with dose adjustment and/or dose interruption (cut-off 30-Sept-2016). AEs with a frequency exceeding 5% in any cohort are presented in table 52. Overall, 87 (71%) subjects had at least 1 AE. ALT/AST increased, febrile neutropenia and blood bilirubin increased were the most common AEs reported by preferred term. The higher incidence of AEs of transaminases increased in combined Cohort 3 + Extension Cohort relative to Cohort 1 and Cohort 2, must be interpreted with caution and might be attributed to the differences in how increased LFT were reported as AEs between the cohorts. All liver safety events such as ALT, AST, total bilirubin and ALP labs of any grade were source document verified and should be used primarily when assessing hepatotoxicity.

Table 52. AE irrespective of relationship to treatment occurring commonly (by 5% or more) by preferred term and highest grade (Study AUS01T) (cut-off 30-Sept-2016).

	Cohort 1 N=30		Cohort 2 N=31		Cohort 3 + Extension N=62	
	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)
All AEs	**19 (63.3)**	**16 (53.3)**	**21 (67.7)**	**18 (58.1)**	**47 (75.8)**	**39 (62.9)**
Liver function adverse events						
ALT increased	1 (3.3)	1 (3.3)	4 (12.9)	4 (12.9)	17 (27.4)	17 (27.4)
AST increased	0	0	1 (3.2)	1 (3.2)	12 (19.4)	12 (19.4)
Blood bilirubin increased	5 (16.7)	5 (16.7)	5 (16.1)	5 (16.1)	9 (14.5)	9 (14.5)
Non-liver function adverse events						
Febrile neutropenia	2 (6.7)	2 (6.7)	5 (16.1)	5 (16.1)	10 (16.1)	10 (16.1)
Serum sickness	0	0	2 (6.5)	2 (6.5)	6 (9.7)	5 (8.1)
Infusion related reaction	0	0	0	0	3 (4.8)	1 (1.6)
Lung infection	2 (6.7)	2 (6.7)	1 (3.2)	1 (3.2)	3 (4.8)	3 (4.8)
Skin hyperpigmentation	0	0	0	0	3 (4.8)	0
Abdominal pain	2 (6.7)	1 (3.3)	1 (3.2)	1 (3.2)	2 (3.2)	2 (3.2)
Device related infection	0	0	2 (6.5)	2 (6.5)	2 (3.2)	2 (3.2)
Hypokalaemia	0	0	0	0	2 (3.2)	2 (3.2)
Stomatitis	2 (6.7)	0	0	0	1 (1.6)	0
Depression	2 (6.7)	1 (3.3)	0	0	0	0
Gastrooesophageal reflux disease	2 (6.7)	0	1 (3.2)	0	0	0
Oedema peripheral	2 (6.7)	0	1 (3.2)	1 (3.2)	0	0
Urinary tract infection	1 (3.3)	0	2 (6.5)	1 (3.2)	0	0

AEs include on-treatment assessments collected no later than 30 days after last dose of study drug (eltrombopag). Preferred terms are sorted in descending frequency in "Cohort 3 + Extension".

The AEs reported in the combined Cohort 3 + Extension Cohort during cut-off 28-Feb-2018 were similar to what was observed at the original cut-off (with 5% or less difference), with the exception of upper respiratory tract infection (7.6% at update cut-off vs. 1.6% at original cut-off). Additionally, there was a small increase (< 5%) in hypertension (5.4% at the update cut-off vs. 1.6% at the original cut-off). The increase in upper respiratory tract infection was not considered as clinically relevant as none of these events required hospitalisation and, hypertension is a known effect of CsA.

The rules for reporting grade 3 and 4 liver function test (LFT) laboratory abnormalities as AEs were inconsistently applied at the NIH throughout the study. For this reason queries were issued to the investigator for all grade 3 and 4 liver function abnormalities from the beginning of the study to see if they should have been reported as an AE and presented in comparison with what was reported at the original submission (Table 53). This led to an increase (≥10%) in Cohorts 1 and 2 in reported liver AEs. This increase of liver AEs in these cohorts is a consequence of the query process. In the combined Cohort 3 + Extension Cohort, the incidences of hepatobiliary events at the update cut-off were similar to what was observed at original cut-off.

Table 53. Incidence of hepatobiliary events by preferred term-original AEs and revised AEs at original cut-off and events at update cut-off-Safety set.

Cutoff date	30-Sep-2016 original[a]				30-Sep-2016 revised[a]				28-Feb-2018
	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=62 n (%)	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=62 n (%)	Cohort 3 + Extension N=92 n (%)
All events	**5 (16.7)**	**7 (22.6)**	**14 (45.2)**	**25 (40.3)**	**11 (36.7)**	**12 (38.7)**	**15 (48.4)**	**27 (43.5)**	**38 (41.3)**
ALT increased	1 (3.3)	4 (12.9)	11 (35.5)	17 (27.4)	3 (10.0)	8 (25.8)	11 (35.5)	19 (30.6)	27 (29.3)
AST increased	0	1 (3.2)	7 (22.6)	12 (19.4)	2 (6.7)	3 (9.7)	7 (22.6)	12 (19.4)	16 (17.4)
Blood bilirubin increased	5 (16.7)	5 (16.1)	4 (12.9)	9 (14.5)	11 (36.7)	8 (25.8)	6 (19.4)	11 (17.7)	16 (17.4)
Ascites	0	0	0	0	0	0	0	0	1 (1.1)
Blood ALP increased	0	0	0	1 (1.6)	0	0	0	1 (1.6)	1 (1.1)
Cholestasis	0	0	0	1 (1.6)	0	0	0	1 (1.6)	1 (1.1)
Liver injury	0	0	0	1 (1.6)	0	0	0	1 (1.6)	1 (1.1)
Ocular icterus[b]	0	0	1 (3.2)	1 (1.6)	0	0	0	0	0

a. cutoff date30-Sep-2016 original are data as reported at the original cutoff 30-Sep-2016 revised are data at original cutoff as reported following the revision by the Investigator for AEs of LFT laboratory abnormalities, as described in Section 2.5.2.
b. The event ocular icterus was recorded in Subject AUS01T-065 in the SOC hepatobiliary disorders at the original analysis, but has since been revised to the SOC eye disorder.
Preferred terms are sorted in descending frequency in "Cohort 3 + Extension - 28-Feb-2018".

AEs occurring during the first 13 days and during the first 3 months

Cohort 1 and 2 had a staggered start of eltrombopag on Day 14 while Cohort 3 and Extension Cohort began all 3 drugs concurrently. Therefore, the evaluation of toxicity was done by comparing the AE and laboratory parameters between Day 1 and Day 13 between these 2 groups (Cohort 1 and Cohort 2 (double therapy: h-ATG + CsA), relative to Cohort 3 and Extension Cohort (triple therapy h-ATG + CsA + eltrombopag)), for a comparison of the toxicity when eltrombopag is given concurrently with h-ATG/CsA *vs.* the staggered initiation.

Furthermore, data collected during the first 3 months were analysed in order to consider whether the concurrent initiation of treatment would be lead to a different safety profile beyond the initial 13 days. This analysis was driven by the anticipation that the concurrent initiation of eltrombopag together with h-ATG/CsA might lead to intolerable hepatotoxicity as each of the 3 drugs has a known potential for hepatotoxicity. The known differences in the reporting of grade 3 and 4 LFTs as AEs make them unreliable for assessment and therefore the lab parameters should be primarily used for assessment of hepatotoxicity.

During both time points (first 13 days and the first 3 months) and after first cut-off period (30-Sept-2016), the incidences of AEs were typically similar in the 2 groups (< 5% differences), with the exception of AST and ALT increased and serum sickness. All AEs of serum sickness (in all cohorts) began within 13 days of start of treatment, were reported as unlikely or unrelated to eltrombopag and resolved within one week. Of note, neither the AEs, AST and ALT increased nor the AEs serum sickness led to study discontinuation. There is no pharmacological rationale how eltrombopag can induce serum sickness and this event has not been seen as a safety issue in earlier studies with eltrombopag (there was no AE of serum sickness reported in Study AUS28T refractory SAA subjects who received eltrombopag alone). When comparing the number of increased liver laboratory parameters (AST/ALT/ and TBIL) in the first 13 days after the first cut-off period (30-Sept-2016), they were consistent between the two groups with AST/ALT > 3xULN and TBIL > 2ULN for Day 1-13 in Cohort 1 and 2 observed in 9 subjects (14.8%) and in Cohort 3 + Extension observed in 3 subjects (4.8%). Furthermore, when looking at the liver function laboratory test up to 3 months, there were a limited number of subjects who had an increase of the liver function tests after Day 13 with AST/ALT > 3xULN and TBIL > 2ULN in Cohort 1 and 2 observed in 14 subjects (23.0%) and in Cohort 3 + Extension observed in 7 subjects (11.3%) (Table 54 and 55).

Table 54. Number of subjects with elevation of liver chemistry tests collected within the first 13 days by cohort (safety set) (cut-off 30-Sept-2016).

	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension Cohort N=62 n (%)
ALT or AST >3xULN	32 (52.5)	32 (51.6)
ALT or AST >5xULN	24 (39.3)	19 (30.6)
ALT or AST >8xULN	12 (19.7)	8 (12.9)
ALT or AST >20xULN	5 (8.2)	3 (4.8)
TBIL >2xULN	14 (23.0)	8 (12.9)
TBIL >2xULN with DBIL/TBIL ≥35%	8 (13.1)	2 (3.2)
ALT or AST >3xULN and TBIL >1.5xULN	23 (37.7)	15 (24.2)
ALT or AST >3xULN and TBIL >1.5xULN with DBIL/TBIL ≥ 35%	14 (23.0)	10 (16.1)
ALT or AST >3xULN and TBIL >2xULN	9 (14.8)	3 (4.8)
ALT or AST >3xULN and TBIL >2xULN with DBIL/TBIL ≥ 35%	6 (9.8)	1 (1.6)
ALT or AST >3xULN and TBIL >2xULN and ALP <2xULN or missing	8 (13.1)	3 (4.8)

Categories are based on worst post-baseline value for any specific parameter.
Categories with multiple parameters are based on worst post-baseline value for each parameter.
Worst post-baseline value refers to maximum post-baseline value except for ALP for which it refers to the minimum post-baseline value.
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, TBIL = total bilirubin, DBIL = direct bilirubin

Table 55. Number of subjects with elevation of liver chemistry tests collected within the first 3 months cohort (safety set) (cut-off 30-Sept-2016).

	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension Cohort N=62 n (%)
ALT or AST >3xULN	34 (55.7)	35 (56.5)
ALT or AST >5xULN	27 (44.3)	21 (33.9)
ALT or AST >8xULN	14 (23.0)	11 (17.7)
ALT or AST >20xULN	5 (8.2)	4 (6.5)
TBIL >2xULN	24 (39.3)	17 (27.4)
TBIL >2xULN with DBIL/TBIL ≥35%	11 (18.0)	5 (8.1)
ALT or AST >3xULN and TBIL >1.5xULN	25 (41.0)	19 (30.6)
ALT or AST >3xULN and TBIL >1.5xULN with DBIL/TBIL ≥ 35%	13 (21.3)	10 (16.1)
ALT or AST >3xULN and TBIL >2xULN	14 (23.0)	7 (11.3)
ALT or AST >3xULN and TBIL >2xULN with DBIL/TBIL ≥ 35%	9 (14.8)	3 (4.8)
ALT or AST >3xULN and TBIL >2xULN and ALP <2xULN or missing	9 (14.8)	4 (6.5)

Categories are based on worst post-baseline value for any specific parameter.
Categories with multiple parameters are based on worst post-baseline value for each parameter.
Worst post-baseline value refers to maximum post-baseline value except for ALP for which it refers to the minimum post-baseline value.
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, TBIL = total bilirubin, DBIL = direct bilirubin

As observed at the original cut-off, during the first 13 days after cut-off 28-Feb-2018, the incidences of adverse events were usually similar in the two groups (<5% differences), with the exception of AEs elevated AST/ALT and serum sickness. Both were manageable and none led to discontinuation.

Considering the updated data after cut-off period 28-Feb-2018, the incidences of AEs of elevated ALT/AST, including AEs that required dose interruption/adjustment, were higher in the combined Cohort 3 + Extension Cohort than in combined Cohorts 1 + 2 (table 56, 57 and 58).

Table 56. AEs occurring during the first 13 days in all subjects in Cohort 1+2 or in Cohort 3 + extension-Safety set (cut-off 28-Feb-2018).

Cutoff date	28-Feb-2018	
	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension N=92 n (%)
All AEs	**20 (32.8)**	**49 (53.3)**
ALT increased	5 (8.2)	23 (25.0)
AST increased	2 (3.3)	14 (15.2)
Serum sickness[a]	2 (3.3)	8 (8.7)
Blood bilirubin increased	2 (3.3)	5 (5.4)
Febrile neutropenia	2 (3.3)	4 (4.3)
Hypertension	0	4 (4.3)
Headache	0	2 (2.2)
Retinal vascular disorder	0	2 (2.2)
Abdominal pain	2 (3.3)	1 (1.1)
Gastrooesophageal reflux disease	2 (3.3)	1 (1.1)

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension ".
a. all AEs of serum sickness were reported as unlikely related or not related to eltrombopag.

Table 57. SAE occurring during the first 13 days in Cohort 1+2 or in Cohort 3 + extension-Safety set (cut-off 28-Feb-2018).

Cutoff date	28-Feb-2018	
	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension N=92 n (%)
All SAEs	**7 (11.5)**	**17 (18.5)**
Serum sickness[a]	2 (3.3)	8 (8.7)
Retinal vascular disorder	0	2 (2.2)
Atrial fibrillation	0	1 (1.1)
Colitis	0	1 (1.1)
Headache	0	1 (1.1)
Hypertension	0	1 (1.1)
Lung infection	0	1 (1.1)
Meningeal disorder	0	1 (1.1)
Papilloedema	0	1 (1.1)
Pharyngitis	0	1 (1.1)
Pulmonary oedema	1 (1.6)	1 (1.1)
Sinusitis	0	1 (1.1)
Uveitis	0	1 (1.1)
Cardiac failure	1 (1.6)	0
Febrile neutropenia	2 (3.3)	0
Myocardial infarction	1 (1.6)	0
Nephrolithiasis	1 (1.6)	0
Small intestinal haemorrhage	1 (1.6)	0

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension - 28-Feb-2018".
a. All AEs of serum sickness were reported as unlikely related or not related to eltrombopag.

Table 58. AEs that requires dose interruption/adjustment occurring the first 13 days in Cohort 1+2 or in Cohort 3 +extension- Safety set (cut-off 28-Feb-2018).

Cutoff date	28-Feb-2018	
	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension N=92 n (%)
All AEs	**0**	**18 (19.6)**
ALT increased	0	16 (17.4)
AST increased	0	11 (12.0)
Ascites	0	1 (1.1)
Blood bilirubin increased	0	1 (1.1)
Pulmonary oedema	0	1 (1.1)

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension"

No subjects discontinued due these events when all 3 drugs were administered concurrently as in Cohort 3 + Extension or when eltrombopag was staggered as in Cohorts 1 and 2. Note that the rules for reporting ALT/AST grade 3 and 4 LFTs laboratory abnormalities reported as AEs differed between cohorts, however LFTs laboratory data of grade 3 and 4 ALT and AST collected during this period were similar (< 5% differences) between the 2 groups, or lower in the group Cohort 3 + Extension Cohort when compared to the group Cohorts 1 + 2.

Overall, the analysis of liver related AEs in conjunction with the LFTs laboratory abnormalities captured during the first 13 days of study treatment showed that the concomitant dosing of eltrombopag with IST (h-ATG + CsA) did not lead to an increase in hepatic toxicity when compared with dosing with IST alone.

The analysis of AEs, SAEs and AEs that required dose interruption/adjustment during the first 3 months and after the cut-off 28-Feb-2018 are presented in table 59, 60 and 61.

As seen during the first 13 days of study therapy, the analysis at 3 months showed higher incidences of AEs of elevated ALT/AST, including AEs that required dose interruption/adjustment, in Cohort 3 + Extension Cohort relative to Cohorts 1+2. No subjects discontinued due to these events (in any cohorts). No subjects discontinued due to these events when all 3 drugs were administered concurrently as in Cohort 3 + Extension or when eltrombopag was staggered as in Cohorts 1 and 2. Note that the rules for reporting ALT/AST grade 3 and 4 LFTs laboratory abnormalities reported as AEs differed between cohorts, however LFTs laboratory data of grade 3 and 4 ALT and AST collected during this period were similar (< 5% differences) between the 2 groups, or lower in the group Cohort 3 + Extension Cohort when compared to the group Cohorts 1 + 2.

Table 59. AEs occurring during the first 3 months in at least 3subjects in Cohort 1+2 or in Cohort 3 + extension-Safety set cut-off 28-Feb-2018

Cutoff date	28-Feb-2018	
	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension N=92 n (%)
All AEs	**39 (63.9)**	**66 (71.7)**
ALT increased	10 (16.4)	26 (28.3)
AST increased	4 (6.6)	16 (17.4)
Blood bilirubin increased	15 (24.6)	14 (15.2)
Febrile neutropenia	7 (11.5)	13 (14.1)
Serum sickness[a]	2 (3.3)	8 (8.7)
Hypertension	0	4 (4.3)
Lung infection	2 (3.3)	4 (4.3)
Upper respiratory tract infection	1 (1.6)	4 (4.3)
Abdominal pain	3 (4.9)	3 (3.3)
Bacteraemia	0	3 (3.3)
Pharyngitis	1 (1.6)	3 (3.3)
Rash	0	3 (3.3)
Rash maculopapular	1 (1.6)	3 (3.3)
Skin hyperpigmentation	0	3 (3.3)
Gastroesophagal reflux disease	3 (4.9)	1 (1.1)
Urinary tract infection	3 (4.9)	1 (1.1)

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension".
a: All AEs of serum sickness were reported as unlikely related or not related to eltrombopag.

Table 60. SAE occurring during the first 3 months in Cohort 1+2 or in Cohort 3 + extension- Safety set (cut-off 28-Feb-2018).

Cutoff date	28-Feb-2018	
	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension N=92 n (%)
All SAEs	**21 (34.4)**	**38 (41.3)**
Serum sickness[a]	2 (3.3)	8 (8.7)
Febrile neutropenia	7 (11.5)	7 (7.6)
Bacteraemia	0	3 (3.3)
Lung infection	1 (1.6)	3 (3.3)
Pharyngitis	0	3 (3.3)
Rash maculo-papular	1 (1.6)	3 (3.3)
Upper respiratory tract infection	1 (1.6)	3 (3.3)
Abdominal pain	0	2 (2.2)
Enterocolitis infectious	0	2 (2.2)
Hypertension	0	2 (2.2)
Retinal vascular disorder	0	2 (2.2)
Sinusitis	1 (1.6)	2 (2.2)
Headache	2 (3.3)	1 (1.1)
Device related infection	2 (3.3)	0

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension".
a: All events of serum sickness were reported as unlikely related or not related to eltrombopag.

Table 61. AEs that requires dose interruption/adjustment occurring the first 3 months in Cohort 1+2 or in Cohort 3 +extension- Safety set (cut-off 28-Feb-2018).

Cutoff date	28-Feb-2018	
	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension N=92 n (%)
All AEs	**3 (4.9)**	**24 (26.1)**
ALT increased	2 (3.3)	17 (18.5)
AST increased	0	13 (14.1)
Blood bilirubin increased	0	2 (2.2)

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension".

Adverse events suspected to be drug related by the Investigator

All AEs reported as "unlikely", "possible" and "probably" related or with missing relationship to study drug are considered suspected to be study drug related. The 5 "suspected" cases of serum sickness were all reported as "unlikely" related to eltrombopag (including the case reported in Cohort 2 which occurred before the start of eltrombopag).

Table 62. Frequent AEs (at least 2 subjects in any cohort) with suspected relationship to study drug by preferred term-Safety set (cut-off 30-Sept-2016).

	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=62 n (%)
All	**13 (43.3)**	**13 (41.9)**	**22 (71.0)**	**38 (61.3)**
ALT increased	0	1 (3.2)	11 (35.5)	16 (25.8)
AST increased	0	0	7 (22.6)	12 (19.4)
Blood bilirubin increased	4 (13.3)	2 (6.5)	4 (12.9)	8 (12.9)
Serum sickness[a]	0	1 (3.2)	3 (9.7)	4 (6.5)
Febrile neutropenia	0	5 (16.1)	2 (6.5)	3 (4.8)
Skin hyperpigmentation	0	0	2 (6.5)	3 (4.8)
Hypokalaemia	0	0	2 (6.5)	2 (3.2)
Skin infection	0	0	1 (3.2)	2 (3.2)
Stomatitis	2 (6.7)	0	1 (3.2)	1 (1.16)
Gastrooesophageal reflux disease	2 (6.7)	1 (3.2)	0	0
Oedema peripheral	2 (6.7)	0	0	0

a The 5 cases of serum sickness were all reported as "unlikely" related to eltrombopag

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension".

On retrospective review of the data, the rules to translate LFT labs to AEs appeared inconsistently applied, see Section 9.5.3.1. The LFTs from laboratory recording were source document verified. For consistent reporting of grade 3-4 liver toxicity lab results are preferred, see Section 12.4.2.

In the combined Cohort 3 + Extension Cohort, the individual AEs suspected to be study drug (eltrombopag) related were similar to what was observed at the original cut-off (≤ 5% difference) (table 62-2).

The AEs of increased ALT and AST in combined Cohort 3 + Extension Cohort did not result in discontinuation. When looking at the LFT laboratory abnormalities, there was no increase in grade 3 and 4 ALT/AST in combined Cohort 3 + Extension Cohort relative to other cohorts. Although AEs of lung infection and bacteraemia are reported as suspected to be related to study drug, they are likely related to the underlying disease.

Table 62-2. AEs with suspected relationship to study drug occurring in at least 3 subjects-Safety set (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016* Cohort 3 + Extension N=62 n (%)	28-Feb-2018 Cohort 3 + Extension N=92 n (%)
All AEs	**38 (61.3)**	**65 (70.7)**
ALT increased	16 (25.8)	26 (28.3)
AST increased	12 (19.4)	16 (17.4)
Blood bilirubin increased	8 (12.9)	15 (16.3)
Febrile neutropenia	3 (4.8)	6 (6.5)
Serum sickness[a]	4 (6.5)	6 (6.5)
Upper respiratory tract infection	0	5 (5.4)[b]
Lung infection	1 (1.6)	4 (4.3)
Rash	1 (1.6)	4 (4.3)
Bacteraemia	0	3 (3.3)

Cutoff date	30-Sep-2016*	28-Feb-2018
	Cohort 3 + Extension N=62 n (%)	Cohort 3 + Extension N=92 n (%)
Nausea	1 (1.6)	3 (3.3)
Rash maculo-papular	3 (4.8)	3 (3.3)
Skin hyperpigmentation	3 (4.8)	3 (3.3)
Tonsillitis	0	3 (3.3)

* Result in Cohort 3 + Extension as of 30-Sep-2016 cutoff were not revised following the queries described in Section 2.5.2.
a. The cases of serum sickness were all reported as unlikely related or not related to eltrombopag.
b. None of the cases of upper respiratory tract infection required hospitalization.
Preferred terms are sorted in descending frequency in "Cohort 3 + Extension - 28-Feb-2018".

Analysis of adverse events by severity

The majority (>50%) of AEs were ≥grade 3 across all cohorts: 53.3% in Cohort 1, 58.1% in Cohort 2, 67.7% in Cohort 3 and 62.9% in combined Cohort 3 + Extension Cohort. Persistent high grades AEs for increased ALT and AST occurred with an incidence of ALT and AST increased in 35.5% and 22.6% of the subjects in Cohort 3, and in 27.4% and 19.4% of the subjects in combined Cohort 3 + Extension Cohort.

Common adverse events in Study E1202

Preferred terms

The most common (in ≥3 subjects) AEs on treatment were nausea (6 subjects, 60.0%), headache (5 subjects, 50.0%), constipation, edema, pyrexia, renal impairment and vomiting (4 subjects each, 40.0%), ALT increased, blood bilirubin increased, hyperglycemia, hypertension, myalgia, and stomatitis (3 subjects each; 30.0%).

Adverse events suspected to be drug related by the Investigator

Of the 10 subjects treated with eltrombopag, 5 (50.0%) had 17 AEs related to eltrombopag (regardless of their relationship with r-ATG or CsA). Of the 17 AEs, 15 related to eltrombopag were reported by the Week 26 assessment, and an additional 2 AEs (impetigo and nausea) by the Week 52 assessment. The most common AEs related to eltrombopag (≥2 subjects) were myalgia (3 subjects), blood bilirubin increased and nausea (2 subjects each).

Analysis of adverse events by severity

The majority of AEs (80%; in 8 subjects) reported on treatment were grade 3 or grade 4. All grade 3 or 4 AEs occurred in single subject. Grade 3 AEs were reported in 8 subjects (80%) and grade 4 AEs were reported in 2 subjects (20%). No fatal AEs were reported.

Common adverse events in Study E1201

Preferred terms

The most common AEs (≥ 3 subjects) on treatment were nasopharyngitis (8 subjects, 38.1%), hepatic function abnormal and urticaria (3 subjects each, 14.3%).

Adverse events suspected to be drug related by the Investigator

Of the 21 subjects treated with eltrombopag, 12 (57.1%) had at least one drug related AE on treatment. The majority of AEs considered related to eltrombopag were hepatobiliary disorders (hepatic function abnormal, hyperbilirubinemia, and blood alkaline phosphatase increased in 2 subjects each; ALT increased and blood bilirubin increased in one subject each) and skin and subcutaneous tissue disorders (rash in 2 subjects, purpura and urticaria in one subject each).

Analysis of adverse events by severity

The majority (61.9%) of AEs reported on treatment were grade 1 to grade 2. Seven subjects (33.3%) had grade 3 AEs and one subject had a grade 4 AE (4.8%) on treatment. No subject had a fatal AE.

Deaths

Deaths in study AUS01T

Up to the update cut-off, 7 deaths have been reported and none was considered related to study treatment by the investigator. All subjects died during the follow-up except Subject-23 who died while on-treatment.

Three subjects died as of the data cut-off date (30-Sept-2016), all in Cohort 1:

- Subject 23, aged 55 years, died on Day 85 while on-treatment with eltrombopag and CsA, from paraneoplastic encephalopathy that was attributed to thymoma that predated study entry.
- Subject 15, aged 37 years, died during the follow-up due to hematopoietic stem cell transplantation (HSCT)-related cause, approximately 1 year after the end of therapy.
- Subject 9, aged 66 years, died during the follow-up due to HSCT-related cause, approximately 2 years after the end of therapy.

None of the deaths were reported by the Investigator as related to the study treatment.

At the update cut-off (28-Feb-2018), 4 additional subjects had died:

- Subject 42 in Cohort 2 aged 29 years died on Day 971, during the follow-up 881 days after last dose of eltrombopag, due to infection (study site communication: septic shock).
- Subject 80 in Cohort 3 aged 72 years died on Day 864, during the follow-up 676 days after last dose of eltrombopag, of unknown cause.
- Subject 111 in Extension Cohort aged 65 years died on Day 419, during the follow-up 225 days after last dose of eltrombopag, due to infection (study site communication: septic shock).
- Subject 113 in Extension Cohort aged 65 years died on Day 121, during the follow-up 109 days after last dose of eltrombopag, due to infection (study site communication: pneumonia).

Deaths in studies E2102 and E2101

No subjects died during the studies.

Other serious adverse events

Study AUS01T

After original cut-off (30-Sept-2016) all SAEs are considered known effects of eltrombopag, of one of the medications used in IST or due to underlying disease. No trends were observed in the type of SAEs reported. The only SAEs observed in more than 2 subjects per cohorts were febrile neutropenia and serum sickness; five of the serum sickness SAEs were reported as unlikely to be related to eltrombopag, and 3 were reported as unrelated to eltrombopag.

In combined Cohort 3 + Extension Cohort, 26 (41%) had at least 1 SAE. The SAEs observed in more than 2 subjects were serum sickness (6 subjects, 9.7%), febrile neutropenia (5 subjects, 8.1%) and rash (3 subjects, 4.8%).

In the combined Cohort 3 + Extension Cohort (cut-off 28-Feb-2018), the SAEs reported were similar to what was observed at the original cut-off (Table 63).

Table 63. SAEs occurring in at least 2 subjects-Safety set (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016*	28-Feb-2018
	Cohort 3 + Extension N=62 n (%)	Cohort 3 + Extension N=92 n (%)
All SAEs	**26 (41.9)**	**46 (50.0)**
Febrile neutropenia	5 (8.1)	8 (8.7)
Serum sickness[a]	6 (9.7)	8 (8.7)
Upper respiratory tract infection	1 (1.6)	6 (6.5)
Lung infection	2 (3.2)	5 (5.4)
Bacteraemia	0	4 (4.3)
Hypertension	1 (1.6)	3 (3.3)
Pharyngitis	2 (3.2)	3 (3.3)
Rash maculopapular	3 (4.8)	3 (3.3)
Sinusitis	2 (3.2)	3 (3.3)
Abdominal pain	1 (1.6)	2 (2.2)
Enterocolitis infectious	1 (1.6)	2 (2.2)
Headache	0	2 (2.2)
Infusion related reaction	2 (3.2)	2 (2.2)
Retinal vascular disorder	1 (1.6)	2 (2.2)
Tonsillitis	0	2 (2.2)
Viral infection	0	2 (2.2)

* Result in Cohort 3 + Extension as of 30-Sep-2016 cutoff were not revised following the queries described in Section 2.5.2.
a. The cases of serum sickness were reported as unlikely related or not related to eltrombopag
Preferred terms are sorted in descending frequency in "Cohort 3 + Extension - 28-Feb-2018".

Study E1202

Two subjects (20.0%) experienced at least 1 SAE. SAEs of febrile neutropenia (grade 3) and nephrolithiasis (grade 3) were reported in 1 subject each and were considered to be unrelated to study treatment.

Study E1201

Four subjects (19.0%) experienced at least 1 SAE. The SAEs reported were retinal detachment, enterocolitis, pain, decreased appetite (1 subject each) and were considered to be unrelated to study treatment

Adverse events leading to discontinuation

Study AUS01T

After original cut-off period (30-Sept-2016) AEs leading to treatment discontinuation were few, and were considered known effects of eltrombopag, or one of the drugs used in the IST (h-ATG and/or CsA) or due to the underlying disease. Overall, 6 subjects (4.9%) had an AE leading to treatment discontinuation: 1 AE of encephalopathy (leading to the subject death; Cohort 1), 4 AEs of rash, and 1 AE of colitis (Cohort 3 + Extension cohort).

All 4 events of rash were reported as SAEs; 3 grade 3 and 1 grade 2 event which was associated with fever and oral pain, resulting in hospitalization and discontinuation of eltrombopag. Of the 4 events, 1 occurred in Cohort 2 (Subject 54), 1 occurred in Cohort 3 (Subject 86) and 2 occurred in the Extension Cohort (Subjects 94 and 107). Subjects 86 and 107 were paediatric (6 and 16 years old, respectively).

Overall, few subjects discontinued treatment due to an AE, and at the update cut-off (28-Feb-2018) no additional subject discontinued treatment due to an AE (Table 64).

Table 64. AEs leading to treatment discontinuation-Safety set (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016 Cohort 3 + Extension N=62 n (%)	28-Feb-2018 Cohort 3 + Extension N=92 n (%)
All AEs	**4 (6.5)**	**4 (4.3)**
Rash maculopapular	3 (4.8)	3 (3.3)
Colitis	1 (1.6)	1 (1.1)
Encephalopathy	0	0

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension Cohort - 28-Feb-2018".

Study E1202

One subject discontinued treatment due to ECG QT prolonged (grade 2) which was considered not related to study treatment by the Investigator.

Study E1201

One subject discontinued treatment with study medication due to an abnormal hepatic function (ALT >5 × ULN and AST >3 × ULN). This was considered by the Investigator to be related to eltrombopag.

Adverse events leading to dose interruption or adjustment

Study AUS01T

Most AEs requiring eltrombopag dose adjustment/interruption were transaminases increased. This is considered a known effect of eltrombopag. After original cut-off period (30-Sept-2016) overall, 17 subjects (13.8%) had AEs requiring dose adjustment or interruption. Most events were ALT / AST increased: 12 (9.8%)/9 (7.3%) subjects, respectively. All other AEs requiring dose interruptions/adjustments were observed in 1 subject only.

Almost all ALT / AST increases requiring dose interruptions/adjustments were observed in the combined Cohort 3 + Extension Cohort: 11 (17.7%) / 9 (14.5%) subjects, respectively. Only 1 AE ALT increased requiring dose adjustment or interruption was observed in Cohort 1, and none in Cohort 2.

At the update cut-off (28-Feb-2018) the incidences of AEs requiring dose interruptions/adjustments were similar to what was observed at the original cut-off (Table 65).

Table 65. AEs requiring dose interruption/adjustment in at least 2 sujects-Safety set (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016 Cohort 3 + Extension N=62 n (%)	28-Feb-2018 Cohort 3 + Extension N=92 n (%)
All AEs	**15 (24.2)**	**28 (30.4)**
ALT increased	11 (17.7)	18 (19.6)
AST increased	9 (14.5)	13 (14.1)
Blood bilirubin increased	1 (1.6)	2 (2.2)

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension Cohort - 28-Feb-2018".

Study E1202

Three subjects (30.0%) had AEs that led to dose reduction or interruption of eltrombopag. The AEs were: nausea (2 subjects), ALT increased, blood bilirubin increased, dyspepsia, GGT increased, vomiting (1 subject each).

Study E1201

No subject had dose reduction due to an AE. Five subjects (23.8%) had dose interruptions due to an AE. The AEs were chronic gastritis, dyspepsia, hepatic function abnormal, hyperbilirubinemia, rash (1 subject each).

Adverse events of special interest

Study AUS01T

AESIs occurring during the 6 months of study treatment or within 30 days of eltrombopag discontinuation were reported, except for the malignancies which were reported for the duration of the study.

New cytogenetic abnormalities were evaluated by peripheral blood and bone marrow evaluations. They were not considered as AEs per protocol or per evaluation by the Principal Investigator, as they are known events of the natural evolution of SAA and they occur with IST. However, it is included as an AESI in order to assess long term safety.

- *Bleeding events:* Bleeding is considered an expected event due to the underling disease and could occur at any time the platelet counts are low. Treatment emergent AESIs of bleeding did not cluster to a specific type of bleeding. After original cut-off period (30-Sept-2016) in Cohort 1, 2 subjects had several types of haemorrhage (one subject had ileal haemorrhage, hematoma and lower gastrointestinal haemorrhage, and one subject had epistaxis and conjunctival hemorrhageIn Cohort 2, Cohort 3 and Cohort 3 + Extension, these events were observed in 1 subject in each cohort (ovarian haemorrhage, mouth haemorrhage and menorrhagia, respectively). None of the bleeding events led to therapy discontinuation, or led to dose interruption/adjustment. After updated cut-off (28-Feb-2018) the incidences were similar to the original cut-off.
- *Hepatobiliary events*: The trial was designed by sequential cohort with each cohort informing the design of the subsequent cohort (duration of eltrombopag, addition of maintenance CsA, and concurrent administration of all 3 drugs). After original cut-off period (30-Sept-2016) increased aminotransferases (ALT and AST) and increased blood bilirubin were reported in 27.4%, 19.4%, and 14.5% of subjects, respectively, in the combined Cohort 3 + Extension Cohort. Most aminotransferases increased and one event each of increased blood bilirubin and liver injury required dose interruption/adjustment. None of the hepatobiliary events led to therapy discontinuation.

The protocol specified grade 3 and 4 LFTs labs under certain circumstances to be captured as AEs. However, on retrospective review of the study data, the rules to translate LFT labs to AEs appeared inconsistently applied. Considering the above information, the laboratory results should be the primary evidence of hepatotoxicity, as all LFT lab values were source document verified.

There were more liver AEs reported in Cohort 3 and Extension Cohort relative to Cohort 1 and Cohort 2, which can be attributed to differences in the reporting concept. When considering liver related laboratory parameters, i.e. AST and ALT, there was no meaningful difference between the cohorts.

Since the original cut-off, queries were issued to the Investigator for all grade 3 and 4 liver function laboratory abnormalities from the beginning of the study to see if they should have been reported as an AE. This led to an increase (≥ 10%) in Cohorts 1 and 2 in reported liver AEs (table 43). This increase of liver AEs in these cohorts is a consequence of the query process. Independently from the reporting of hepatobiliary AEs by the Investigator, it is to be noted that the analyses displayed in clinical laboratory evaluation section (below) on the basis of actual LFTs laboratory measures and objective criteria, should remain the primary evidence for assessment of hepatotoxicity. All ALT, AST, TBIL and ALP abnormalities of any grade are presented in in the mentioned section. In the combined Cohort 3 + Extension Cohort,

the incidences of hepatobiliary events at the update cut-off were similar to what was observed at original cut-off.

- *Thromboembolic events*: AESI of thromboembolic events were rare in all cohorts (original cut-off 30_sept-2016) (2 subjects in Cohort 2, who had transient blindness and myocardial infarction, 1 subject in Cohort 3 and 2 subjects in combined Cohort 3 + Extension Cohort all of whom had embolisms: one was a catheter-related thrombosis in the basilica vein and the other was a non-occlusive clot in the subclavian vein). None led to therapy discontinuation or to dose interruption/adjustment. No new events were recorded at the update cutoff (28-Feb-2018).
- *Renal events*: After the original cut-off AESI of renal events (AE of acute kidney injury) was observed in one subject in Cohort 2 and in one subject in Extension Cohort. These events did not lead to therapy discontinuation or to dose interruption/adjustment.
- No AEs of haematological malignancies, bone marrow fibrosis, or recurrence of thrombocytopenia after discontinuation of eltrombopag were reported.

Study E1202

One subject had thromboembolic AE of blood creatinine phosphokinase increased. Seven subjects had hepatobiliary AEs (ALT increased, blood bilirubin increased, blood alkaline phosphatase increased, GGT increased, hepatic function abnormal, and liver injury; grade 1/2). Two subjects had hepatobiliary laboratory abnormalities. Five subjects had renal AEs (renal impairment, dysuria, renal disorder); grade 1 or 2. Three subjects had bleeding AEs (haematuria, haemorrhoidal haemorrhage, petechiae, and subcutaneous hematoma). None of these events were considered related to eltrombopag.

One subject was detected with a cytogenetic abnormality that was not associated with dysplasia or an increase in bone marrow blasts; no progression to MDS was reported. This event was not reported as an AE by the Investigator. No AEs of malignancies or post-therapy thrombocytopenia was reported. Of the 10 subjects treated with eltrombopag, 9 subjects had evaluable samples of the bone marrow biopsy at screening. The worsening in grade of reticulin through Week 52 was observed in 2 subjects for European Consensus Scale, and in 3 subjects for Bauermeister scale. These changes were not reported as AEs.

Study E1201

AESIs (hepatobiliary, renal-related, bleeding, and cytogenetic abnormalities) were infrequent. One subject with elevated baseline aminotransferases (ALT: 81 IU/L, AST: 75 IU/L) experienced hepatic function abnormal (grade 3) and eltrombopag was discontinued; the subject had ALT levels $\geq 5 \times$ ULN at the time of treatment withdrawal. The event of hepatic function abnormal was suspected to be treatment-related. Three subjects (all with normal karyotype at baseline) had a new cytogenetic abnormality detected after treatment, none of which was a hematologic malignancy. Of these, no subject had cytogenetic abnormalities affecting the structure or number of chromosome 7 by FISH. No AEs related to thromboembolic events, post-therapy thrombocytopenia or malignancies were reported. Eighteen of the enrolled subjects had evaluable samples of the bone marrow biopsy at screening. The worsening in grade of reticulin through Week 52 was observed in 2 subjects for European Consensus Scale, and in 1 subject for Bauermeister scale. These changes were not reported as AEs.

Adverse drug reaction in the target indication

Adverse events as reported in Study AUS01T were selected as candidates for further evaluation for their relationship with treatment with eltrombopag for the purpose of the labelling document.

The strategy for ADR selection:

- AEs occurring in at least 2 subjects in the combined Cohort 3 + Extension cohort (corresponding to a frequency of at least 3.2%); AEs were assessed at the level of preferred terms;

- AEs from Cohorts 1, 2, 3 and Extension cohort, which were on the Novartis list of designated medical events;
- AEs from Cohorts 1, 2, 3 and Extension cohort that were included in the Risk Management Plan as an important identified or potential risks but were not included as AEs in the product information.

AEs identified in the candidate selection were considered 'ADRs' when there was enough evidence of a causal relationship between the drug and the event. The AEs which have been defined as 'candidate ADRs' were evaluated based on Bradford-Hill criteria. ADRs as defined may differ from the Investigator determined related adverse events.

Special focus was given whether an AE has been associated with either h-ATG or CsA by reviewing the respective label-documents (US PI for h-ATG or NVS-CDS for CsA):

An event which has been listed for either h-ATG or CsA was not considered related to eltrombopag unless:

- There is a clear pharmacological rationale to expect a relationship to eltrombopag or
- It is a known ADR for eltrombopag in other indications.

Furthermore, events which are clearly associated with the underlying disease were not considered as ADRs.

Upon review of safety data as of 28-Feb-2018, using the same ADR selection criteria as described in the original submission, an additional ADR of 'skin discolouration' was recognized.

Of note, as Cohort 3+Extension reflects the chosen dosage regimen (h-ATG+CSA+Eltrombopag concurrently from Day 1) for this indication, this cohort was utilized in the selection of ADRs in patients with definitive immunosuppressive therapy-naïve SAA.

Novartis proposes to include a separate ADR section using MedDRA version 21.0 for the definitive immunosuppressive therapy-naïve SAA patient population to provide clarity on the ADRs that were experienced in this patient population. The following ADR table was utilised to populate these ADRs:

Table 67. Adverse drug reactions.

Preferred term	Number of patients with ADRs in Cohort 3+Extension as of 30-Sep-2016 (n=62)	%	Frequency category	Number of patients with ADRs in Cohort 3+Extension as of 28-Feb-2018 (n=92)	%	Frequency category
Investigations						
Alanine amino-transferase (ALT) increased	17	27.4	Very common	27	29.3	Very common
Aspartate amino-transferase (AST) increased	12	19.4	Very common	16	17.4	Very common
Blood bilirubin increased (including ocular icterus)	10	16.1	Very common	16	17.4	Very common
Skin and subcutaneous tissue disorders						
Rash	4	6.5	Common	7	7.6	Common
Skin discolouration including hyperpigmentation*				5	5.4	Common
Gastrointestinal disorders						
Abdominal pain	2	3.2	Common	3	3.3	Common
Diarrhoea	2	3.2	Common	3	3.3	Common
Nausea	2	3.2	Common	4	4.3	Common

*At the original cut-off of 30-Sep-2016 the ADR of Skin hyperpigmentation was observed at a rate of 4.8% (3/62). At the new cut-off date of 28-Feb-2018, the ADR of Skin discoloration was observed at a rate of 2.2% (2/92). Novartis recognized the two terms to be of the same medical concept and hence grouped both the terms to read 'Skin discoloration including hyperpigmentation' with a combined frequency of 5.4% (5/92).

Laboratory findings

Hematology in Study AUS01T

As anticipated in a population of subjects with SAA, there were high incidences of high CTC grade (≥grade 3) haemoglobin, neutrophil and platelets abnormalities. After the original cut-off period (30-Sept-2016) there was no major differences between the cohorts, (Table 68). Subjects had transfusions at baseline, which could improve their haematology evaluation at that time. Most haematology abnormalities were already observed during the first 13 days.

After the cut-off 28-Feb-2018 the incidences of worsening from baseline of haematology abnormalities, were similar to what was observed at the original cut-off, and most of these worsening haematology abnormalities were already observed during the 13 first days.

Table 68. Haematology abnormalities grade worsening from baseline.

		Cohort 1 N=30		Cohort 2 N=31		Cohort 3 + Extension N=62	
		Total	n (%)	Total	n (%)	Total	n (%)
Hemoglobin	Grade 1	0	0	0	0	0	0
	Grade 2	6	1 (16.7)	6	1 (16.7)	11	2 (18.2)
	Grade 3	27	25 (92.6)	25	22 (88.0)	57	49 (86.0)
Neutrophils	Grade 1	0	0	0	0	1	1 (100)
	Grade 2	1	1 (100)	0	0	2	0
	Grade 3	3	2 (66.7)	0	0	5	2 (40.0)
	Grade 4	15	8 (53.3)	11	10 (90.9)	21	10 (47.6)
Platelets	Grade 1	0	0	0	0	0	0
	Grade 2	2	0	1	0	1	0
	Grade 3	8	0	10	0	10	0
	Grade 4	24	24 (100)	22	22 (100)	41	41 (100)

Hemoglobin and platelet assessment at baseline could have been done after the subject has been transfused.
Total = number of subjects who had missing or less than grade x at baseline and with at least one post-baseline value for the considered parameter.
n (%) = number (%) of subjects whose the grade worsened from missing or less than grade x at baseline to grade x post-baseline. All on-treatment laboratory data at any time are included in this table.

Haematology in Study E1202

Hematology assessments during the study included haemoglobin, lymphocytes, neutrophils and white blood cell count. Although most subjects had shifts in grades with regard to haematology parameters, the observed grade changes were consistent with those expected in subject with the underlying disease.

Haematology in Study E1202

Hematology assessments during the study included haemoglobin, lymphocytes, neutrophils and white blood cell count. The grade changes seen were common observations due to underlying disease.

Clinical chemistry in AUS01T

All 3 drugs are labelled for liver function abnormalities, and eltrombopag and CsA are labelled for hyperbilirubinemia. In subjects with SAA receiving CsA and h-ATG and eltrombopag, increased aminotransferase (AST/ALT) liver enzymes and increased bilirubin are anticipated.

After the original cut-off (30-Sept-2018) there were no meaningful differences between the cohorts in liver related laboratory parameters, i.e. AST and ALT (Table 69). The elevations of the LFTs were typically transient and most subjects had recovered completely at data cut-off. Some subjects had elevations in transaminases (ALT/AST) that were sequential and not concurrently to the increases in bilirubin and no subjects discontinued due to transaminase elevation.

Table 69. Liver function test abnormalities based on CTC grade worsening from baseline (Study AUS01T) (cut-off 30-Sept-2016).

		Cohort 1 N=30		Cohort 2 N=31		Cohort 3 + Extension N=62	
		Total	n (%)	Total	n (%)	Total	n (%)
Aspartate amino-transferase increased	Grade 1	25	15 (60.0)	29	11 (37.9)	56	17 (30.4)
	Grade 2	30	3 (10.0)	31	7 (22.6)	62	9 (14.5)
	Grade 3	30	4 (13.3)	31	7 (22.6)	62	10 (16.1)
	Grade 4	30	2 (6.7)	31	2 (6.5)	62	2 (3.2)
Alanine amino-transferase increased	Grade 1	20	7 (35.0)	22	7 (31.8)	47	12 (25.5)
	Grade 2	29	7 (24.1)	31	3 (9.7)	58	16 (27.6)
	Grade 3	30	8 (26.7)	31	15 (48.4)	61	19 (31.1)
	Grade 4	30	3 (10.0)	31	2 (6.5)	62	2 (3.2)
Bilirubin increased	Grade 1	19	4 (21.1)	22	4 (18.2)	46	13 (28.3)
	Grade 2	26	12 (46.2)	27	13 (48.1)	54	25 (46.4)
	Grade 3	30	12 (40.0)	31	10 (32.3)	62	9 (14.5)
	Grade 4	30	0	31	1 (3.2)	62	1 (1.6)
Alkaline phosphatase increased	Grade 1	24	17 (70.8)	21	14 (66.7)	39	17 (43.6)
	Grade 2	30	4 (13.3)	30	7 (23.3)	62	11 (17.7)
	Grade 3	30	0	31		62	1 (1.6)
	Grade 4	30	0	31	0	62	0

Total = number of subjects who had missing or less than grade x at baseline and with at least one post-baseline value for the considered parameter.
n (%) = number (%) of subjects whose the grade worsened from missing or less than grade x at baseline to grade x post-baseline.
All on-treatment laboratory data at landmark at any time are included in this table.

In total, 40 cases met the biochemical criteria of ALT or AST >3xULN and TBIL >2xULN and (ALP <2xULN or missing), where the 3 minimum laboratory parameters met the defined thresholds (xULN) within a 30 day period (Table 70).

Table 70. Elevations of liver chemistry tests (Study AUS01T) (cut-off 30-Sept-2016).

	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=62 n (%)
ALT or AST > 3xULN	18 (60.0)	20 (64.5)	23 (74.2)	40 (64.5)
ALT or AST > 5xULN	11 (36.7)	17 (54.8)	13 (41.9)	22 (35.5)
ALT or AST > 8xULN	8 (26.7)	12 (38.7)	6 (19.4)	12 (19.4)
ALT or AST > 20xULN	3 (10.0)	2 (6.5)	1 (3.2)	2 (3.2)
TBIL > 2xULN	17 (56.7)	17 (54.8)	15 (48.4)	25 (40.3)
TBIL > 2xULN with DBIL/TBIL ≥ 35%	6 (20.0)	12 (38.7)	7 (22.6)	12 (19.4)
ALT or AST > 3xULN and TBIL > 1.5xULN	13 (43.3)	19 (61.3)	17 (54.8)	29 (46.8)
ALT or AST > 3xULN and (TBIL > 1.5xULN with DBIL/TBIL ≥ 35%)	7 (23.3)	14 (45.2)	9 (29.0)	16 (25.8)
ALT or AST > 3xULN and TBIL > 2xULN	9 (30.0)	14 (45.2)	11 (35.5)	17 (27.4)
ALT or AST > 3xULN and (TBIL > 2xULN with DBIL/TBIL ≥ 35%)	5 (16.7)	11 (35.5)	6 (19.4)	10 (16.1)
ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing)	9 (30.0)	14 (45.2)	11 (35.5)	17 (27.4)
ALT or AST > 3xULN and (TBIL > 2xULN with DBIL/TBIL ≥ 35%) and (ALP < 2xULN or missing)	5 (16.7)	11 (35.5)	6 (19.4)	10 (16.1)

Categories with multiple parameters are based on worst post-baseline value for each parameter, obtained from samples collected within maximum 30 days of each other.
- ALP = Alkaline phosphatase, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, TBIL = Total bilirubin, DBIL = Direct bilirubin

Of these 40 cases, 26 met the biochemical criteria for DILI/ Hy's law prior to eltrombopag initiation, but its contribution to subsequent elevations is unclear. The remaining 14 cases met the criteria after

initiation of eltrombopag. None of these cases were confirmed as DILI related to eltrombopag. The LFT elevations were typically transient and most subjects recovered completely. Some subjects had elevations in aminotransferase (ALT/AST) that were sequential and not concomitant to the increases in bilirubin. Other subjects had confounding factors in their medical history, and some were also receiving concomitant drugs known to induce transient LFT increases.

The majority of elevated LFTs first occurred during the first 13 days in a similar way across all cohorts, and therefore the addition of eltrombopag did not change the hepatic safety profile. None of the subjects discontinued eltrombopag due to LFT elevations.

Similar to the original cut-off, the incidences of biochemistry abnormalities, new or worsening from baseline, were mostly ≤grade 3 and the grade 4 increases aminotransferase (AST/ALT) liver enzyme and increased bilirubin were reported in ≤5% of the subjects in combined Cohort 3 + Extension Cohort (Table 71). The incidences of elevation of liver chemistry tests were also similar to what was observed at the original cut-off (Table 72), as well as elevation of liver chemistry tests observed in the paediatric population (Table 73), or during the first 13 days and first 3 months (table 74 and table 75), respectively.

Table 71. Biochemistry abnormalities based on CTC grade worsening from baseline - Safety set (cut-off 28-Feb-2018).

Cutoff date		30-Sep-2016 Cohort 3 + Extension N=62		28-Feb-2018 Cohort 3 + Extension N=92	
Worsening from Baseline to:		Total	n (%)	Total	n (%)
AST	Grade 1	56	17 (30.4)	84	30 (35.7)
	Grade 2	62	9 (14.5)	92	12 (13.0)
	Grade 3	62	10 (16.1)	92	14 (15.2)
	Grade 4	62	2 (3.2)	92	2 (2.2)
ALT	Grade 1	47	12 (25.5)	71	19 (26.8)
	Grade 2	58	16 (27.6)	87	27 (31.0)
	Grade 3	61	19 (31.1)	91	24 (26.4)
	Grade 4	62	2 (3.2)	92	4 (4.3)
Bilirubin	Grade 1	46	13 (28.3)	70	22 (31.4)
	Grade 2	54	25 (46.3)	81	38 (46.9)
	Grade 3	62	9 (14.5)	91	11 (12.1)
	Grade 4	62	1 (1.6)	92	1 (1.1)
ALP	Grade 1	39	17 (43.6)	62	34 (54.8)
	Grade 2	62	11 (17.7)	92	14 (15.2)
	Grade 3	62	1 (1.6)	92	1 (1.1)
	Grade 4	62	0	92	0
Creatinine	Grade 1	61	16 (26.2)	91	27 (29.7)
	Grade 2	62	3 (4.8)	92	3 (3.3)
	Grade 3	62	0	92	0
	Grade 4	62	0	92	0
Hyperglycemia	Grade 1	48	27 (56.3)	68	39 (57.4)
	Grade 2	59	23 (39.0)	89	35 (39.3)
	Grade 3	61	3 (4.9)	91	5 (5.5)
	Grade 4	62	0	92	0
Hypoglycemia	Grade 1	62	11 (17.7)	92	17 (18.5)
	Grade 2	62	0	92	0
	Grade 3	62	0	92	0
	Grade 4	62	0	92	0

Total = number of patients who had missing or less than grade x at baseline and with at least one post-baseline value for the considered parameter.
n (%) = number (%) of patients whose the grade worsened from missing or less than grade x at baseline to grade x post-baseline.
All on-treatment laboratory data at landmark visits and outside these visits are included in this table.

Table 72. Elevations of liver chemistry tests - Safety set (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016	28–Feb-2018
	Cohort 3 + Extension N=62 n (%)	Cohort 3 + Extension N=92 n (%)
ALT or AST > 3xULN	40 (64.5)	58 (63.0)
ALT or AST > 5xULN	22 (35.5)	29 (31.5)
ALT or AST > 8xULN	12 (19.4)	17 (18.5)
ALT or AST > 20xULN	2 (3.2)	4 (4.3)
TBIL > 2xULN	25 (40.3)	41 (44.6)
with DBIL/TBIL ≥ 35%	12 (19.4)	20 (21.7)
ALT or AST > 3xULN and TBIL > 1.5xULN	29 (46.8)	40 (43.5)
with DBIL/TBIL ≥ 35%	16 (25.8)	22 (23.9)
ALT or AST > 3xULN and TBIL > 2xULN	17 (27.4)	29 (31.5)
with DBIL/TBIL ≥ 35%	10 (16.1)	17 (18.5)
ALT or AST > 3xULN and TBIL > 2xULN and ALP < 2xULN or missing	17 (27.4)	29 (31.5)
with DBIL/TBIL ≥ 35%	10 (16.1)	17 (18.5)

Categories with multiple parameters are based on worst post-Baseline value for each parameter, obtained from samples collected within maximum 30 days of each other.

Table 73. Elevations of liver chemistry tests in the paediatric group - Safety set (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016				28–Feb-2018
	Cohort 1 N=5 n (%)	Cohort 2 N=6 n (%)	Cohort 3 N=8 n (%)	Cohort 3 + Extension N=18 n (%)	Cohort 3 + Extension N=26 n (%)
ALT or AST > 3xULN	2 (40.0)	0	5 (62.5)	8 (44.4)	13 (50.0)
ALT or AST > 5xULN	2 (40.0)	0	3 (37.5)	4 (22.2)	5 (19.2)
ALT or AST > 8xULN	0	0	2 (25.0)	2 (11.1)	3 (11.5)
ALT or AST > 20xULN	0	0	0	0	1 (3.8)
TBIL > 2xULN	3 (60.0)	0	6 (75.0)	8 (44.4)	14 (53.8)
with DBIL/TBIL ≥ 35%	0	0	2 (25.0)	2 (11.1)	5 (19.2)
ALT or AST > 3xULN and TBIL > 1.5xULN	1 (20.0)	0	4 (50.0)	7 (38.9)	11 (42.3)
with DBIL/TBIL ≥ 35%	0	0	2 (25.0)	3 (16.7)	6 (23.1)
ALT or AST > 3xULN and TBIL > 2xULN	1 (20.0)	0	3 (37.5)	3 (16.7)	8 (30.8)
with DBIL/TBIL ≥ 35%	0	0	2 (25.0)	2 (11.1)	5 (19.2)
ALT or AST > 3xULN and TBIL > 2xULN and ALP < 2xULN or missing	1 (20.0)	0	3 (37.5)	3 (16.7)	8 (30.8)
with DBIL/TBIL ≥ 35%	0	0	2 (25.0)	2 (11.1)	5 (19.2)

Categories with multiple parameters are based on worst post-Baseline value for each parameter, obtained from samples collected within maximum 30 days of each other.

Table 74. Elevations of liver chemistry tests collected during the first 13 days in Cohort 1+2 or in Cohort 3 + Extension - Safety set (cut-off 28-Feb-2018).

Cutoff date	28–Feb-2018	
	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension N=92 n (%)
ALT or AST > 3xULN	35 (57.4)	50 (54.3)
ALT or AST > 5xULN	25 (41.0)	23 (25.0)
ALT or AST > 8xULN	13 (21.3)	7 (7.6)
ALT or AST > 20xULN	5 (8.2)	2 (2.2)
TBIL > 2xULN	13 (21.3)	10 (10.9)
with DBIL/TBIL ≥ 35%	8 (13.1)	5 (5.4)
ALT or AST > 3xULN and TBIL > 1.5xULN	20 (32.8)	20 (21.7)
with DBIL/TBIL ≥ 35%	13 (21.3)	10 (10.9)
ALT or AST > 3xULN and TBIL > 2xULN	10 (16.4)	6 (6.5)
with DBIL/TBIL ≥ 35%	6 (9.8)	3 (3.3)
ALT or AST > 3xULN and TBIL > 2xULN and ALP < 2xULN or missing	9 (14.8)	5 (5.4)
with DBIL/TBIL ≥ 35%	5 (8.2)	2 (2.2)

Categories with multiple parameters are based on worst post-Baseline value for each parameter, obtained from samples collected within maximum 30 days of each other.

Table 75. Elevations of liver chemistry tests collected during the first 3 months in Cohort 1+2 or in Cohort 3 + Extension - Safety set (cut-off 28-Feb-2018).

Cutoff date	28–Feb-2018	
	Cohort 1 + Cohort 2 N=61 n (%)	Cohort 3 + Extension N=92 n (%)
ALT or AST > 3xULN	37 (60.7)	57 (62.0)
ALT or AST > 5xULN	28 (45.9)	27 (29.3)
ALT or AST > 8xULN	15 (24.6)	11 (12.0)
ALT or AST > 20xULN	5 (8.2)	4 (4.3)
TBIL > 2xULN	25 (41.0)	22 (23.9)
with DBIL/TBIL ≥ 35%	11 (18.0)	7 (7.6)
ALT or AST > 3xULN and TBIL > 1.5xULN	21 (34.4)	33 (35.9)
with DBIL/TBIL ≥ 35%	12 (19.7)	14 (15.2)
ALT or AST > 3xULN and TBIL > 2xULN	11 (18.0)	14 (15.2)
with DBIL/TBIL ≥ 35%	8 (13.1)	6 (6.5)
ALT or AST > 3xULN and TBIL > 2xULN and ALP < 2xULN or missing	7 (11.5)	7 (7.6)
with DBIL/TBIL ≥ 35%	6 (9.8)	2 (2.2)

Categories with multiple parameters are based on worst post-Baseline value for each parameter, obtained from samples collected within maximum 30 days of each other.

In review of elevation of liver chemistry tests, 29 subjects in the combined Cohort 3 + Extension Cohort met the criteria of ALT or AST > 3xULN and TBIL > 2xULN and (ALP < 2xULN or missing), where the 3 minimum laboratory parameters met the defined thresholds (ULN) within a 30 day period of each other. Similarly to what was reported at the original cut-off, the elevations of the LFTs were usually transient and mostly the subjects recovered completely. Some subjects had confounding factors in their medical history and some subjects were also receiving concomitant drugs known to induce transient increases of the LFTs. None of the subjects discontinued eltrombopag due to LFT elevations.

Clinical chemistry in E1202

In Study E1202, the majority of the worst post-baseline grade in the clinical chemistry parameters was grade 1 or grade 2 through Week 52 except for one subject whose sodium levels shifted from grade 0 (baseline) to grade 3 post-baseline. No clinical chemistry laboratory parameters changed to severity grade 4.

Clinical chemistry in E1201

In Study E1201, the majority of grade changes were to grade 1 except one subject for whom elevated AST values shifted from grade 1 (at baseline) to grade 2 worst post-baseline and another subject for whom elevated ALT values shifted from grade 1 (at baseline) to grade 3 worst post baseline. No clinical chemistry laboratory parameters changed to severity grade 4.

Vital signs, physical findings and other observations related to safety

No clinically relevant changes were seen in systolic blood pressure, diastolic blood pressure, pulse rate, weight and temperature in Study AUS01T. Neither were seen in Studies E1202 and E1201.

Electrocardiogram

None of the ECG findings were considered as clinically relevant, except for 1 ECG finding (Cohort 2) that was associated with an SAE of grade 4 myocardial infarction, with an onset prior to treatment with eltrombopag.

ECG at Month 3 was mandated starting from Subject AUS01T-051 (Cohort 1). No clinically meaningful differences on ECG shift from baseline were recorded.

In Study E1202, one subject had clinically significant change from baseline in QTcF (> 60 msec) which was reported as an AE (electrocardiogram QT prolonged) which led to discontinuation of eltrombopag.

The outcome of the electrocardiogram QT prolonged was reported as recovered/resolved and the event was considered unrelated to study treatment.

In Study 1201, no clinically significant findings were noted in ECG results.

Historical controls

Safety analysis from Scheinberg *et al (2009)* and Scheinberg *et al (2011)* is reported as presented in the publication and no further information about these studies are available. A direct comparison cannot be conducted; however, the regimen reported in these two publications appears similar to the IST used in US01T up to the landmark visit of 6 months, and the information is presented as a guide to the events as they occur with IST alone. Limited safety data from other published literature, Tisdale *et al (2000)* and Rosenfeld *et al (2003)*, are also presented in this section.

Scheinberg *et al* (2011)

The most frequently observed SAEs were infections (neutropenic fever, negative culture was reported in 23 subjects in the h–ATG group and in 16 subjects in the r-ATG group). 2 subjects in the h-ATG group and 9 in the r-ATG group could not be evaluated at 6 months because of death and progressive disease, respectively.

Clonal evolution was defined as a new clonal cytogenetic abnormality or characteristic dysplastic or leukemic changes in the bone marrow. The cumulative incidence of clonal evolution at 3 years (in all subjects, those with and those without a response) was 21% (95% CI, 7 to 33) in the h-ATG group and 14% (95% CI, 1 to 25) in the r-ATG group (p=0.69). Among subjects treated with h-ATG, one each had deletion 3, deletion 5q, deletion 13q, deletion 20q, and leukemia, and 4 had monosomy 7. In 2 subjects, monosomy 7 was preceded by t(12;13) and deletion 13q. In the r-ATG group, 5 subjects had monosomy 7, and one had deletion 13q.

Scheinberg *et al* (2009)

The most frequently observed SAEs were infections (infections of the ears, nose and throat) reported in 9 subjects in the h-ATG + CsA group and 7 subjects in the h-ATG + CsA + sirolimus group.

7 subjects showed evidence of clonal evolution; 3 subjects in the h-ATG + CsA + sirolimus group (one loss of chromosome 18, one deletion 13q, and one t (6,14) and 4 subjects in the h-ATG + CsA group (3 with monosomy 7 and one with complex cytogenetics).

Tisdale *et al* (2000)

The trial was terminated prematurely after 3 early deaths in the cyclophosphamide group. Analyses were by intention to treat. The median follow-up was 21.9 months (range 1–33).

There was excess morbidity in the cyclophosphamide group (invasive fungal infections, 4 vs. none; p=0.043) as well as excess early mortality (3 deaths within the first 3 months vs. none; p=0.101). There was no significant difference at 6 months after treatment in the overall response rates among evaluable subjects (6 of 13 [46%] on cyclophosphamide vs. 9 of 12 [75%] on ATG). Subjects who received cyclophosphamide sustained greater duration of profound neutropenia than those receiving ATG.

A chromosomal abnormality classically attributed to MDS has been detected in one complete responder in the ATG group (trisomy 8); however, detection of this abnormality 3 months after treatment raises the possibility that it was present but not detectable due to poor in-vitro marrow-cell growth at presentation. A longer period of observation would be necessary to assess late clonal complications.

Rosenfeld *et al* (2003)

16 subjects (13%) died before their 3-month evaluation (mostly due to fungal infection). Despite persistent thrombocytopenia, few subjects died of haemorrhage. 6 subjects died due to complications following bone marrow transplant.

13 (10.6%) subjects evolved to a new cytogenetic abnormality, involving predominantly chromosome 7 (monosomy in 9 subjects and deletion 7p in 1 subject) and chromosome 8 (trisomy in 2 subjects). Monosomy 7 usually occurred with either a minimal initial clinical response or clinical relapse to severe pancytopenia. Seven subjects with this finding died, 4 of refractory pancytopenia and 3 after evolution to acute myelogenous leukaemia. In contrast, trisomy 8 was associated with a good long-term prognosis.

Safety in special populations

After the original cut-off (30-Sept-2016) in Study AUS01T, there were no meaningful differences in the incidence of AEs by subgroup analyses by age category, gender, or race.

- Elderly subjects

In the safety assessment of the elderly subgroup (≥65 years), there were 5 subjects in Cohort 1, 2 subjects in Cohort 2 and 10 subjects in combined Cohort 3 + Extension Cohort, and AEs were reported in 3 (60.0%) subjects, 2 (100%) subjects, and 8 (80.0%) subjects, respectively.

The AEs that were observed in at least 2 elderly subjects overall, irrespective of causal relationship, were ALT/AST increased in 4 subjects each, blood bilirubin increased in 3 subjects and acute kidney injury in 2 subjects. Of the 2 events of kidney injury one was reported as unlikely related to eltrombopag in a subject with diabetes and recovered, and the other was reported as unrelated to eltrombopag in a subject with diarrhoea and dehydration which was ongoing at the data cut-off date.

1 AE of colitis in a 65 years subject occurred concomitantly with sepsis, haemorrhagic typhlitis and a cecal infection; the event typhlitis was reported as unrelated to eltrombopag. None of the AEs had a fatal outcome. The AEs observed were consistent with those observed in non-elderly subjects with the exception of the 2 cases of renal injury and typhlitis.

During the updated cut-off (28-Feb-2018), in the safety assessment of the elderly subgroup (≥ 65 years), there were 15 subjects in the combined Extension Cohort, that is an additional 5 subjects from the original cut-off. The AEs that were observed in at least 2 elderly subjects in the combined Cohort 3 + Extension Cohort, irrespective of causal relationship, were ALT increased (6 subjects, 40.0%), AST and blood bilirubin increased (4 subjects, 26.7% each), lung infection (3 subjects, 20.0%), and hypertension (2 subjects, 13.3%). The AEs in elderly observed in the combined Extension Cohort were consistent with those observed in non-elderly subjects.

- Paediatric subjects

In the safety assessment of the paediatric subgroups after the original cut-off (30-Sept-2016), there were 29 subjects aged 2-17 years: 2 subjects 2-5 years; 8 subjects 6-11 years; 19 subjects 12-17 years with AEs reported in 1, 6 and 13 subjects, respectively. The AEs that were observed in 2 or more than 2 paediatric subjects (Table 76) overall irrespective of causal relationship were febrile neutropenia in 8 subjects, ALT/AST increased in 4 and 2 subjects, respectively; blood bilirubin increased, serum sickness, and lung infection in 3 subjects each; and device related infection, infusion related reaction, sinusitis, and maculopapular rash in 2 subjects each. The 2 events of maculopapular rash led to discontinuation of treatment in one subject aged 6 years and another subject aged 16 years. No other AE led to treatment discontinuation and none of the AEs had a fatal outcome. The AEs observed were consistent with those observed in the overall study population included in the same study.

Table 76. AEs by paediatric subgroups observed in at least 2 paediatric subjects overall - Safety set

	Cohort 1[a]	Cohort 2			Cohort 3 + Extension		
Age group (year)	12-17 N=5 n (%)	2-5 N=1 n (%)	6-11 N=1 n (%)	12-17 N=4 n (%)	2-5 N=1 n (%)	6-11 N=7 n (%)	12-17 N=10 n (%)
All	**4 (80.0)**	**1 (100)**	**1 (100)**	**1 (25.0)**	**0**	**5 (71.4)**	**8 (80.0)**
ALT increased	0	0	0	0	0	1 (14.3)	3 (30.0)
Blood bilirubin increased	1 (20.0)	0	0	0	0	0	2 (20.0)
Febrile neutropenia	1 (20.0)	1 (100)	1 (100)	0	0	3 (42.9)	2 (20.0)
AST increased	0	0	0	0	0	1 (14.3)	1 (10.0)
Device related infection	0	0	1 (100)	0	0	0	1 (10.0)
Infusion related reaction	0	0	0	0	0	1 (14.3)	1 (10.0)
Serum sickness[a]	0	1 (100)	0	1 (25.0)	0	0	1 (10.0)
Sinusitis	0	0	0	0	0	1 (14.3)	1 (10.0)
Rash maculopapular	0	0	0	0	0	1 (14.3)	1 (10.0)
Lung infection	1 (20.0)	0	0	0	0	2 (28.6)	0

a The cases of serum sickness were all reported as "unlikely" related to eltrombopag

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension age 12-17".

a. No subject aged 2-11 years was recruited in Cohort 1.

AEs suspected to be drug related were observed in 1, 4, and 8 subjects in the 2-5 years, 6-11 years and 12-17 years paediatric subgroups, respectively . Febrile neutropenia was the most frequent SAE, reported in 1 subject in each of the 2-5 years and 12-17 years paediatric subgroups and in 4 subjects in the 6-11 years subgroup .

No AESIs were reported in the 2-5 years paediatric subgroups. The few AESIs in the 6-11 years and 12-17 years paediatric subgroups are mentioned below:

- *Bleeding events* were observed in the 12-17 years paediatric subgroup, in 1 subject each in Cohort 1 and combined Cohort 3 + Extension Cohort.
- *Hepatobiliary events* were observed in the 6-11 years paediatric subgroup in 1 subject in the combined Cohort 3 + Extension Cohort and in the 12-17 years subgroup in 1 subject in Cohort 1 and 4 subjects in the combined Cohort 3 + Extension Cohort. The hepatobiliary events were aminotransferase increased and blood bilirubin increased.
- The analysis of *chemistry laboratory abnormalities* in paediatric subjects across all cohorts and all ages showed that out of the 29 paediatric subjects, no grade 4 were reported, and the incidence of grade 3 were ALT: 20.7% (6 subjects), AST 6.9% (2 subjects), bilirubin 13.8% (4 subjects), hyperglycemia: 3.4% (1 subject); there was no grade 3 of hypoglycemia, creatinine or ALP. No subjects discontinued due to increased ALT or AST.
- No incidence of *thromboembolic events*, renal events, malignancies, bone marrow fibrosis, and recurrences of thrombocytopenia was observed in the paediatric subgroup.

Of the 9 subjects with cytogenetic abnormalities, 3 were reported in paediatric subjects, including one (Subject 78: 16 years) who had the loss of chromosome 7, the other 2 abnormalities were of unclear significance.

At the update cut-off, 8 additional paediatric subjects had been enrolled (all in the Extension Cohort). There were no notable differences in AEs recorded in the combined Cohort 3 + Extension Cohort when compared to the analysis at the original cut-off (Table 77).

Overall in the study, all cohorts combined, the AEs recorded in paediatric subjects were consistent with those recorded in adult subjects, with the exception of a higher incidence of febrile neutropenia in paediatric (13 over 37 subjects 35.1%) vs. adult (10 over 116 subjects, 8.6%), and a higher incidence of upper respiratory tract infection in paediatric (4 over 37 subjects, 10.8%) vs. adult (5 over 116 subjects, 4.3%). None resulted in discontinuation.

Table 77. AEs by paediatric subgroups occurring in at least 2 pediatric subjects overall-Safety set.

Cutoff date	30-Sep-2016*							28-Feb-2018		
	Cohort 1 N=5	Cohort 2 N=6			Cohort 3 + Extension N=18			Cohort 3 + Extension N=26		
Age group (year)	12-17 N=5 n (%)	2-5 N=1 n (%)	6-11 N=1 n (%)	12-17 N=4 n (%)	2-5 N=1 n (%)	6-11 N=7 n (%)	12-17 N=10 n (%)	2-5 N=1 n (%)	6-11 N=11 n (%)	12-17 N=14 n (%)
All AEs	**4 (80.0)**	**1 (100)**	**1 (100)**	**1 (25.0)**	**0**	**5 (71.4)**	**8 (80.0)**	**0**	**10 (90.9)**	**11 (78.6)**
Febrile neutropenia	1 (20.0)	1 (100)	1 (100)	0	0	3 (42.9)	2 (20.0)	0	7 (63.6)	3 (21.4)
ALT increased	0	0	0	0	0	1 (14.3)	3 (30.0)	0	3 (27.3)	3 (21.4)
Upper respiratory tract infection	0	0	0	0	0	0	0	0	3 (27.3)	1 (7.1)
AST increased	0	0	0	0	0	1 (14.3)	1 (10.0)	0	2 (18.2)	1 (7.1)
Blood bilirubin increased	1 (20.0)	0	0	0	0	0	2 (20.0)	0	0	3 (21.4)
Headache	0	0	0	0	0	1 (14.3)	0	0	1 (9.1)	2 (14.3)
Lung infection	1 (20.0)	0	0	0	0	2 (28.6)	0	0	2 (18.2)	1 (7.1)
Sinusitis	0	0	0	0	0	1 (14.3)	1 (10.0)	0	2 (18.2)	1 (7.1)
Enterocolitis	0	0	0	0	0	0	0	0	0	2 (14.3)
Hypertension	0	0	0	0	0	0	0	0	0	2 (14.3)
Bacteraemia	0	0	0	0	0	0	0	0	1 (9.1)	1 (7.1)
Infusion related reaction	0	0	0	0	0	1 (14.3)	1 (10.0)	0	1 (9.1)	1 (7.1)
Nausea	0	0	0	0	0	1 (14.3)	0	0	1 (9.1)	1 (7.1)
Pharyngitis	0	0	0	0	0	1 (14.3)	0	0	2 (18.2)	0

Cutoff date	30-Sep-2016*							28-Feb-2018		
	Cohort 1 N=5	Cohort 2 N=6			Cohort 3 + Extension N=18			Cohort 3 + Extension N=26		
Age group (year)	12-17 N=5 n (%)	2-5 N=1 n (%)	6-11 N=1 n (%)	12-17 N=4 n (%)	2-5 N=1 n (%)	6-11 N=7 n (%)	12-17 N=10 n (%)	2-5 N=1 n (%)	6-11 N=11 n (%)	12-17 N=14 n (%)
Rash maculopapular	0	0	0	0	0	1 (14.3)	1 (10.0)	0	1 (9.1)	1 (7.1)
Serum sickness[a]	0	1 (100)	0	1 (25.0)	0	0	1 (10.0)	0	1 (9.1)	1 (7.1)
Tonsillitis	0	0	0	0	0	0	0	0	2 (18.2)	0
Device related infection	0	0	1 (100)	0	0	0	1 (10.0)	0	0	1 (7.1)
Tooth infection	1 (20.0)	0	0	0	0	0	0	0	1 (9.1)	0

* Result in as of 30-Sep-2016 cutoff were not revised following the queries described in Section 2.5.2.
a. The cases of serum sickness were reported as not related or unlikely related to eltrombopag.
Preferred terms are sorted by frequency in Cohort 3 + Extension all pediatric ages combined - 28-Feb-2018.

The SAEs recorded in the combined Cohort 3 + Extension Cohort were similar to what was recorded at the original cut-off, with differences that were not considered as clinically meaningful (Table 78).

Table 78. SAEs by paediatric subgroups occurring in at least 2 paediatric subjects overall – Safety set

Cutoff date	30-Sep-2016							28-Feb-2018		
	Cohort 1 N=5	Cohort 2 N=6			Cohort 3 + Extension N=18			Cohort 3 + Extension N=26		
Age group (year)	12-17 N=5 n (%)	2-5 N=1 n (%)	6-11 N=1 n (%)	12-17 N=4 n (%)	2-5 N=1 n (%)	6-11 N=7 n (%)	12-17 N=10 n (%)	2-5 N=1 n (%)	6-11 N=11 n (%)	12-17 N=14 n (%)
All SAEs	**4 (80.0)**	**1 (100)**	**1 (100)**	**1 (25.0)**	**0**	**5 (71.4)**	**5 (50.0)**	**0**	**10 (90.9)**	**8 (57.1)**
Febrile neutropenia	1 (20.0)	1 (100)	1 (100)	0	0	3 (42.9)	0	0	6 (54.5)	0
Upper respiratory tract infection	0	0	0	0	0	0	0	0	2 (18.2)	1 (7.1)
Sinusitis	0	0	0	0	0	1 (14.3)	1 (10.0)	0	2 (18.2)	1 (7.1)
Lung infection	1 (20.0)	0	0	0	0	1 (14.3)	0	0	1 (9.1)	1 (7.1)
Bacteraemia	0	0	0	0	0	0	0	0	1 (9.1)	1 (7.1)
Headache	0	0	0	0	0	0	0	0	0	2 (14.3)
Hypertension	0	0	0	0	0	0	0	0	0	2 (14.3)
Pharyngitis	0	0	0	0		1 (14.3)	0	0	2 (18.2)	0
Rash maculopapular	0	0	0	0	0	1 (14.3)	1 (10.0)	0	1 (9.1)	1 (7.1)

Cutoff date	30-Sep-2016							28-Feb-2018		
	Cohort 1 N=5	Cohort 2 N=6			Cohort 3 + Extension N=18			Cohort 3 + Extension N=26		
Age group (year)	12-17 N=5 n (%)	2-5 N=1 n (%)	6-11 N=1 n (%)	12-17 N=4 n (%)	2-5 N=1 n (%)	6-11 N=7 n (%)	12-17 N=10 n (%)	2-5 N=1 n (%)	6-11 N=11 n (%)	12-17 N=14 n (%)
Serum sickness[a]	0	1 (100)	0	1 (25.0)	0	0	1 (10.0)	0	1 (9.1)	1 (7.1)
Tonsillitis	0	0	0	0	0	0	0	0	2 (18.2)	0
Tooth infection	1 (20.0)	0	0	0	0	0	0	0	1 (9.1)	0

a.The cases of serum sickness were reported as not related or unlikely related to eltrombopag
Preferred terms are sorted by frequency in Cohort 3 + Extension all pediatric ages combined - 28-Feb-2018

Cytogenetic abnormality, including clonal evolution

The protocol does not define cytogenetic abnormality as an AE, and they were not considered as AEs by the Investigator due to their relationship with the underlying disease and IST. However, all cases of cytogenetic clonal evolution are recorded in the clinical database regardless of the date of occurrence and SAE status.

In **study AUS01T**, after the original cut-off (30-Sept-2016) with a median follow up of 22.19 months (range: 0.1 to 51.0 months), clonal cytogenetic evolution occurred in 9 of 123 (7%) subjects (including 3 paediatric subjects) which is within the range (14% to 20%) that would be expected with IST alone in subjects with SAA at 2 years after the initiation of treatment (Townsley *et al (2017),* Maciejewski *et al (2002),* Scheinberg *et al (2012),* Scheinberg *et al (2011)*:

- 3 subjects (Subject 6: 17 years, Subject 7: 39 years, and Subject 50: 7 years), chromosomal aberrations were of unclear significance.
- Five subjects (Subject 9: 64 years, Subject 18: 69 years, Subject 40: 48 years, Subject 65: 60 years, and Subject 78: 16 years) had a loss of chromosome 7, either alone or in combination with complex cytogenetic abnormalities, and in 3 of the 5 subjects this was accompanied by morphologic evidence of dysplasia or full myeloid malignant transformation; and 4 of the 5 occurred within 6.1 months.
- One subject (Subject 14: 68 years), the chromosomal abnormality was deletion of chromosome 13, considered a good prognostic factor in aplastic anaemia.

It is unclear if these evolutions occurred due to the underlying disease, the IST and/or eltrombopag, however, it does not appear that eltrombopag is associated with higher frequency of clonal evolution.

At update cut-off, 6 additional cases of clonal evolution had occurred in adult subjects (1 in Cohort 1 at Year 5 assessment, and 5 in the Extension Cohort) and none in paediatric subjects. The total number of cases was 15 of 154 subjects, 10%:

- 4 subjects had chromosomal aberrations of unclear significance.
- 7 of these 15 subjects had loss of chromosome 7, either alone or in combination with complex cytogenetic abnormalities (and in 6 of the 7 subjects the alteration in chromosome 7 occurred within 6.1 months); in 3 of the 7 subjects this was accompanied by morphologic evidence of dysplasia or full myeloid malignant transformation.
- One subject had a follow-up bone marrow assessment at 5 years which was markedly changed compared to prior bone marrow assessment, with features of dysplasia with hypercellularity concerning for potential development of MDS.

It is unclear if these evolutions occurred due to the underlying disease, the IST and/or eltrombopag, however it does not appear that eltrombopag is associated with higher frequency or earlier onset of clonal evolution.

At the update cut-off time to clonal evolution is presented in table 79. In all cohorts, estimated probability of being clonal evolution-free was above 90% up to 24 months, and later it decreased below 90% only in

Cohort 1. The evolution to MDS/AML was < 5% in all cohorts except Cohort 1 (16.7%). However, the overall median follow-up now extends to 61, 47, 33 and 22 months in Cohort 1, 2, 3 and combined Cohort 3 + Extension Cohort, respectively and the difference seen between cohorts in clonal evolution might be partially explained by the longer follow-up of the earlier cohorts. These observations are consistent with what has been reported in the studies in refractory SAA subjects who received eltrombopag alone (Winkler *et al* 2017).

Table 79. Time to clonal evolution – FAS (cumulative as of 28-Feb-2018).

	Cohort 1 N=30 n (%)	Cohort 2 N=31 n (%)	Cohort 3 N=31 n (%)	Cohort 3 + Extension N=92 n (%)
Clonal evolution[a]	**6 (20.0)**	**2 (6.5)**	**2 (6.5)**	**7 (7.6)**
Evolution to MDS/AML	5 (16.7)	1 (3.2)	1 (3.2)	3 (3.3)
Other evolution	1 (3.3)	1 (3.2)	1 (3.2)	4 (4.3)
No clonal evolution	**24 (80.0)**	**29 (93.5)**	**29 (93.5)**	**85 (92.4)**
Follow up ongoing	7 (23.3)	19 (61.3)	20 (64.5)	60 (65.2)
Discontinued the study	17 (56.7)	10 (32.3)	9 (29.0)	25 (27.2)
Time to clonal evolution - Percentiles (95% CI) - months				
25th	48.3 (3.0, NE)	NE (24.1, NE)	NE	NE
50th	60.5 (48.3, NE)	NE	NE	NE
Estimates probability of being clonal evolution-free (95% CI)				
6 months	92.9 (74.3,98.2)	100 (NE,NE)	96.8 (79.2,99.5)	95.1 (87.5,98.1)
12 months	92.9 (74.3,98.2)	96.6 (77.9,99.5)	93.5 (76.6,98.3)	90.6 (81.1,95.5)
18 months	92.9 (74.3,98.2)	96.6 (77.9,99.5)	93.5 (76.6,98.3)	90.6 (81.1,95.5)
24 months	92.9 (74.3,98.2)	96.6 (77.9,99.5)	93.5 (76.6,98.3)	90.6 (81.1,95.5)
30 months	81.9 (57.8,93.0)	92.4 (72.5,98.0)	93.5 (76.6,98.3)	90.6 (81.1,95.5)
36 months	81.9 (57.8,93.0)	92.4 (72.5,98.0)	93.5 (76.6,98.3)	90.6 (81.1,95.5)
48 months	81.9 (57.8,93.0)	92.4 (72.5,98.0)	NE	NE
60 months	72.8 (43.4,88.6)	NE	NE	NE

a. Subject AUS01T-004 in Cohort 1 had a clonal evolution observed after Year 5 assessment follow-up; this event is not recorded in this table. See Table 2-46 for a description of this case.
Percentiles with 95% CIs were calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). % clonal evolution probability estimate was the estimated probability that a subject will be free of clonal evolution at the specified time point. % clonal evolution probability estimates were obtained from the KM survival estimates; Greenwood formula is used for CIs of KM estimates.
NE = Not estimable.

In **Study E1202**, of the 10 treatment-naïve MAA and SAA subjects treated with eltrombopag, a cytogenetic abnormality was detected in one (10%) subject who discontinued eltrombopag on the Day 355 due to lack of efficacy (relapse after the ATG therapy), and the cytogenetic abnormality (46,XX,del (6) (q?)[2]/ 46,XX[18]), which was detected at the withdrawal visit and reported after the data cut-off at Week 26. This cytogenetic abnormality was not associated with dysplasia nor increase in bone marrow blasts; no progression to MDS was reported. This event was not reported as an AE by Investigator.

In **Study E1201**, of the 21 MAA and SAA subjects refractory to IST treated with eltrombopag, 19 had normal karyotype and 1 subject had insufficient metaphases to assess karyotype at screening. The remaining subject had no data to perform cytogenetics at screening for this study; however, no cytogenetic abnormality was observed within 3 months before the study entry. Of the 20 subjects with normal karyotype or insufficient metaphases at screening, 18 had a normal karyotype after treatment and 3 (14%) subjects (all with a normal karyotype at baseline) had a new cytogenetic abnormality detected after treatment:

- In one subject, trisomy 8 was detected in 3/20 metaphases with ≥10% of erythroid dysplasia.

- In another, deletion of chromosome Y in 3/20 metaphase.
- In the third, karyotype was 46XY, inv(10) (p13q24) in 2 metaphases.

Of these, none had an abnormality involving chromosome 7 by FISH.

In **Study US28T**, of the 43 subjects refractory to IST, 7 (16.2%) developed clonal cytogenetic abnormalities after treatment. Of these:

- 5 subjects had cytogenetic abnormalities affecting the structure or number of chromosome 7; all 5 were non-responders to eltrombopag. One of these 5 had insufficient bone marrow aspirate at baseline, so it is unknown whether the cytogenetic abnormality was present in the bone marrow prior to treatment with eltrombopag. In one subject, the monosomy 7 was transient and was not present on repeat bone marrow examination 21 days later.
- The 2 remaining subjects had trisomy 8 (Subject 8) and deletion of chromosome 13 (Subject 26).

Three of the seven subjects with a cytogenetic abnormality detected after treatment had evidence of dysplasia in their bone marrow examinations, and two were considered to have MDS. For the 7 subjects who had a cytogenetic abnormality detected during the study, the median time on study to a cytogenetic abnormality was 2.9 months.

In **Study US18T** with a median time of initial treatment of 10 months (6-68 months), of the 40 subjects refractory to IST, 6 (18%) subjects developed cytogenetic abnormalities during eltrombopag administration; and one subject with no metaphases grown at baseline and profound pancytopenia developed AML at 2 months; upon re-review of subject's baseline marrow biopsy showed already blasts suggestive for transformation to AML prior to start eltrombopag. Two of the 6 cytogenetic abnormalities were in chromosome 7. The author hypothesized that due to the temporal relationship between clonal evolution and drug exposure it suggests that in a subgroup of subjects, eltrombopag may promote expansion of dormant pre-existing clones with an aberrant karyotype (*Winkler et al 2017*).

Given the similar rates of clonal evolution in these two studies (Study US18T and Study US28T), a pooled analysis of cytogenetic progression for all subjects (n=83) at up to 8 years of follow-up was performed. Sixteen of 83 (18%) subjects clonally evolved. Clonal evolution was an early event after eltrombopag initiation: occurred within 6 months in 13/16 evolvers (81%), and in 6/6 evolvers with high risk chromosome 7 abnormalities (5/6 within 3 months) (Winkler *et al 2017*).

In **historical studies** where SAA subjects received standard IST (h-ATG + CsA) without eltrombopag as first-line, the incidence of clonal evolution in Scheinberg *et al* (2009) and Scheinberg *et al* (2012) at a median follow-up of 3 years was 9.5% and 21%, respectively. In Rosenfeld et al (2003), clonal evolution was reported in 10.6% of the subjects. In Tisdale *et al (2000)*, one chromosomal abnormality classically attributed to myelodysplastic syndrome was in reported in the ATG group.

The overall incidence of clonal evolution in Study AUS01T was 7% and not higher relative to historic data, with 5 events of clonal evolution occurred within 6.1 months of starting treatment 4 of which had abnormalities in chromosome 7.

Safety related to drug-drug interactions and other interactions

No new information has been generated as a result of Study AUS01T. Results of drug-drug interaction are described in the approved prescribing information.

Discontinuation due to adverse events

Study AUS01T

After original cut-off period (30-Sept-2016) AEs leading to treatment discontinuation were few, and were considered known effects of eltrombopag, or one of the drugs used in the IST (h-ATG and/or CsA) or due to the underlying disease. Overall, 6 subjects (4.9%) had an AE leading to treatment discontinuation: 1 AE of encephalopathy (leading to the subject death; Cohort 1), 4 AEs of rash, and 1 AE of colitis (Cohort 3 + Extension cohort).

All 4 events of rash were reported as SAEs; 3 grade 3 and 1 grade 2 event which was associated with fever and oral pain, resulting in hospitalization and discontinuation of eltrombopag. Of the 4 events, 1 occurred in Cohort 2 (Subject 54), 1 occurred in Cohort 3 (Subject 86) and 2 occurred in the Extension Cohort (Subjects 94 and 107). Subjects 86 and 107 were paediatric (6 and 16 years old, respectively).

Overall, few subjects discontinued treatment due to an AE, and at the update cut-off (28-Feb-2018) no additional subject discontinued treatment due to an AE (Table 64).

Table 64. AEs leading to treatment discontinuation-Safety set (cut-off 28-Feb-2018).

Cutoff date	30-Sep-2016	28-Feb-2018
	Cohort 3 + Extension N=62 n (%)	Cohort 3 + Extension N=92 n (%)
All AEs	**4 (6.5)**	**4 (4.3)**
Rash maculopapular	3 (4.8)	3 (3.3)
Colitis	1 (1.6)	1 (1.1)
Encephalopathy	0	0

Preferred terms are sorted in descending frequency in "Cohort 3 + Extension Cohort - 28-Feb-2018".

Study E1202

One subject discontinued treatment due to ECG QT prolonged (grade 2) which was considered not related to study treatment by the Investigator.

Study E1201

One subject discontinued treatment with study medication due to an abnormal hepatic function (ALT >5 × ULN and AST >3 × ULN). This was considered by the Investigator to be related to eltrombopag.

Post marketing experience

The IBD of Revolade is 20-Nov-2008 (United States).The product is referred to as Promacta, Revolade or eltrombopag. GSK was the original MAH until 2015 when Novartis acquired eltrombopag. The MAH transfer from GSK to Novartis is still ongoing or has been completed in the countries where the product is approved (dates and status vary per country).Novartis is currently the MAH in more than 70 countries.

Eltrombopag is registered in the following indications:

- Adult chronic ITP [European Union (EU) approval 28-Jan-2016, US approval 20-Nov- 2008.

- Paediatric chronic ITP (since 04 Apr 2016 in EU and 11-Jun-2015 in US).

- Treatment of thrombocytopenia in subjects with chronic HCV (since 19-Sep-2013 in EU and 16-Nov-2012 in US).

- SAA in subjects refractory to prior IST (since 25-Aug-2015 in EU and 26-Aug-2014 in the US).

- Aplastic anemia (25-Aug-2017 in Japan).

Estimates of the cumulative subject exposure, based upon actual exposure data from completed and ongoing clinical trials until 30-Sep-2017 is 4463 subjects. The algorithm used to derive post marketing exposure data is based on daily dose of 12.5 mg, 25 mg, 50 mg or 75 mg tablets. This brings the cumulative exposure to 106,493 subject years worldwide, from the first launch until June 2016.

Overall, safety data provided in PSUR version 10 (dated 22-Nov-2017) demonstrates that the overall benefit-risk assessment balance of eltrombopag in the approved indications remains positive.

2.5.1. Discussion on clinical safety

This safety review is mainly based on the results of Study AUS01T which evaluated the safety and efficacy of eltrombopag in combination with h-ATG and CsA in subjects with SAA who had not received prior definitive IST. Study AUS01T was designed with sequential cohorts with each cohort informing the design of the subsequent one (in relation to the duration of eltrombopag treatment, addition of maintenance CsA treatment and concurrent administration of all 3 drugs). As supportive data, the MAH submitted two studies conducted in Japan, Study E1201 and Study E1202, and also historical studies in subjects treated with h-ATG and CsA (Tisdale *et al* (2000), Rosenfeld *et al* (2003), Scheinberg *et al* (2009) and Scheinberg *et al* (2011)). Additional supportive safety data from the refractory studies for cytogenetic abnormalities are provided from Study US28T and Study US18T. Is important to note that the safety assessment is hampered by the lack of a controlled study including the standard treatment (h-ATG+CsA).

In Study AUS01T the most common AEs (regardless of causal relationship to study drug) observed with an incidence ≥10% were febrile neutropenia (known to occur in SAA), ALT/AST increase (known to occur with eltrombopag, h-ATG and CsA), blood bilirubin increase and serum sickness (known to occur with h-ATG).

Febrile neutropenia (grade 3.4 or 5) was not reported with higher frequencies in Cohort 3 and Extension Cohort vs. the other cohorts (6.7% for Cohort 1, 16.1% for Cohort 2 and 16.1% for Cohort 3 and Extension Cohort). These results are maintained when updated cut-off is considered.

The protocol specified grade 3 and 4 liver function tests (LFT) laboratory values under certain circumstances to be captured as AEs. Hepatobiliary AEs were reported more commonly in Cohort 3 and in combined Cohort 3 + Extension Cohort original cut-off (40% to 45%) compared to Cohort 1 and Cohort 2 (17% to 23%). However, on retrospective review of the data, this rule was inconsistently applied. Therefore, MAH considered that these differences were attributed to divergences in the reporting concept. Considering this information, for assessment of liver function as a safety observation, laboratory results were used as the primary evidence of hepatotoxicity. Due to these divergences in the reporting concept and after the updated cut-off (28-Feb-2018) queries were issued to the investigator for all grade 3 and 4 liver function abnormalities from the beginning of the study to see if they should have been reported as an AE and presented in comparison with what was reported at the original submission. This led to an increase (⩾10%) in Cohorts 1 and 2 in reported liver AEs. This increase of liver AEs in these cohorts is a consequence of the query process. Therefore, when considering liver related laboratory parameters there was no appreciable difference between the cohorts. Most of these AEs reflect increased aminotransferase and/or increased blood bilirubin. From Day 1 to Day 13, subjects in Cohort 1 and Cohort 2 were receiving IST only (h-ATG for 4 days + CsA) while subjects in Cohort 3 and Extension Cohort were concurrently receiving IST + eltrombopag. As Cohort 1 and Cohort 2 had a staggered start for eltrombopag vs. concurrent start in Cohort 3 and Extension Cohort, AEs occurring during the first 13 days in these 2 groups allows comparison of the double therapy (h-ATG + CsA) vs. the triple therapy (h-ATG + CsA + eltrombopag). When comparing the number of increased liver laboratory parameters (AST/ALT/ and TBIL)

in the first 13 days, they were consistent between the two groups with AST/ALT > 3xULN and TBIL > 2ULN for Day 1-13 in Cohort 1 and 2 observed in 9 subjects (14.8%) and in Cohort 3 + Extension observed in 3 subjects (4.8%). Results obtained for this parameter for the updated data were similar (n=5, 5.4%). Furthermore, when looking at the liver function laboratory test up to 3 months, there were a limited number of subjects who had an increase of the liver function tests after Day 13 with AST/ALT > 3xULN and TBIL > 2ULN in Cohort 1 and 2 observed in 7 subjects (11.5%) and in Cohort 3 + Extension observed in 7 subjects (11.3%). Results obtained for this parameter for the updated data were similar (n=7, 7.6%). None led to treatment discontinuation and none fulfilled the criteria of severe DILI according to "Hy's law".

In the combined Cohort 3 + Extension Cohort, the incidences of hepatobiliary events at the update cut-off were similar to what was observed at original cut-off.

As previously mentioned, the lack of a comparator arm makes it difficult to elucidate which adverse events are due to eltrombopag treatment. However, alterations of liver function are described as adverse reactions in Revolade SmPC that are not likely to be reported in patients receiving IST alone.

All AEs of serum sickness, (eight in all cohorts) began during the first 13 days of start of treatment and resolved within one week. Five of them were reported as unlikely to be related to eltrombopag and the remaining 3 AEs reported as unrelated. Serum sickness was observed more frequently in Cohort 3 and Extension Cohort original cut-off (6 subjects) where all 3 study drugs were given concurrently, compared to the other cohorts where eltrombopag was started on Day 14 (none in Cohort 1, 2 in Cohort 2). With the updated data 8 subjects reported serum sickness in cohort 3+extension. There is no pharmacological rationale how eltrombopag can induce serum sickness and this event has not been seen in earlier studies with eltrombopag as a safety issue (there was no AE of serum sickness reported in US28T study in refractory SAA subjects who received eltrombopag alone).

No deaths related to the study treatment were reported. All SAEs were considered known effects of eltrombopag, of one of the medications used in IST, or due to the underlying disease.

With the original cut-off few AEs led to treatment discontinuation: Of 6, 1 AE of encephalopathy (leading to the on-treatment death as above), 4 AEs of rash, and 1 AE of colitis. At the updated cut-off no aditional subject discontinue treatment due to an AE. Most of the AEs requiring dose interruption/adjustment with the original cut-off (17 subjects) were increased ALT and AST. After this period the incidence of dose interruptions/adjustments were similar to the ones reported at original cut-off.

Regarding the adverse events of special interest, already described, no events of recurrence of thrombocytopenia, bone marrow fibrosis, or hematologic malignancies were reported. Renal events, thromboembolic events and bleeding events were rare in all cohorts. None of these events led to treatment discontinuation or to dose interruption/adjustment. After the updated cut-off no new AE of special interest were reported.

In study AUS01T, 29 (23.6%) subjects were in the paediatric age range (<18 years) with the original cut-off and 8 additional paediatric patients were included. The AEs that were observed in the paediatric subgroups of 2-5 years, 6-11 years and 12-17 years were similar to those observed in the overall safety population. No new safety signals were seen in this population, for both cut-off periods.

The safety profile observed in other supportive and historical studies included in this application (despite of the difference in the safety reporting criteria and the treatment given) is consistent with the known safety profile of eltrombopag, the medications used in IST or to the underlying disease. To what extent the safety profile of eltrombopag + IST differs from that of standard IST alone, cannot be properly answered in the absence of a comparator.

Considering the adverse reactions proposed to be included in the labelling document for the target indication, the strategies carried out for the identification of adverse events described in study AUS01T as candidates for establish the relationship with eltrombopag were based on Novartis list of designated medical events and EMA list of designated medical events which was considered acceptable.

A serious complication of AA is its evolution to clonal hematologic diseases such as myelodisplasia and leukemia, which is usually associated with the appearance of a citogenetic abnormality in bone marrow cells. Cytogenetic abnormalities are not necessarily associated with a bad outcome, a change in symptoms or diagnosis of malignancy. In addition, and despite evident short-term efficacy, long-term benefits of IST have been questioned as the late complications of immunosuppression include high rates of relapse, evolution to paroxysmal nocturnal haemoglobinuria, myelodysplasia and leukemic transformation (Rosenfeld *et al* 2003).

In this context, the analysis of the 2 historical controls studies where SAA subjects received standard IST (h-ATG + CsA) without eltrombopag as first-line, the incidence of clonal evolution was 9.5% and 21% at 3 years in Scheinberg *et al* 2009 and Scheinberg *et al* 2011 respectively. The analysis of the studies where SAA subjects received eltrombopag alone, the incidence of clonal evolution in the 2 studies with IST refractory subjects (Study US18T and Study US28T) was 18%; in the Japanese refractory subjects it was 14% and in the Japanese treatment-naïve subjects it was 10%.

In Study AUS01T and with the original cut-off, clonal cytogenetic evolution occurred in 9 of 123 (7%) subjects which is not higher compare to historical data, with 5 events of clonal evolution occurred within 6.1 months of starting treatment, 4 of which had abnormalities in chromosome 7. With the updated data, a total of 15/154 subjects (10%) reported clonal evolution. These observations are consistent with what has been reported in the studies in refractory SAA subjects who received eltrombopag alone (Study US18T and Study US28T). Although it does not appear that eltrombopag is associated with higher frequency or earlier onset of clonal evolution, a final conclusion about the early onset of cytogenetic abnormalities relative to SAA, immunosuppression treatment or eltrombopag need more data on a higher number of patients with a long-term follow-up. In this sense, cytogenetic abnormalities are still included in the RMP as an important potential risk.

2.5.2. Conclusions on clinical safety

The main uncertainties related to the assessment of the safety profile of eltrombopag in naïve SAA patients have to do with the severity of the underlying condition, the lack of control arm and the overall limited database provided.

Overall, the safety and tolerability of eltrombopag in treatment-naïve SAA patients seems similar to the already known safety profile in refractory SAA. Nevertheless, whether the safety profile of eltrombopag + IST differs from that of standard IST alone cannot be answered due to the lack of comparator in AUS01T study. No new or unexpected findings have been identified for eltrombopag based on the data presented. Most of the AE and SAE identified are related to the underlying condition and seem manageable in clinical practice.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 52.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH applied for an extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia for Revolade in combination with standard immunosuppressive therapy.

3.1.2. Available therapies and unmet medical need

The only curative treatment is the hematopoietic cell transplantation (HCT). However, immunosuppressant therapy (IST) with ATG/CsA has changed the prognosis of the disease in patients who are not candidates to HCT. First line therapy is selected according to the age of the patient, which correlates with ability to tolerate HCT, the severity of the disease and the availability of an appropriate donor (basically a fully HLA-matched family member). The treatment must balance the relative toxicities and long-term efficacy of the therapies, which differ over time (i.e. higher up-front mortality but greater chance of cure with HCT), and according to patient age. Published prospective long-term studies show that standard initial IST (horse ATG and CsA) achieve haematological recovery in 60-70% and excellent long-term survival among responders.

3.1.3. Main clinical studies

For this indication no specific dose finding studies for adults or children have been performed. The proposed dose is based on results from refractory SAA study (AUS28T), the exposure observed for paediatric and adult ITP patients *vs.* paediatric SAA patients as well as the PK/PD results and the safety profile obtained from the AUS01T updated cut-off (28-Feb-2018).

The main evidence of efficacy of eltrombopag in treatment-naïve patients with SAA is provided by the study AUS01T, a phase I/II, non-randomized, single-arm, single-center study designed to evaluate the efficacy and safety of eltrombopag treatment, in combination with the regimen of h-ATG and CsA, in immunosuppressive therapy-naïve subjects with SAA. This study followed an adaptive design which is commonly used in phase I/II single arm trials to assess response rate at an interim time point and allow early termination of a cohort if efficacy is not shown.

Complete response rate at Month 6 was the primary endpoint and it was defined as absolute neutrophil count >1×103/ µL, and platelet count >100×103/ µL, and Hgb>10 g/dL.

Overall, the pivotal study submitted included treatment-naïve patients with SAA in principle not candidates to HCT. In all 30 patients were included in cohort 1, 31 in cohort 2 and 3. In addition, it was proposed to add the extension cohort to recruit more subjects with the same dosing regimen as Cohort 3, and collect more data for the analysis of the secondary endpoints within the target regimen.

3.2. Favourable effects

Complete response (CR), the primary endpoint, was observed in 33.3%, 25.8% and 58.1% of subjects in cohort 1, cohort 2 and cohort 3, respectively (FAS population) at month 6 of treatment. When cohort 3 and the extension cohort were pooled (cut-off 28 feb-2018) CR was observed in 43.7% of patients at month 6.

More than 75% of the whole population achieved an OR (PR or CR) at month 3 (76.7%, 77.4%, 87.1% and 79.6%, for Cohort 1, 2, 3 and 3+extension, respectively) and improved at month 6 (80%, 87.1%, 93.51% and 84.8%, for Cohort 1, 2, 3 and 3+extension, respectively). Updated data have been provided with a cut-off of February 2018 for study AUS01T. In this study, eltrombopag has a durable effect since 50% of patients achieved a complete response at any time, and 83.1% of them still responded at month 18. Among the patients with overall response during the study (76.1%), 72.9% of patients still responded 18 months later.

Some comparisons versus historical controls have been provided, suggesting that the combination could have better efficacy in adults over h-ATG+CsA alone in terms of CR at month 6.

3.3. Uncertainties and limitations about favourable effects

Study AUS01T is a small phase I/II study in which 92 patients were included in cohort 3+extension (cut-off 28-February 2018). This study followed an adaptive design that it is acceptable in early steps of development where dose response and the best regimen are being studied. However, this study has been submitted as the pivotal evidence for efficacy in the new indication. Although conducting a randomized controlled trial in this clinical setting may be challenging, the performance of a controlled trial would have been crucial to assess in a robust way the efficacy results in the treatment-naïve severe aplastic anemia. In fact, a study comparing hATG+CsA vs hATG+CsA+Eltrombopag for SAA (Study RACE) sponsored by European Group for Blood and Marrow Transplantation with Novartis and Pfizer as collaborators is ongoing showing that a comparative study to support the first line indication in SAA patients is feasible.

The absence of a comparator is the main limitation for the assessment of the addition of eltrombopag to IST. In the comparison versus historical controls the MAH has made an effort to match patients to assure the comparability of the groups. However, the use of external comparators has relevant limitations since in the absence of randomisation it is not possible to control all known and unknown prognostic factors that can have an impact on the results. For a robust evaluation of efficacy, a phase III trial with randomisation and a comparison with the standard treatment would be needed. Since the RACE study differs mainly in the dose regimen of IST and eltrombopag in relation to AUS01T study, this study could be considered supportive for a 1st line indication when results become available.

The maintenance of the effect beyond 6 months is not demonstrated as a decline in OR is observed at month 12 for patients on all cohorts. The MAH has provided updated results (cut-off of February 2018) showing that 83.1% of patients who achieved a CR at any time of the study and 72.9% of those with OR during the study still responded 18 months later, but it should be considered that patients did not receive eltrombopag beyond month 6 while they remained on CsA for the whole follow-up period. Therefore, the prolonged effect is likely to be related to the continuous administration of CsA.

Data on the effect of eltrombopag + IST on transfusion requirements are clinically relevant and important from the patient perspective. While the MAH states that transfusion data were not systematically

recorded in study AUS01T it is known that legislation compels blood transfusion centres/hospitals to record every transfusion done including information about the receptors (i.e. type and date of transfusion as well as patient identification). The MAH has provided some data on transfusion-free interval. However, the lack of a comparator in the pivotal study is the key point that prevents from concluding on the true benefit/risk balance of Revolade as first line option in SAA patients.

No efficacy data are available for r-ATG. Considering that the only ATG available in different countries in the EU is r-ATG, this could potentially have an impact on the efficacy results. Available data comparing both ATG efficacy are conflicting and it is not possible to reach a clear conclusion on if one of the two ATG performs better. Information on the type of ATG used in the trial would have had to be included in the SmPC if this application would have been considered acceptable.

Few children and adolescents were included in study AUS01T. Updated data (cut-off 28-Feb_2018) contributed with 13 children older than 12 years of age of whom only 6 patients reached CR. None of the patients in the subgroup of 2-5 years of age and only 1 out of 11 patients between 6 and 11 years old reached CR. Although efficacy in adolescents seems similar to that in adults it is based on very limited data and the comparison with historical studies was not feasible due to the lack of efficacy data by age group in those studies. Therefore, the inclusion of this population in the indication is not sufficiently supported.

3.4. Unfavourable effects

Overall, the safety and tolerability of eltrombopag in treatment-naive SAA patients appears consistent with what was shown in previous indications as no new or unexpected findings have been identified. Most of the AE and SAE identified are related to the underlying condition and are manageable in clinical practice.

In study AUS01T the most common AEs (regardless of causal relationship to study drug) observed with an incidence ≥10% were febrile neutropenia (known to occur in SAA), ALT/AST increase (known to occur with eltrombopag, h-ATG and CsA), blood bilirubin increase and serum sickness (known to occur with h-ATG).

No deaths related to the study treatment were reported.

Few AEs led to treatment discontinuation: Of 6, 1 AE of encephalopathy (leading to the on-treatment death as above), 4 AEs of rash, and 1 AE of colitis. Most of the AEs requiring dose interruption/adjustment (17 subjects) were increased ALT and AST.

Regarding the adverse events of special interest already described, no events of recurrence of thrombocytopenia, bone marrow fibrosis, or hematologic malignancies were reported. Renal events, thromboembolic events and bleeding events were rare in all cohorts. None of these events led to treatment discontinuation or to dose interruption/adjustment.

A serious complication of AA is its evolution to clonal hematologic diseases such as myelodisplasia and leukemia, which is usually associated with the appearance of a cytogenetic abnormality in bone marrow cells. In Study AUS01T, clonal cytogenetic evolution occurred in 9 of 123 (7%) subjects which is not higher compared to historical data, with 5 events of clonal evolution occurred within 6.1 months of starting treatment, 4 of which had abnormalities in chromosome 7. These observations are consistent with what has been reported in the studies in refractory SAA subjects who received eltrombopag alone (Study US18T and Study US28T).

3.5. Uncertainties and limitations about unfavourable effects

The assessment of safety of eltrombopag in this population is hampered by the severity of the underlying condition, the lack of control arm and the overall limited database. Although the safety profile seems similar to that observed for the refractory SAA indication the lack of comparator prevents from ascertaining which adverse events are related to the addition of eltrombopag.

A final conclusion about the early onset of cytogenetic abnormalities relative to SAA, immunosuppressant treatment or eltrombopag cannot be reached until having more data on a higher number of patients with a long-term follow-up more data on additional subjects is needed. In this regard, "cytogenetic abnormalities" is already included in the RMP as an important potential risk.

Six deaths (5 on-treatment and 1 in screening) have been reported in study SOAR. The aim of this study was to assess the efficacy and safety of the combination of eltrombopag and cyclosporine alone in naïve SAA patients. The impact that this can have in the B/R balance of the current application is unknown. The MAH has provided information about the possible reasons regarding these deaths. In principle, the available data do not suggest that eltrombopag is the cause. The lack of efficacy related to the infra-therapeutic dose of CsA and the lack of h-ATG in the treatment scheme were discarded. This issue can only be further understood when the SOAR study will end.

3.6. Effects Table

Table 65: Effects Table for Revolade in SAA naïve patients in association with IST treatment (data cut-off: 28/February/2018).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
CR	Complete response rate at 6 months as absolute neutrophil count>1x10^3/µl, platelet count >100x10^3/µl and Hb>10 g/dl	%	43.7%	20.0% 11.9% 25.0%	26.9%(14.6;39.3)[1] 28.4%(13.0;43.7)[1] 27.1%(11.7;42.5)[1]	Scheinberg et al 2011. Scheinberg et al 2009. Tisdale et al 2000.
OR	(PR+CR) at month 6. PR as equivalent to at least 2 of the 3 criteria of absolute neutrophil count > 500/µL, Platelet count > 20x10^3/µL and reticulocyte count > 60x10^3/µL	%	79.3%	68.3% 61.9% 61.5% 56.3%	16.3%(5.8;26.7)[1] 10.4%(-3.4;24.3)[1] 9.9%(-2.4;22.1)[1]	Scheinberg et al 2011. Scheinberg et al 2009. Rosenfeld et al 2003.Tisdale et al 2000.
Unfavourable Effects						
Febrile neutropenia		%	6.5%	[2]		
ALT/AST increase		%	28.3% /17.4%	[2]		
Blood bilirubin		%	16.3%	[2]		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
increase						
Serum sickness		%	6.5%	(2)		
Clonal disease		%	7%	(2)		

OR=Overall response; PR= partial responses.

(1) Indirect comparisons to pooled historical control using fixed effects model, propensity scores matching and IPTW propensity scores, respectively.

(2) Data presented in publication from the historical studies appears similar to AUS01T study.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The only curative treatment is the hematopoietic cell transplantation (HCT). In patients who are not candidate to hematopoietic cell transplantation treatment is based on immunosuppressant therapy (IST) with ATG/CsA. As there are still patients who do not achieve a complete haematological response with this treatment any medicinal product improving clinical outcomes is welcome.

In this variation the MAH is seeking the first line use of eltrombopag+IST in SAA patients. Efficacy results for the whole population show that around 44% of patients reached CR (primary endpoint) and 79% achieved OR (CR or PR) at month 6 when treated with eltrombopag+IST. However, the lack of a direct comparison versus the current standard of care severely limits the efficacy conclusions.

Data on haematological response from AUS01T study were compared with historical data that used standard of care. Data seem promising but the limitations of such comparisons are well known and prevent from drawing any sound conclusions. A randomised clinical trial showing better results of the combination versus IST alone would solve the uncertainties. Other relevant clinical data are transfusion requirements that have an important impact on morbidity and QoL of patients. As stated by the MAH, these data were not systematically recorded in AUS01T study, although legislation regarding transfusions compels blood transfusion centres/hospitals to record every transfusion done including information about the receptors (i.e type and date of transfusion as well as patient identification). The MAH provided some data on transfusion-free interval. However, the lack of a comparator in the pivotal study remains the main unresolved issue that prevents from concluding on the positive benefit/risk balance of Revolade as first line option in SAA patients.

In relation to the maintenance of the effect, since patients did not received eltrombopag after Month 6 the effect beyond this time point is likely to be related to the continuous administration of CsA.

3.7.2. Balance of benefits and risks

Improvement in blood counts has been shown over time in study AUS01T. However, the evidence provided is weak as it comes from a phase I/II, single arm clinical trial in combination with IST and mainly relies on the haematological response compared with historical controls. Such comparisons are problematic due to the impossibility that all known and unknown prognostic factors that can impact on the results have been controlled in the absence of randomisation. These limitations prevent reaching a sound conclusion on the contribution of Revolade to the effect observed. Data on improvement of transfusion-free interval and the correlation between complete responses and longer relapse-free survival have been provided. However, no comparison versus IST has been given.

The safety profile of eltrombopag in naive SAA patients seems similar to that of the refractory SAA population although the data provided are rather limited. Nevertheless, whether there are relevant

differences in the safety profile between eltrombopag + IST and the standard IST alone, cannot be answered due to the lack of comparator.

Uncertainties remain on the potential risk of inducing cytogenetic abnormalities/MDS progression, given that these are expected findings in the studied population.

There are scarce data in paediatric population and efficacy in children younger than 11 years of age has not been demonstrated. For adolescents, efficacy has not been sufficiently demonstrated. Given all this, a conclusion on the benefit/risk balance for this population is not possible.

Some treatment effect of eltrombopag on top of IST as first line treatment in SAA adults in terms of CR and OR has been found. Data provided are encouraging despite the difficult interpretation caused by the lack of a comparator arm in the clinical trial receiving IST alone. The use of external cohorts for comparison with standard of care suggest better response with the addition of eltrombopag but the limitations of such comparisons are well known and alleviate only partially the concerns.

The safety profile of eltrombopag in naive SAA patients seems similar to that of the refractory SAA population although the data provided are rather limited. Nevertheless, whether there are relevant differences in the safety profile between eltrombopag + IST and the standard IST alone, cannot be answered due to the lack of comparator. Reported alteration of liver function suggest that they are related to the addition of eltrombopag to IST.

The benefit-risk balance for eltrombopag for the first-line treatment of acquired severe aplastic anaemia (SAA) in combination with standard immunosuppressive therapy in adult and paediatric patients aged 12 years and above who are not eligible for a haematopoietic stem cell transplant at the time of diagnosis is negative.

The study RACE, comparing eltrombopag+IST versus IST in adult SAA patients, currently ongoing, could be used only as supportive evidence considering the differences in the posology with the pivotal trial. A comparative study versus standard of care is considered necessary to demonstrate the benefit of adding eltrombopag to IST in the first line treatment of SAA patients.

From a safety point of view, no unexpected findings have been identified compared to the refractory SAA population. However, due to the absence of a comparator in study AUS-01T including the standard of care it is not possible to know the contribution of eltrombopag to the safety profile of the combination in this setting.

3.7.3. Additional considerations on the benefit-risk balance

Data in adolescent and children are specially limited and it is not possible to conclude on the benefit/risk balance in this subsets.

3.8. Conclusions

The overall B/R of Revolade is negative.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation not acceptable and therefore does not recommend by a majority of 31 out of 33 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of Indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia for Revolade in combination with standard immunosuppressive therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 50 has also been submitted.

During the initial application, the company changed the indication to patients aged 12 years and above.

Grounds for refusal

Whereas:

- The efficacy and safety data of eltrombopag on top of standard of care as first line treatment of patients with severe aplastic anemia has not been sufficiently demonstrated. The submitted data, based on study NIH AUS01T, do not allow a reliable and valid assessment of the benefit of Revolade when added to the standard of care (SOC) due to the lack of a robust comparison against established treatment. The indirect comparison with historical data cannot overcome this deficiency.

Therefore, it is not possible to establish a positive benefit risk balance for Revolade in the proposed indication.

Divergent positions to the majority recommendation are appended to this report.

5. Re-examination of the CHMP opinion of 27 June 2019

Following the CHMP conclusion that Revolade was not approvable because the efficacy and safety data of eltrombopag on top of standard of care as first line treatment of patients with severe aplastic anaemia has not been sufficiently demonstrated, the MAH submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The MAH presented in writing and at an oral explanation arguments refuting the grounds for refusal. The MAH argumentation was as follows:

Grounds for refusal:

- The efficacy and safety data of eltrombopag on top of standard of care as first line treatment of patients with severe aplastic anaemia has not been sufficiently demonstrated. The submitted data, based on study NIH AUS01T, do not allow a reliable and valid assessment of the benefit of Revolade when added to the standard of care (SOC) due to the lack of a robust comparison against established treatment. The indirect comparison with historical data cannot overcome this deficiency.

Executive summary

Novartis acknowledges the Agency's concern on the lack of a robust comparison against the established treatment in the pivotal study AUS01T and the challenges generally faced with single-arm studies to adequately assess clinical benefit of a treatment. Nonetheless, Novartis is of the opinion that the results

shown in AUS01T in consideration of the high unmet medical need for patients with SAA who are unsuitable for a HSCT, justify the addition of eltrombopag to standard IST (h-ATG/CsA) for the first-line treatment of SAA.

As of today, the treatment of SAA with standard IST (h-ATG/CsA) remains suboptimal with few complete responses and high rate of relapses and refractoriness (Desmond et al. 2015, Townsley et al. 2017). These patients remain at risk of morbidities due to prolonged pancytopenia which is difficult for patients to sustain and for treating physicians to manage (Desmond et al. 2015, Scheinberg. 2018, Townsley et al. 2017). The outcome of SAA patients being treated with standard IST (h-ATG/CsA) is predictable and has not changed for the last 20 years despite many endeavours in trying to improve this outcome through using additional immunosuppressive agents or adding growth factors, until eltrombopag, a thrombopoeitin mimetic, has proven efficacy in the refractory SAA setting, through stimulation of the bone marrow stem and progenitor cells (Desmond et al. 2015, Townsley et al. 2017). Based on this novel discovery and the exciting prospect of breaking the 'ceiling effect' in response that has been observed for so long with IST alone, the AUS01T trial was set up to investigate eltrombopag in combination with standard IST (h-ATG/CsA) for the first-line treatment of SAA (Desmond et al. 2015, Scheinberg. 2018, Townsley et al. 2017).

At the time the AUS01T study was designed, eltrombopag treatment had never been initiated together with h-ATG and CsA, thus uncertainties existed on the tolerability and efficacy of this triple drug regimen. Therefore, the design of the AUS01T pilot study was adapted for each cohort based on the accumulated knowledge from previous cohorts to optimize the treatment regimen. The highest quality and durability of haematological response was observed in Cohort 3 + Extension when eltrombopag was added concomitantly on Day 1 to IST for 6 months, followed by low dose of maintenance CsA treatment: a complete response (CR) rate of 44% and an overall response (OR) rate of 79%.

In the absence of a direct comparison against the standard of care in the AUS01T study, the study results were compared to high-quality and rigorously selected historical controls, confirming the unprecedented treatment effect observed by adding eltrombopag to IST in the first-line SAA setting (2-3-fold increase in CR rate observed in AUS01T; see section 3.4.2). The safety of the combination of eltrombopag with IST was acceptable with no patient discontinuing for a hepatic event and no increase of the rate of clonal evolutions; the safety profile was in line with the already known safety of the three drugs, as reported in their respective product information, further supporting the positive benefit-risk of adding eltrombopag to IST for the first-line treatment of SAA.

In addition to the above and in order to address the Agency's concern on the lack of representativeness in the historical controls, Novartis conducted a sensitivity analysis comparing the results of the AUS01T study to a broader list of studies that did not meet the initial stringent selection criteria for the historical controls. The results of these analyses are consistent with the findings of the primary comparison to the historical control and further confirm the conclusion that eltrombopag when added to IST, brings a significant increase in haematological response (see section 3.6).

Novartis also engaged discussions with the EBMT in order to provide early data from the RACE study during the re-examination process of this application.

In summary, the key points discussed in this detailed grounds for re-examination include:

- Unmet medical need for SAA patients remains high despite IST treatment and with no drug currently approved in EU for this disease;
- The current standard of care in SAA is shifting worldwide to use eltrombopag in combination with IST for the first-line treatment of SAA;

- Significant and robust improvement in CR rate observed in a well-designed study AUS01T by the NIH, as compared to matched historical controls;
- The responses in AUS01T (CR and OR) also compare favourably to a broader pool of historical trials conducted worldwide, which supports the generalizability of AUS01T findings;
- Safety profile of eltrombopag in first-line SAA is in line with the known safety profile in the other approved indications, with no new safety signals identified.

Based on this, Novartis strongly believes that the benefit of adding eltrombopag to IST for the first-line treatment of SAA patients outweighs the risks and justifies the present request for re-examination.

Novartis remains committed to help make this disease-modifying treatment available as quickly as possible in Europe to address a high unmet medical need in patients with SAA and would like to kindly request the Agency to re-evaluate its negative opinion. The detailed grounds for re-examination are presented thereafter and specifically address the Agency's major concerns:

Unmet medical need in SAA remains high despite IST

SAA is a rare, life threatening bone marrow disease characterised by tri-lineage pancytopenias and lack of haematopoietic stem and progenitor cells (HSPCs). SAA has a very low incidence in Europe and North America, with about two cases per million/year and a bimodal distribution with peaks occurring mainly in patients aged 15 to 25 years old and those over 60 (Young et al. 2006, Young and Kaufman 2008, Marsh et al 2009).

Historically, SAA was nearly uniformly a fatal diagnosis due to infections or excessive bleedings resulting from prolonged pancytopenia: untreated SAA can result in 80-90% mortality in 1-2 years (Rosenfeld et al 2003). HSCT is the preferred treatment option when possible, however, less than 30% of SAA patients are suitable candidates for HSCT due to the lack of a matched sibling donor, infectious complications, and graft failure especially in older patients (Rosenfeld et al. 2003, Desmond et al. 2015).

Treatment with IST consisting of h-ATG combined with CsA, proved to be the treatment of choice for SAA patients who do not qualify for HSCT. However, of those patients treated with this regimen, one quarter to one third will not respond, and 40% of responders relapse (Rosenfeld et al. 2003, Desmond et al. 2015, Townsley et al. 2017)

Patients who relapse or are refractory to a first course of IST may be eligible for salvage therapies including eltrombopag, however, more than half of patients who receive eltrombopag monotherapy in the refractory/relapsed setting will not respond, and those who respond usually require continued use (Desmond et al. 2015, Marsh and Kulasekararaj. 2013). Other therapies such as a second course of IST add on toxicity and do not lead to better outcome (Scheinberg et al. 2012, Scheinberg et al. 2006).

The outcome remains poor for patients who have an insufficient response to IST or relapse, with limited treatment options (Desmond et al. 2015, Townsley et al. 2017). These patients are exposed longer to higher risks of ongoing morbidity such as infections or bleeding because of their pancytopenia. Approximately 40% of unresponsive patients die within 5 years of diagnosis. Therefore, every effort to reduce the pool of SAA patients who relapse or are refractory to IST is highly preferable (Rosenfeld et al. 2003, Desmond et al. 2015, Townsley et al. 2017).

In addition to the above, it is important to note that the majority of the haematological responses observed following initial IST are partial responses, with only a few patients achieving complete responses. Partial responders remain at higher risk of morbidity and need further transfusions and ultimately relapse (Rosenfeld et al. 2003, Desmond et al. 2015).

Young age, baseline absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) are known prognostic factors in SAA and were in general associated with better response to IST (Rosenfeld et al. 2003, Scheinberg et al. 2009). However, a favourable response to IST with a better quality of response (CR versus partial response (PR)) cannot be routinely or reliably predicted (Scheinberg et al. 2009) and it is therefore not possible to identify the population of patients that will or will not respond or relapse after a first course of IST, thus making it important to treat all SAA patients early with eltrombopag combined with IST, to reduce the pool of refractory and relapsed patients who experience significant morbidity, and improve outcome overall.

It is also noteworthy to mention that since the successful addition of CsA to h-ATG, the outcome of SAA patients has not changed for over 20 years. Several efforts to introduce growth factors, androgens, other immunosuppressants (mycophenolate mofetil, sirolimus) or the use of more potent lymphocytotoxic agents (rabbit ATG, cyclophosphamide, alemtuzumab) were shown to be unsuccessful, with no improvement in response rates and/or prohibitive toxicity (Scheinberg P, Young NS. 2012). This led to the conclusion that a 'ceiling effect' was reached with IST alone, until the compelling results shown by adding eltrombopag concomitantly to IST (h-ATG/CsA) in the pivotal study AUS01T (Desmond et al. 2015, Townsley et al. 2017, Scheinberg. 2018).

In summary, in treatment-naive patients with SAA, increasing the speed and the quality of the haematologic recovery, shortens the time at risk for infections, bleeding, transfusions, clonal evolution and increases the potential for improved survival (Rosenfeld et al. 2003). Treatment with IST alone in the first-line setting is a suboptimal treatment with a predictable outcome demonstrated by decades of clinical practice, therefore, the objective of adding eltrombopag in the pivotal study AUS01T early and concomitantly to standard immunosuppressive treatment (h-ATG/CsA) aimed at both improving the quality of the response and reducing the pool of refractory patients which represent a high unmet medical need.

Rationale for using eltrombopag added to IST in first-line SAA

Aplastic anaemia is characterised by a very limited number of HSCs due to a T cell autoimmune-mediated destruction of the bone marrow. Several preclinical experiments have demonstrated positive effect of TPO and the TPO-receptor on expansion of HSPCs (Zeigler et al. 1994, Alexander et al. 1996, Kimura et al. 1998, Qian et al. 2007).

TPO is an important regulator of haematopoiesis and is known to have distinct properties in stimulating HSCs. At first, TPO was associated with megakaryocyte stimulation and platelet production (Kuter et al. 1994). However, results from *in vitro* studies indicated that the hormone played rather an important role in the stem cell proliferation and maintenance, mainly for the below reasons:

- Unlike the receptors for erythropoietin and G-CSF, the TPO-receptor (c-MPL) is expressed on HSCs (Yoshihara et al. 2007);
- In TPO knockout mice models, significant reductions in HSCs were observed in addition to megakaryocytopenia and thrombocytopenia (Alexander et al. 1996, Qian et al. 2007, Fox et al. 2002);
- TPO is frequently used with other growth factors to stimulate stem cells *in vitro* (Yoshihara et al. 2007);
- Mutations in the c-MPL results in multi-lineage cytopenias (Ballmaier et al. 2003, Ihara et al. 1999, Tonelli et al. 2000, Ballmaier et al. 2001).

Eltrombopag, a TPO receptor agonist (TPO-RA), was thought to be active in ameliorating not only megakaryocyte proliferation but also the marrow function through its involvement in HSC haematopoiesis

as well as thrombopoiesis. At first, the very high level of endogenous TPO in SAA patients suggested that TPO-RA may not be effective, however, the efficacy of eltrombopag (as monotherapy) was first confirmed through the compelling results observed in the refractory SAA setting, resulting in 40% responses including multi-lineage responses and then in the first-line SAA setting in combination with IST leading to a complete response rate of 44% (Desmond et al. 2014, Scheinberg. 2018, Townsley et al. 2017) and supported by a unique mechanism of action.

Eltrombopag was found to bind to the c-MPL at a different site than endogenous TPO. Furthermore, recent studies indicate that Interferon gamma (IFNγ) in SAA, would be released by autoreactive cytotoxic T cells (CTL) and forms heteromeric complexes with TPO, thus blocking the TPO from binding to the c-MPL at both high and low affinity, and eltrombopag is thought to evade this process (Alvado et al. 2019). All the mechanisms by which eltrombopag improves the marrow function are diverse and still being investigated (Scheinberg et al. 2018).

Considering the pathophysiology of SAA, the results of the studies investigating stronger immunosuppressant associated with the theory of a T cells mediated autoimmune disease suggest that autoimmune T cells survive the assault of IST compounded with an important destruction of the primitive haematopoietic compartment preventing the haematopoietic cells from recovering, even after the immune reaction is controlled (Scheinberg et al. 2018).

Taking this into account, eltrombopag, when added earlier and before the bone marrow becomes depleted from the immune assault, complements the immunosuppressive effect of IST by increasing the pool of haematopoietic stem cells, leading to a more robust and durable response than with IST alone (Townsley et al. 2017), which is associated with better long-term outcome and decreased risk of clonal evolution, since a larger and more heterogeneous stem cell reserve is thought to ensure less stress on individual clone thus limiting oncogenesis (Rosenfeld et al. 2003, Desmond et al. 2015).

Compelling results from a well conducted study

Study AUS01T, designed to optimize the treatment regimen

In SAA, eltrombopag was first investigated in SAA patients unresponsive to initial IST. In the dose escalation study (pivotal study supporting the refractory SAA indication) thereafter referred to as AUS028T, treatment with eltrombopag monotherapy led to a 40% response rate (Desmond et al. 2014). Multi-lineage responses as well as improvement in marrow cellularity were observed suggesting the stimulation of HSCs by eltrombopag (Desmond et al. 2015). These results were further confirmed by a subsequent Phase 2 study (AUS18T) initiated after AUS01T, in which 39 patients were treated with a 150 mg dose of eltrombopag during 6 months. Improvement in response rates was consistent with what was observed in AUS28T with 49% at Month 6 and with even more frequent multi-lineage responses given the higher starting dose and the longer duration of treatment (Winkler T et al. 2017).

Based on the results observed in the first refractory SAA study AUS028T which were later confirmed by the AUS18T study, eltrombopag was for the first time evaluated in the first-line setting in combination with the standard of care IST (CsA+h-ATG), in the pivotal study AUS01T. The intent of adding eltrombopag to IST was to counter the 'ceiling effect' in haematological responses reached by h-ATG/CsA alone and reduce the pool of refractory patients. As discussed previously, the refractoriness to IST treatment in about one third of the patients suffering from SAA, is thought to be due to a profound destruction of HSCs that could not recover, even with immunosuppression (Desmond et al. 2015).

The AUS01T is the first study in which eltrombopag was studied in combination with CsA and h-ATG and considering that the safety and efficacy of the triple drug combination was not known at the time, conducting a randomized study was considered premature. The AUS01T is a well-conducted trial by

worldwide recognised medical experts at the NIH with a broad knowledge and expertise in the treatment of SAA patients. The study was appropriately designed to optimize the treatment regimen through three sequential cohorts and an extension cohort that differed by the time and duration of treatment of eltrombopag and maintenance CsA (see Figure 3-1).

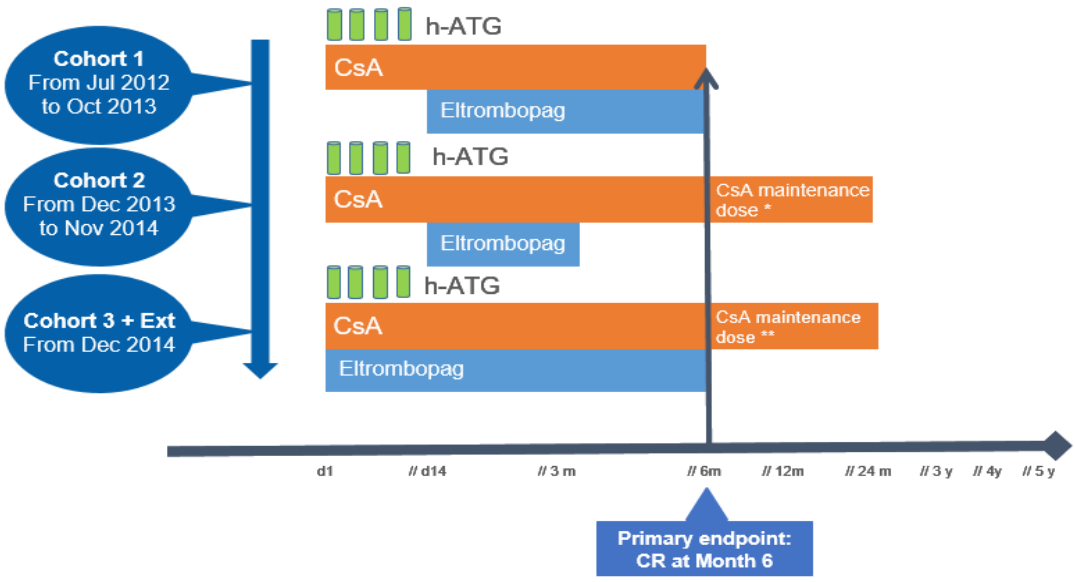
In study AUS01T, the starting dose of eltrombopag at 150 mg (75 mg in East Asian patients) was based on the results from study AUS028T, the pivotal refractory study, where all but three patients escalated eltrombopag to a 150 mg dose, and there were no responders below that dose.

In Cohort 1 of AUS01T study, eltrombopag was started at 150 mg on Day 14 and combined with standard IST (h-ATG+CsA) for a total treatment duration of 6 months. This regimen resulted in a significant CR rate of 33%. The reason for starting eltrombopag on Day 14 was to avoid potential hepatotoxicity from the combination of the three drugs.

In Cohort 2, eltrombopag was also added to IST on Day 14 at 150 mg but only given for 3 months in an effort to obtain the same promising results observed in Cohort 1 with less exposure to eltrombopag. This regimen, however, resulted in a drop of CR rate to 26%. Sustained haematological response correlates with better survival since patients are less exposed to risks for morbidities (Rosenfeld et al. 2003). Therefore, in order to maintain the responses seen by combining eltrombopag to IST with the intent to improve survival, low dose maintenance CsA was added to responding patients after Month 6.

Based on the reassuring safety results observed in Cohorts 1 and 2 and in order to increase the number of responders, in Cohort 3 + Extension, eltrombopag was administered concomitantly with h-ATG and CsA on Day 1 for a duration of 6 months followed by low dose maintenance CsA. This optimized treatment regimen resulted in a CR rate of 44%. These results confirmed the optimal treatment regimen leading to earlier and robust haematological recovery which correlates with better long-term outcome and has consequently been recommended as the proposed regimen in the current application for the extension of indication for use of Revolade (eltrombopag) in combination with IST as first-line treatment of SAA.

Figure 3-1 AUS01T study design– pivotal study investigating eltrombopag added to IST in first-line SAA



* Protocol amended to add CsA maintenance in middle of cohort in responders only
** Responders only

Significant treatment effect when eltrombopag is added to IST in first-line SAA

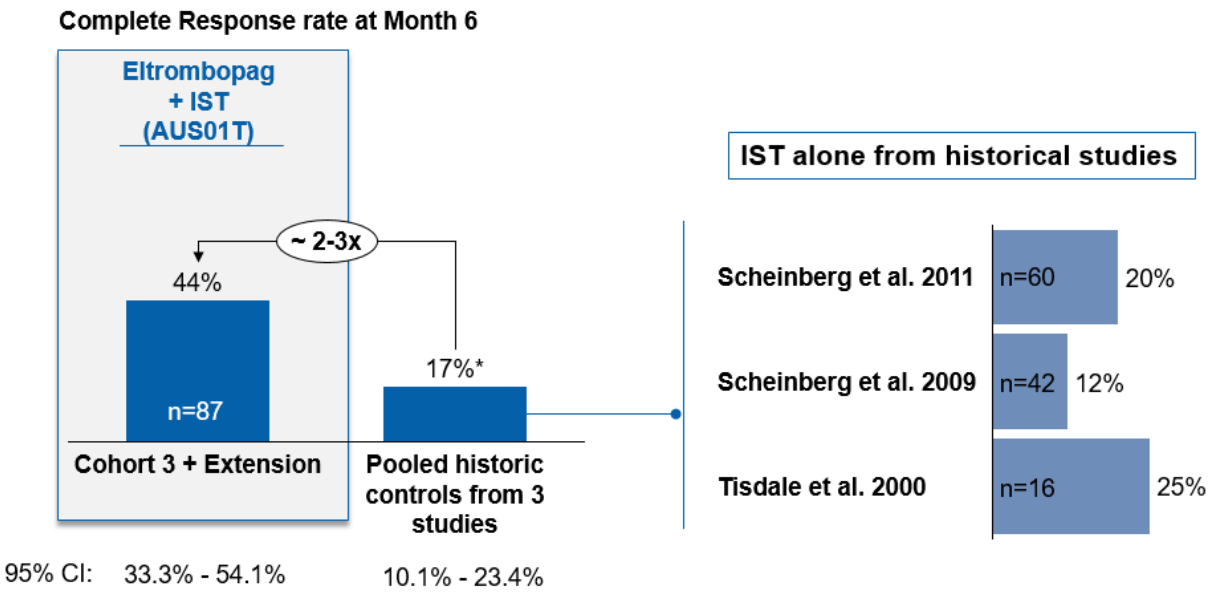
Increase in the haematological response is considered the strongest surrogate for survival in SAA and is therefore the main endpoint when assessing efficacy of a treatment (Rosenfeld et al. 2003).

The primary endpoint in study AUS01T consisting of the CR rate at Month 6, is an objective endpoint based solely on blood counts unaided by blood transfusions and growth factors and, confirmed by a second blood sample collected at least one week later.

To confirm the benefit of adding eltrombopag to IST, the CR rate observed in study AUS01T was compared to three well-matched historical studies (all conducted in the same institution - NIH) using various methods and accounting for the covariates influencing the outcome (see details in section 3.5).

The results of study AUS01T demonstrated an outstanding efficacy. The CR rate in Cohort 3 + Extension exceeded by approximately 27% the CR rate historically reported (see Figure 3-2; CR rate of 44% in AUS01T vs. historical CR rate of 17% obtained from fixed effect meta-analysis). The CR rates were consistent across the three historical control trials conducted over an extended period of time (13 years), further confirming the validity of the historical controls as well as the predictable outcome of IST alone in the first-line setting, thus assuring the acceptability of this pivotal single-arm trial in this indication.

Figure 3-2 Study AUS01T showed significantly higher CR rate compared to historical controls



*Using fixed effect model. Similar results were obtained using subject-level data from the two Scheinberg studies. OR in AUS01T is 79% compared to an OR of 63% from the pooled historical control.

In addition to the above, Novartis would like to emphasise that the results (CR and OR) of the AUS01T study observed in each cohort as well as in all cohorts combined, were higher than historically reported response rates as shown in Table 3-1 below.

Table 3-1 Response rate across cohorts

	COHORT 1 N=30	COHORT 2 N=31	COHORT 3 N=31	EXTENSION N=56	ALL COHORTS N=148
CR rate at Month 6, n (%)	10 (33)	8 (26)	18 (58)	20 (36)	56 (38)
Treatment effect vs. Hx Ctrl[a], 95%CI	17 (-2, 35)	9 (-8, 26)	41 (23, 60)	19 (5, 33)	21 (11, 31)
OR rate at Month 6, n (%)	24 (80)	27 (87)	29 (94)	40 (71)	120 (81)
Treatment effect vs. Hx Ctrl[b], 95%CI	17 (1, 33)	24 (11, 37)	31 (20, 41)	8 (-5, 22)	18 (9, 27)

([a]) Historical CR rate of 17% based on 118 patients from 3 studies, pooled using fixed effects meta-analysis

([b]) Historical OR rate of 63% based on 240 patients from 4 studies, pooled using fixed effects meta-analysis

Novartis would also like to highlight that in patients 12 years and above only, which represent the patient population included in the proposed indication, a CR rate of 49.3% (37/75) was observed in Cohort 3 + Extension, which represents a more significant improvement in CR by 32.2 % (95% confidence interval (CI): [18.9%, 45.6%]) compared to historically reported CR rate of 17% with IST alone (see details in section 3.10).

In addition to the substantially higher CR rate, the efficacy of adding eltrombopag to IST was also demonstrated through the achievement of a long transfusion-free interval and sustained response.

Rigorously selected historical control

Novartis acknowledges that a direct comparison against established treatment in a randomised trial is preferred. However, we conducted a rigorous historical control analysis to ensure comparison of the same patient population, treated with the same IST regimen (in terms of drugs, doses and duration) and evaluated using the same endpoints, in order to minimise bias.

An extensive literature search, described in detail below, was conducted to identify all similarly designed trials that have been published. This included a review of the literature, searching for clinical trials conducted in aplastic anaemia (AA) patients, regardless of the study design, treatment and endpoints.

This search was done in PubMed with the following search criteria:

(((aplastic anemia[Title]) OR aplastic anaemia[Title]) AND clinical trials) AND ("2001/01/01"[Date - Publication]: "2016/09/23"[Date - Publication])

In order to provide a reasonably contemporaneous comparison, all studies reported within a time period of approximately 15 years, 01-Jan-2001 to 23-Sept-2016, were considered for inclusion, in addition to studies prior to 01-Jan-2001 if they were mentioned in AUS01T study protocol as potential historical controls.

A total of 165 publications were retrieved with the above search. Of these, 67 met the criteria for inclusion, i.e., they were clinical studies evaluating a medical therapy in patients with severe aplastic anaemia.

As the search continued during the preparation of the dossier, a later update included publications issued from 23-Sep-2016 to 31-Dec-2017 which resulted in five additional publications, including (Townsley et al 2017) publication reporting results from AUS01T study.

In summary, a total of 71 publications, excluding Townsley et al 2017 (the subject of this application), were considered for further investigation. These trials were evaluated for inclusion using the following criteria:

- IST-naïve patients included in the trial
- IST consisting of h-ATG+CsA for at least one arm
- Definition of complete and/or overall responses based on the same criteria as in AUS01T and response rate at Month 6 reported
- IST regimen comparable to AUS01T in terms of drugs doses and durations

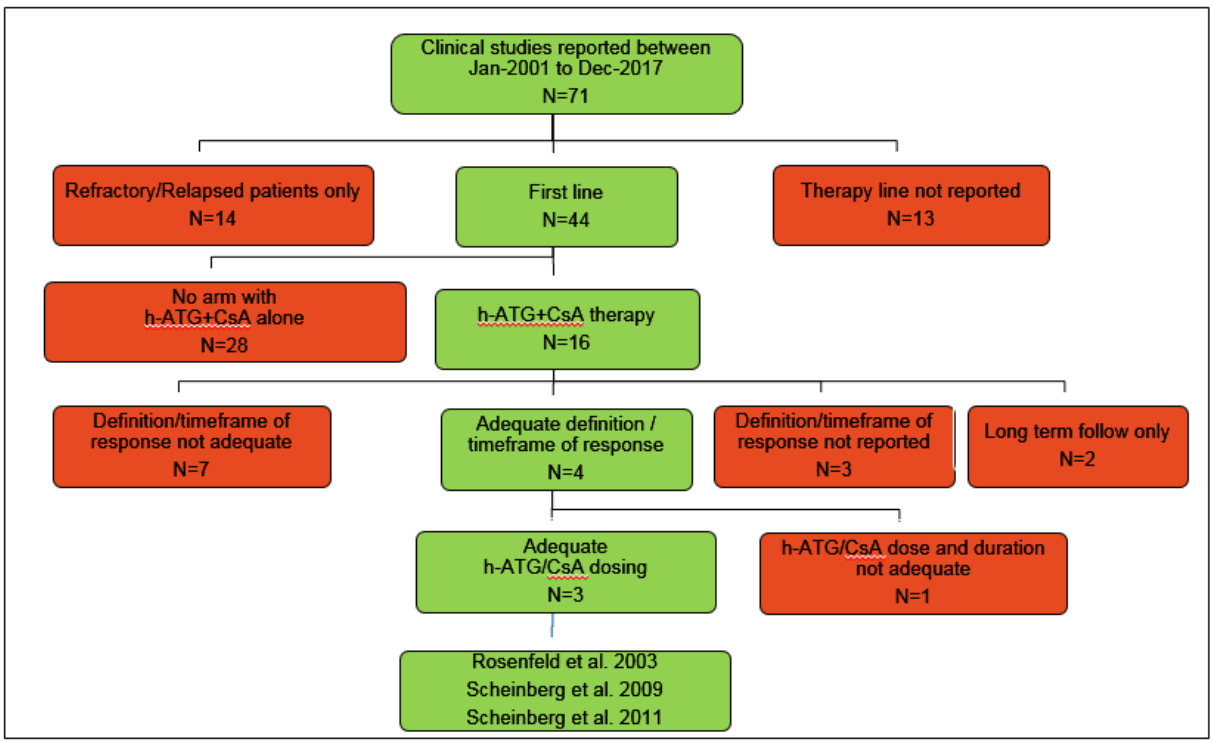
Only studies that met all the criteria above were included as historical controls.

This selection resulted in three studies (Rosenfeld et al 2003, Scheinberg et al 2009 and Scheinberg et al 2011). A fourth study mentioned in the protocol and published earlier (Tisdale et al 2000) met the above criteria and was added to the pool of historical control studies (see Figure 3-3 for details). All four studies were coincidentally conducted at the NIH, the same institution conducting study AUS01T, adding to the validity of the historical controls to minimise bias, since the standard medical management within this single institution was more likely to be similar.

For completeness, a literature search of studies published before 2001 did not show any other study that met the criteria except Tisdale et al 2000 mentioned above and Rosenfeld et al 1995 of which an updated version published in 2003 was already used as a historical control study.

Furthermore, Novartis obtained from the NIH individual patient data from the two most recent studies (Scheinberg et al 2009 and Scheinberg et al 2011), including demographic data and baseline blood counts that define the severity of the disease (age, gender, platelet count, neutrophil count and reticulocyte count). This allowed for a robust comparison to historical control, accounting for the most likely prognostic factors.

Figure 3-3 Selection of historical control studies



Note: Tisdale et al. was published in 2000 but, since it was mentioned in the protocol and it met the other selection criteria, it was added to the pool of historical studies.

In summary, Novartis is of the opinion that despite the lack of a comparator in the pivotal trial, the robust comparison to rigorously selected matched historical control data from the same institution, the NIH, has greatly compensated for the lack of a control arm in study AUS01T.

AUS01T study results compare favourably to expanded pool of historical studies

While Novartis remains of the opinion that all similarities noted between the AUS01T study and the historical controls contribute to the validity of the historical control to reduce bias, Novartis understands the Agency's concern raised during the OE on the lack of variability in the pool of historical controls considering that all were conducted at the same institution as AUS01T, which would affect the generalizability of the findings to other sites and countries.

To address this concern, Novartis relaxed the selection criteria of historical studies to allow inclusion of studies from other sites and countries and conducted sensitivity analyses comparing the results from AUS01T to those from different sets of studies.

Historical studies published at any time, either prospective or retrospective, were selected if they met the following criteria:

1. IST-naïve patients included in the trial
2. Treatment with:
    a. IST consisting of h-ATG or h-ALG (Lymphoglobulin) + CsA for at least one arm, regardless of the doses and durations
    b. Additional treatment(s) on top of h-ATG/h-ALG + CsA were allowed (e.g., growth factors, other immunosuppressive agents)
3. Definition of complete and/or overall responses based on the same parameters irrespective of the threshold considered
4. CR rate and/or OR rate at Month 6 or best CR rate and/or OR rate within 6 months or longer, reported.
5. Different definitions of response were used across these studies and are described in Table 3-2 below:

Table 3-2 Definition of response

Response	Reference	Complete response	Used in
Complete	Ref01	ANC > $1x10^9$/L PLT > $100x10^9$/L Hgb > 10 g/dL	Assi 2018, Scheinberg 2011, Scheinberg 2009, Scheinberg 2006, Tisdale 2000
	Ref02	ANC > $1.5x10^9$/L PLT > $150x10^9$/L Hgb normal for age	Peffault de Latour 2018
	Ref03	ANC > $1.5x10^9$/L PLT > $100x10^9$/L Hgb > 11 g/dL	Kosaka 2008, Teramura 2007, Zheng 2006, Bacigalupo 2000, Kojima 2000

Response	Reference	Complete response	Used in
	Ref04	ANC > 1.5x10^9/L PLT > 150x10^9/L Hgb > 11 g/dL	Tichelli 2011
	Ref05	ANC > 1.5x10^9/L PLT > 100x10^9/L Hgb > 10 g/dL	Atta 2010
Partial	Ref11	No longer meeting SAA criteria i.e. meeting at least 2 / 3: ANC > 0.5x10^9/L PLT > 20x10^9/L ARC > 60x10^9/L	Peffault de Latour 2018, Scheinberg 2011, Afable 2011, Tichelli 2011, Atta 2010, Scheinberg 2009, Teramura 2007, Scheinberg 2006, Rosenfeld 2003, Tisdale 2000
	Ref12	ANC > 0.5x10^9/L PLT > 20x10^9/L Hgb > 8 g/dL	Assi 2018, Kosaka 2008, Kojima 2000, Zheng 2006
	Ref13	ANC > 0.5x10^9/L PLT > 30x10^9/L Hgb > 8 g/dL	Bacigalupo 2000
	Ref14	ANC > 0.5x10^9/L above baseline OR PLT > 30x10^9/L above baseline OR No RBC transfusion	Kim 2003
	Ref15	ANC > 0.5x10^9/L above baseline PLT > 30x10^9/L above baseline ARC > 30x10^9/L above baseline	Frickhofen 1991

Based on the above criteria, 13 studies on top of the four studies initially selected, were retrieved. The expanded list of historical studies is provided in Table 3-3.

Table 3-3 List of historical studies

Author Year (Sites)	Multi-center	CR / PR definition	Time frame	Treatment	Arm	CR rate	OR rate
Assi 2018 (US)	No	Ref01/ Ref12	Best by Month 6	h-ATG+CsA +G-CSF		29% (5/17)	71% (12/17)
Peffault de Latour 2018 (France)	Yes	Ref02/ Ref11	Month 6	h-ATG+CsA		3% (4/142)	47% (67/142)
Afable 2011 (US)	No	Missing /Ref11	Month 6	h-ATG+CsA		6% (4/67)	58% (39/67)
Scheinberg 2011 (US)	No	Ref01/ Ref11	Month 6	h-ATG+CsA		20% (12/60)	68% (41/60)
Tichelli 2011 (EU)	Yes	Ref04/ Ref11	Best by Month 6	h-ATG+CsA +G-CSF	A	12% (12/97)	73% (71/97)
				h-ATG+CsA	B	9% (9/95)	66% (63/95)
Atta 2010 (Brazil)	No	Ref05/ Reff11	Month 6	h-ALG+CsA+ Corticosteroids +G-CSF+EPO +Androgens		12% (5/42)	60% (25/42)

Author Year (Sites)	Multi-center	CR / PR definition	Time frame	Treatment	Arm	CR rate	OR rate
Scheinberg 2009 (US)	No	Ref01/ Ref11	Month 6	h-ATG+CsA	A	12% (5/42)	62% (26/42)
				h-ATG+CsA +Sirolimus	B	0% (0/35)	51% (18/35)
Kosaka 2008 (Japan)	Yes	Ref03/ Ref12	Month 6	h-ALG+CsA	A	20% (17/84)	65% (55/84)
				h-ALG+CsA+ G-CSF	B	17% (20/117)	71% (83/117)
Teramura 2007 (Japan)	Yes	Ref03/Ref11	Month 6	h-ALG+CsA	A	6% (3/47)	55% (26/47)
				h-ALG+CsA +G-CSF	B	4% (2/48)	75% (36/48)
Scheinberg 2006 (US)	No	Ref01/ Ref11	Month 6	h-ATG+CsA +MMF		16% (16/104)	62% (64/104)
Zheng 2006 (China)	No	Ref03/ Ref12	Best by Month 6	h-ALG+CsA	A	60% (28/47)	79% (37/47)
				h-ALG+CsA +G-CSF+EPO	B	60% (18/30)	73% (22/30)
Kim 2003 (South Korea)	No	NA/Ref14	Best by Month 6	h-ATG+CsA		N/A	53% (9/17)
Rosenfeld 2003 (US)	No	NA/Ref11	Month 6	h-ATG+CsA		N/A	61% (74/122)
Bacigalupo 2000 (EU, Australia)	Yes	Ref03/ Ref13	Best, no time frame defined	h-ALG+CsA +G-CSF		48% (48/100)	77% (77/100)
Kojima 2000 (Japan)	Yes	Ref03/ Ref12	Month 6	h-ALG+CsA+ G-CSF+Danazol	A	30% (14/46)	67% (43/64)
				h-ALG+CsA G-CSF	B	N/A	83% (15/18)
Tisdale 2000 (US)	No	Ref01/ Ref11	Month 6	h-ATG+CsA		25% (4/16)	56% (9/16)
Frickhofen 1991 (Germany)	Yes	NA/ Ref15	Month 6	h-ALG+CsA		N/A	65% (20/31)

The resulting historical studies have the following features:

- All studies enrolled IST-naive SAA patients, commonly defined based on Camitta criteria (Camitta et al. 1975), similar to AUS01T study;
- All studies used either h-ATG (ATGAM) at a dose of 40 mg/kg/day for 4 days or h-ALG (Lymphoglobulin) at a dose of 12 to 15 mg/kg/day for 5 days, similar to AUS01T study (assuming that h-ATG and h-ALG are interchangeable);
- All studies used CsA for at least 6 months with one exception (study Teramura 2007) with variable starting dose that was adjusted based on cyclosporine concentrations targeting a therapeutic range of 100 to 400 ng/µL, similar to AUS01T study;
- In some studies, growth factors (G-CSF, EPO), or other immunosuppressive agents (MMF, sirolimus, etc.) were given on top of h-ATG/ h-ALG + CsA.
- CR definition was either similar to the one used in AUS01T study or more stringent;
- PR definition was similar or comparable to the one used in AUS01T study;

- Either the response at Month 6 or the best response within 6 months was reported, except in Bacigalupo 2000 where the timeframe for the best response was not defined.

Several sensitivity analyses for both CR and OR rates, using random effects meta-analyses (due to high heterogeneity between studies), were performed with the following subsets of studies:

1. All historical studies reporting the response rate at Month 6 and using h-ATG + CsA only.
2. All historical studies reporting the response rate at Month 6 and using h-ATG or h-ALG + CsA only.
3. All historical studies which used h-ATG or h-ALG + CsA only, i.e., with no additional treatment such as growth factors or other immunosuppressive agents and reporting either the response at Month 6 or the best response over time (usually by Month 6);
4. All historical studies;

Of note, studies with more than one treatment arm using h-ATG or h-ALG + CsA, with and without other treatments, were analysed separately for each arm.

The CR rate for all historical studies is displayed in Figure 3-4 which shows a high heterogeneity between studies reflecting the heterogeneity of the definitions of CR across studies. In most of the studies, the CR rate ranged between 10 and 30%, however, some studies reported more extreme results as outlined below:

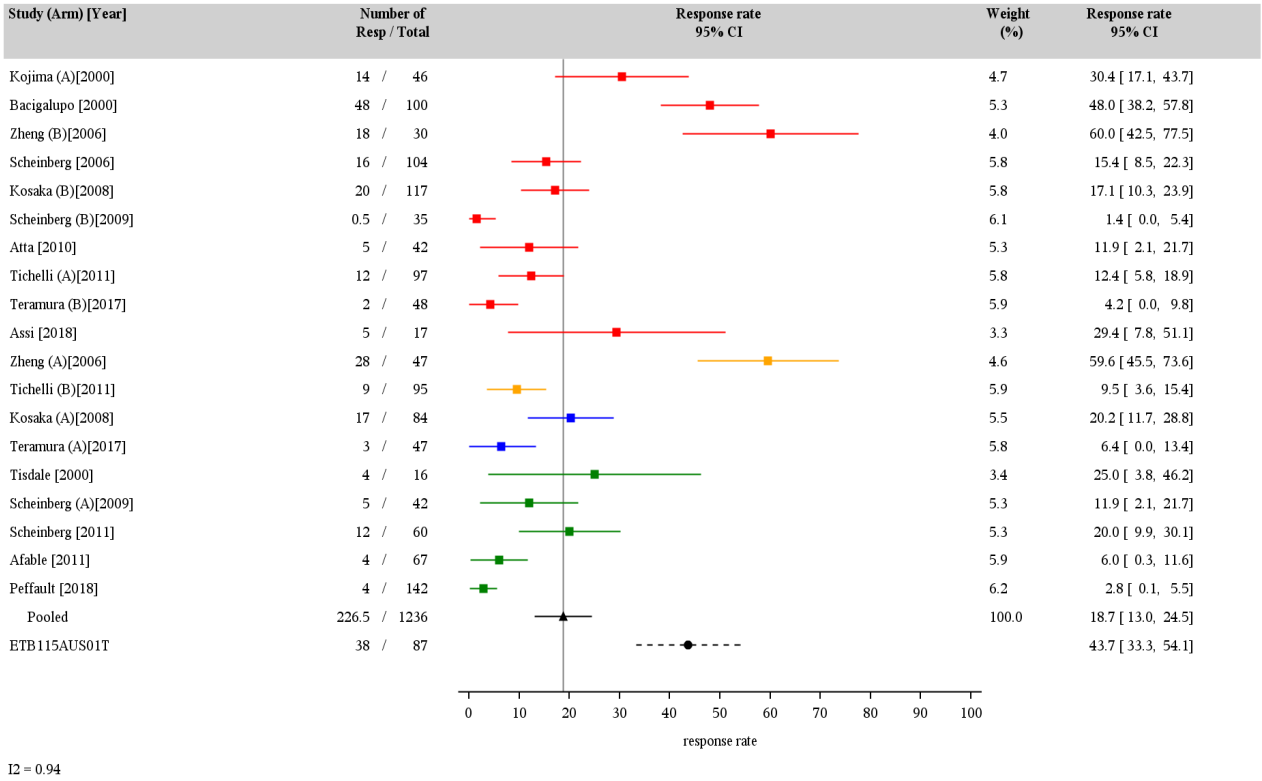
Two historical studies showed higher than expected CR rates:

- Bacigalupo et al. 2000 reported only the CR rate (48%) after one or more courses of h-ATG + CsA + G-CSF. The CR rate after one course of this treatment was not reported and likely much lower, considering that the OR rate after only one course was 50% as compared to 77% after one or more courses.
- Zheng et al. 2006 reported a CR rate of 60% in patients treated with h-ALG+CsA and the same 60% in those treated with h-ALG+CsA+G-CSG+EPO. The publication did not provide an explanation for this unprecedented finding. Such CR rate was never observed in other studies using h-ALG + CsA only.

In contrast, the below historical studies showed very low CR rates:

- Scheinberg et al. 2009 reported a CR rate of 0% in patients treated with h-ATG+CsA+sirolimus. In contrast, patients treated with h-ATG+CsA alone had a CR rate of 12%;
- Peffault de Latour et al. 2018 reported a CR rate of 2.8% which may be explained by the more stringent definition of CR (normal Hb for age, ANC > $1.5x10^9$/L and PLT > 150x109/L);
- Afable et al. 2011 reported a CR rate of 6% in patients treated with h-ATG+CsA only, but the definition of CR was not provided. The publication did not provide an explanation for this low CR rate;
- Teramura et al. 2007 reported a CR rate of 6.4% in patients treated with h-ALG + CsA and 4.2% in those treated with h-ALG + CsA + G-CSF. The CR definition is slightly more stringent than NIH definition;

Figure 3-4 CR rates from historical studies vs. AUS01T Cohort 3 + Extension



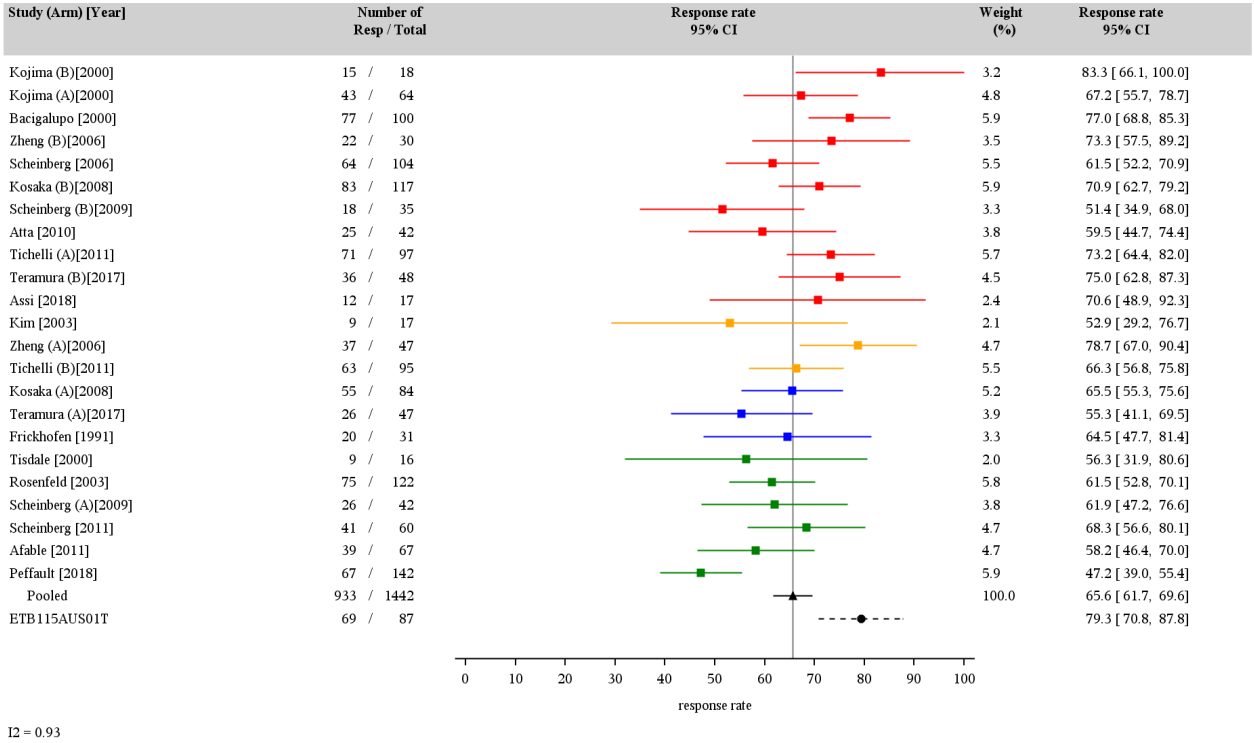
Pooled CR rate was estimated using a random effects meta-analysis.
Confidence intervals are plotted in:

- Green for studies which used h-ATG + CsA only and response at 6 Months,
- Blue for studies which used h-ALG + CsA only with response at 6 Months
- Orange for studies which used h-ATG/h-ALG + CsA with best response,
- Red for studies which used other treatments on top of h-ATG/h-ALG + CsA.

Scheinberg (B) [2009] had no CR; a value of 0.5 complete response was assigned to allow its inclusion in the analysis.
Studies with more than one treatment arm using h-ATG/h-ALG+CsA ± other treatments, are analyzed separately for each arm.

Most of the studies reported an OR rate > 50% with the exception of Peffault de Latour et al. 2018 who reported an OR rate of 47% despite using the same definition as the AUS01T study, see Figure 3-5 below.

Figure 3-5 OR rates from historical studies vs. AUS01T Cohort 3 + Extension



Pooled OR rate was estimated using a random effects meta-analysis.
Confidence intervals are plotted in:

- Green for studies which used h-ATG + CsA only and response at 6 Months,
- Blue for studies which used h-ALG + CsA only with response at 6 Months
- Orange for studies which used h-ATG/h-ALG + CsA with best response,
- Red for studies which used other treatments on top of h-ATG/h-ALG + CsA.

Studies with more than one treatment arm using h-ATG/h-ALG+CsA ± other treatments, are analyzed separately for each arm.

These sensitivity analyses led to similar results as the primary comparison to originally selected historical studies, demonstrating the robustness of the comparison of AUS01T to historical control as shown in Table 3-4 below:

Table 3-4 Comparison of AUS01T to historical control using random effects meta-analysis

	Treatment effect (AUS01T – Control) [95% confidence interval	
Set of historical studies	**CR rate**	**OR rate**
Primary analysis initially reported	27.0% [14.6%, 39.3%]	16.3% [5.8%, 26.7%]
Studies using h-ATG + CsA only and response at Month 6	33.5% [21.1%, 45.9%]	20.8% [9.8%, 31.8%]
Studies using h-ATG or h-ALG + CsA only and response at Month 6	32.6% [20.6%, 44.5%]	19.8% [9.9%, 29.8%]
Studies using h-ATG or h-ALG + CsA only and either best response or response at Month 6	27.6% [14.7%, 40.5%]	17.5% [7.4%, 27.5%]
All historical studies	24.9% [13.1%, 36.8%]	13.7% [4.3% , 23.1%]

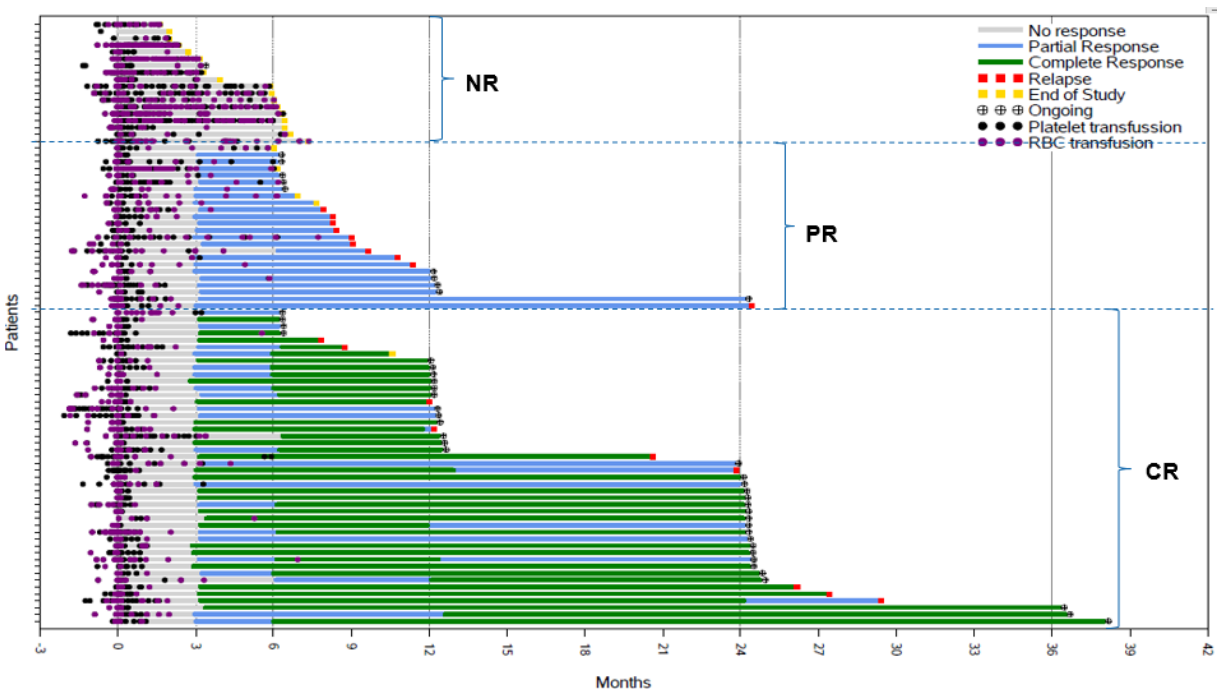
In conclusion, in the AUS01T study, the addition of eltrombopag to h-ATG + CsA increased the CR rate at Month 6 by at least 25 percentage points as compared to historically reported CR rate with IST alone or the combination of IST and growth factors, further confirming that eltrombopag when added to IST led to a significant improvement in haematological response.

Clinical significance of the haematological response – reduction in transfusion burden

The improvement in haematological response, especially achieving a complete response is a surrogate for reduction in morbidities usually due to bleeding events and infections in SAA (Rosenfeld et al. 2003). Although achieving a complete response should also per definition translate into reduction in transfusions, Novartis agrees with the Agency that a correlation between the haematological response and reduction in transfusion burden should be demonstrated. Therefore, following the requests from the Agency, we collected retrospectively all available transfusion data from patients in Cohort 3+ Extension from the NIH blood bank and referral sites.

Based on all collected transfusion data, patients in study AUS01T who achieved haematological responses, demonstrated a substantial reduction in transfusion needs, and as expected, those who achieved complete responses had the best outcome in terms of reduction in transfusion burden and durability of response. This is highly relevant for SAA patients as it clearly correlates the improvement in the haematological response with clinical benefit and better quality of life, considering that these patients were heavily transfused at baseline (by study Day 1) and in the first months until they responded, of either platelets, package red blood cells (pRBC) or both. This can be appreciated from Figure 3-6 that displays individual patients' status and associated transfusion needs and shows that: non-responders continued to be heavily transfused, whereas partial responders required none or much less transfusions, and complete responders no longer required transfusions. This figure also shows that complete responders maintained their response much longer than partial responders as demonstrated by less or later relapses in patients with CRs versus PRs.

Figure 3-6 Plot of patient status over time and transfusion data in Cohort 3 and Extension cohort

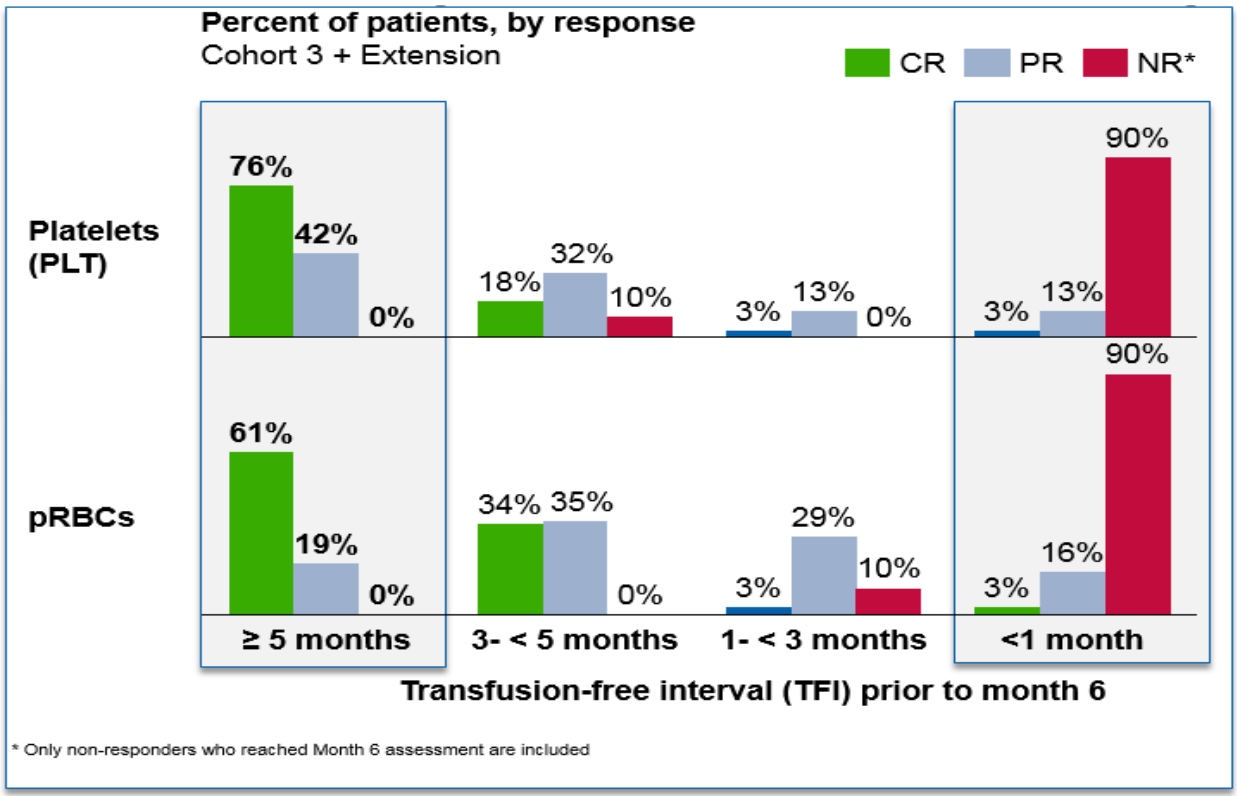


Further to the above, it was also observed that patients who achieved the best responses showed increases in transfusion-free intervals and increased duration of response:

In Cohort 3 + Extension, the median platelet transfusion-free interval prior to Month 6 response assessment, defined as the time from the date of the most recent platelet transfusion prior to Month 6 assessment to the date of Month 6 response assessment, was 164 days, 145 days and 6 days in CR, PR and non-responder (NR) patients, respectively (see [HAQ Table 14.3-1.13r]). Similarly, the pRBC transfusion-free interval prior to Month 6 response assessment was 159.5 days, 114 days and 7.5 days in CR, PR and NR patients, respectively (see [HAQ Table 14.3-1.14r]).

To emphasize the association between the quality of response and transfusion requirement, the transfusion-free interval was categorized and displayed in Figure 3-7 below.

Figure 3-7 Transfusion-free interval prior to Month 6 response



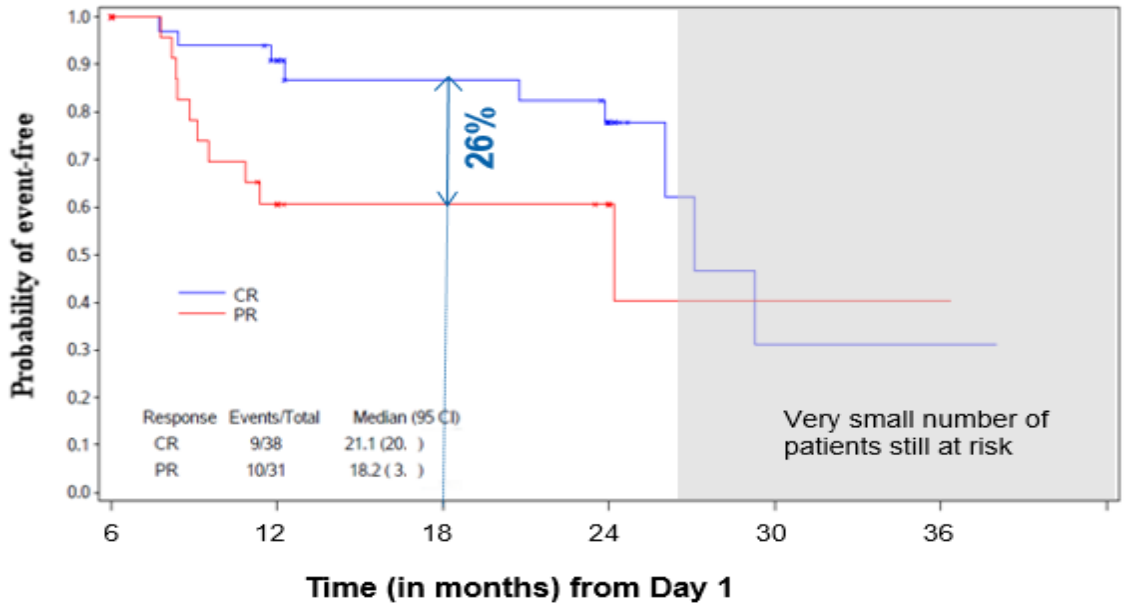
In summary, the above confirms that improving the quality of the haematological response in AUS01T, clearly correlated with less transfusions, longer transfusion-free intervals, less or delayed relapses translating into no or shorter exposure to morbidities, all confirming the clinical benefit and an improvement in quality of life derived from the achievement of complete response.

Contribution of eltrombopag added to IST to long-term effect

The comparison to historical control studies demonstrated that the addition of eltrombopag to IST significantly increased the CR rate at Month 6 as compared to what was historically reported with IST alone (see Figure 3-2). Novartis would like to emphasise that the use of eltrombopag concurrently with CsA and h-ATG in the AUS01T study was during the first 6 months of treatment, followed by lower maintenance dose of CsA alone in responders for 18 months, i.e., until Month 24, to support the maintenance of the responses achieved at 6 months and to reduce the number of relapses. The comparison of haematological response observed in AUS01T versus historical control was done at Month 6 before the start of CsA maintenance dose and is therefore not affected by the latter.

The maintenance of response is not solely due to CsA maintenance dose. By improving the CR rate, eltrombopag when added to IST also contributes to the maintenance of the response. Indeed, as shown in Figure 3-8, the duration of response in patients from Cohort 3+ Ext, all treated with CsA maintenance dose, who achieved a CR is longer compared to patients who achieved a PR, indicating that the quality of response, to which eltrombopag contributed substantially, is associated with better long-term outcome.

Figure 3-8 Kaplan-Meir plot of duration of response by the quality of response at Month 6 in Cohort 3 + Extension



Number of patients still at risk

CR	38	28	20	10	2	2	0
PR	31	13	7	4	1	1	0

To further address the Agency`s concern on the long-term benefit of adding eltrombopag to IST, Novartis would like to clarify that there were indeed 6 patients who did not receive CsA maintenance dose (#006, 012 and 024 in Cohort 1 and #038, #043 and #045 in Cohort 2 and improved their response from PR at Month 6 to CR later without any treatment, indicating the restoration of haematopoiesis may take longer in some patients. This effect is likely due to eltrombopag combined with IST during the first 6 months of treatment and not a function of CsA maintenance alone.

In summary, the addition of eltrombopag to IST contributed to:

- The improvement of the robustness of response (higher CR rate) which correlated with longer relapse-free survival (26% higher in CR patients than PR patients at 18 months);
- The increase of the number of responders (higher OR rate) who could benefit from CsA maintenance dose;

In conclusion, Novartis believes that the above clearly demonstrates that eltrombopag when added to CsA and h-ATG lead to a robust and clinically significant response and to the maintenance of response beyond Month 6.

Safety profile of eltrombopag in first-line SAA is in line with the known safety in other indications

Eltrombopag has a well-established safety profile in the approved ITP (adult and paediatric), HCV and refractory SAA indications, supported by almost 10 years of post-marketing data since its initial approval in the EU in 2010.

In study AUS01T, the safety and tolerability of eltrombopag when added to IST (h-ATG+CsA) in treatment-naïve SAA patients was acceptable with no new or unexpected safety signals. The safety profile of eltrombopag was consistent with the expected safety profile in patients with SAA and the established safety profile in the approved ITP, HCV and refractory SAA indications.

As of the 28-Feb-2018 cut-off date, the overall median (min-max) follow-up extended to 61, 47, 33 and 22 months in Cohort 1, 2, 3 and combined Cohort 3 + Extension, respectively. Seven deaths have been reported in the study and none was considered related to study treatment by the investigators. Amongst the seven reported deaths, three were reported in Cohort 3 + Extension leading to a probability of survival at two years of 96%.

There was no on-treatment fatal infection or bleeding and only two cases of grade 4 infection (sepsis in Cohort 2 and sinusitis in Cohort 3) and no grade 4 bleeding event).

Treatment discontinuation in the study was also relatively low and none was due to hepatotoxicity in any of the 153 treated patients. As of the 28-Feb-2018 cut-off date, five patients discontinued the treatment due to safety reasons: four due to rash and one due to colitis.

No events of recurrence of thrombocytopenia, bone marrow fibrosis, or haematologic malignancies were reported. Renal events, thromboembolic events and bleeding events were rare in all cohorts.

Cytogenetic abnormalities, including clonal evolution occurred in 15 of 153 (10%) patients, which is lower than the range (14% to 20%) that is expected with IST alone at two years after the initiation of treatment. This is also lower than what was reported in the literature for eltrombopag in the refractory setting overall, further supporting that an early and robust response correlates with fewer risks and thus better outcome (Townsley et al 2017, Maciejewski et al 2002, Scheinberg et al 2012, Scheinberg et al 2011, Winkler et al. 2019).

In conclusion, eltrombopag when added to IST for the first-line treatment of SAA is well tolerated and with a safety profile in line with the known safety in the other approved indications. This, in addition to the outstanding treatment effect observed by adding eltrombopag to IST, supports a positive benefit-risk for eltrombopag in combination with standard IST for the first-line treatment of SAA.

With the initial variation application, Novartis proposed to include the paediatric population aged 2 years and above in the indication, however, following the concerns raised by the Agency on the limited number of complete responders among patients below the age of 12 enrolled in the study, Novartis agreed to limit the indication to paediatric patients 12-17 years of age as justified below.

Novartis would like to highlight that despite the rarity of SAA, 37 paediatric patients were enrolled in study AUS01T, including 26 in Cohort 3 + Extension, of whom 25 were evaluable for efficacy (1, 11 and 13 patients in 2-5 year, 6-11 year and 12-17 year age groups, respectively). In the younger age groups (<12 years), 8% (1/12) patients achieved a CR at Month 6. In the 12-17 year age group, 46% (6/13) were complete responders, in line with the overall CR rate in Cohort 3 + Extension (43.7%), and similar to the 50% CR rate observed in adults (31/62). This CR rate (46%) compares favourably with the historically reported CR rate of 25% in this age group as shown in Table 3-5, despite a higher proportion of vSAA in study AUS01T study as compared to the two Scheinberg studies (Scheinberg et al. 2009, Scheinberg et al. 2011) (6/13 vs. 4/12, respectively).

Table 3-5 Haematological response at Month 6 in Cohort 3+ Extension vs. Historical control

	Pooled historical data*			US01T Cohort 3 + Extension		
Age group	**Nt/Nv**	**CR n (%)**	**OR n (%)**	**Nt/Nv**	**CR n (%)**	**OR n (%)**
< 18 years	24/10	5 (21)	17 (71)	25/14	7 (28)	17 (68)
2-5 years	2/2	0	0	1/1	0	1 (100)
6-11 years	10/4	2 (20)	9 (90)	11/7	1 (9)	6 (55)
12-17 years	12/4	3 (25)	8 (67)	13/6	6 (46)	10 (77)
18-64 years	69/21	10 (14)	41 (59)	47/16	26 (55)	42 (89)
≥ 65 years	9/4	2 (22)	9 (100)	15/9	5 (33)	10 (67)
TOTAL	102/35	17 (17)	67 (66)	87/39	38 (44)	69 (79)

Nt/Nv: Total number of patients in the age group / Number of patients with vSAA in the age group
(*) From Scheinberg et al. 2009 and Scheinberg et al. 2011 individual data

Furthermore, several paediatric patients (two, two and three patients in 2-5 year, 6-11 year and 12-17 year age groups, respectively) who were PR at Month 6, improved to CR later.

Excluding paediatric patients <12 years of age, the overall CR rate reached 49.3% (37/75) in study Cohort 3 + Extension, comparing even more favourably to historical control formed by the two Scheinberg studies (Scheinberg et al. 2009, Scheinberg et al. 2011) (after excluding patients <12 years of age) and Tisdale et al. 2000 which enrolled only adults, reporting a pooled CR rate of 17.1% (using the fixed effects model). The improvement in CR rate represented 32.2% (95% confidence interval (CI): [18.9%, 45.6%]) (see Table 3-6).

Table 3-6 Comparison of CR rate in Cohort 3 + Extension vs. historical control with IST alone in patients 12 years and above

		Estimate	95% confidence interval
Treatment	Cohort 3 + Extension	49.33	(38.02, 60.65)
Control	Historical control	17.09	(9.97, 24.21)
Treatment – control		32.24	(18.88, 45.61)

In conclusion, Novartis considers that the CR rates observed in patients 12-17 years of age in study AUS01T as compared to historical controls, justify the inclusion of this age group in this indication.

Novartis' proposed post-approval commitments

Novartis would like to further share with the Agency that based on the results from the AUS01T study, eltrombopag in combination with IST has been approved for the first-line treatment of adult and paediatric SAA patients in several countries as shown in Table 3-7 below:

Table 3-7 Registration status in major markets

Country	Regulatory status	Status date
United States	Approved	Approval: 16-Nov-2018
Japan	Approved	Approval: 25-Aug-2017
Australia	Approved	Approval: 05-Mar-19
Switzerland	Submitted/Positive pre-decision	Positive pre-decision: 25-Apr-2019
Russia	Approved	Approval: 06-Mar-2019
India	Approved	Approval: 02-July-2019
Argentina	Approved	Approval: 04-June-2019

Country	Regulatory status	Status date
Mexico	Approved	Approval: 21-June-2019

Furthermore and as confirmed by the clinical community, clinical practice in the first-line treatment of SAA has changed and eltrombopag added to IST is evolving as the global standard of care.

For the above reasons, a new randomised trial comparing eltrombopag added to IST versus IST alone, would be very difficult to conduct.

Novartis engaged discussions with the EBMT in order to share the early results from the ongoing randomised trial RACE, whenever available during the re-examination process of the present application. Although the regimen used in RACE differs from the AUS01T, Novartis agrees that the results from the RACE trial can be used as supportive of the AUS01T findings to confirm the positive treatment effect of adding eltrombopag to standard IST.

As a reminder, the RACE study is sponsored by the EBMT with Novartis and Pfizer as collaborators. Novartis is not involved in the conduct of the study and does not have access to patient level data and will therefore only be able to provide to the EMA the data as generated by EBMT. The final study report (24 months analysis) is planned to be available at the earliest in Q4 2021, which, in addition to the early results, will also be shared with the Agency once available to Novartis.

In addition to the above and based on the assessment from the Agency of the re-examination request, Novartis is open for further discussions with the Agency on potential post-approval commitment, as applicable.

Novartis' conclusion

Eltrombopag had already demonstrated significant activity in heavily pre-treated refractory SAA patients; as single agent, eltrombopag led to robust results with 40% (17/43) of patients achieving haematologic response, some of which were multi-lineage leading to transfusion independence (Olnes et al. 2012). These results supported the approval of eltrombopag in patients with SAA who have had an insufficient response to immunosuppressive therapy.

The results of the AUS01T pivotal study in first-line SAA patients have confirmed a positive benefit-risk ratio when adding eltrombopag to IST demonstrating an early and robust CR rate approximately 27% higher than historical data of IST alone. This was further confirmed by the improvement in CR in AUS01T as compared to the broader pool of historical controls.

The safety profile of eltrombopag is well characterised in a much larger patient population in the approved indications: ITP, HCV-associated thrombocytopenia and refractory SAA and there are no new emerging safety signals from the AUS01T study.

Novartis has demonstrated that the AUS01T study was well conducted by experts in the field, in a rare disease, and that the significant improvement in efficacy observed by adding eltrombopag to IST as compared to the established efficacy of historical control of IST alone, outweigh the lack of a comparator raised as an uncertainty by the Agency to demonstrate the positive benefit-risk of eltrombopag in the first-line treatment of SAA.

Novartis concludes that the unprecedented treatment benefit combined with the acceptable safety profile of eltrombopag in combination with IST (h-ATG + CsA) demonstrated in study AUS01T a positive benefit-risk for its intended use as first-line treatment in patients aged 12 years and older with SAA.

Ad hoc expert Group consultation

Following a request from the MAH at the time of the re-examination, the CHMP convened an ad Hoc

expert Group inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

The expert group were asked to comment on the CHMP grounds for refusal:

- The efficacy and safety data of eltrombopag on top of standard of care as first line treatment of patients with severe aplastic anemia has not been sufficiently demonstrated. The submitted data, based on study NIH AUS01T, do not allow a reliable and valid assessment of the benefit of Revolade when added to the standard of care (SOC) due to the lack of a robust comparison against established treatment. The indirect comparison with historical data cannot overcome this deficiency.

Therefore, it is not possible to establish a positive benefit risk balance for Revolade in the proposed indication.

Response: Some members of the expert group agreed that the benefit of eltrombopag used in combination with antithymocyte globulin and cyclosporine in adult patients with SAA has been established on the basis of the available evidence from study NIH AUS01T and indirect comparisons with historical data. Given the high level of activity observed, the methodological weaknesses of indirect comparisons were not considered critical.

Others disagreed and considered that the available data are promising but hypothesis-generating only due to the methodological weaknesses of single-arm combination design and the indirect comparisons. According to this view, the benefits even in the adult population were not considered established in the absence of a confirmatory study.

All members agreed that the benefits have not been established in children and adolescents due to apparent lack of a relevant clinical effect in study NIH AUS01T, although numbers were small. Adequate evidence of benefit in this population should be available, at least from an externally controlled trial looking at response rate, before extrapolation on the basis of PK/PD data can be considered. It should be noted that based on the exclusion criteria, the ongoing RACE study will likely not provide useful information to address efficacy and safety in children and adolescents.

Lastly, the experts agreed that there is a significant risk of clonal evolution that needs to be characterised on the basis of long-term safety data (current follow-up is only about 2 years). Such data should ideally be collected systematically using a disease registry and sensitive techniques (e.g., NGS). A registry could also help to address the many existing optimisation questions and further confirm the benefits in the real-life setting (e.g., start of treatment).

In addition, the following questions are raised to the ad hoc group in view of the grounds for re-examination:

1. **Could the experts comment on the overall strength of evidence, including but not limited to:**

    a. **Can the standard of care for SAA patients be considered comparable between the pivotal trial AUS01T and the historical control trials (Rosenfeld et al 2003, Scheinberg et al 2009 and Scheinberg et al 2011)?**

    The standard of care for SAA is generally the same in terms of main therapeutic approaches including antithymocyte globulin (h-ATG), cyclosporine, and stem cell transplantation (see also relevant European guidelines and references). However, clinical practices and guidelines vary in terms of which treatment strategy is used when between regions and often even within regions and different hospitals. Therefore, for some experts,

the different practices add to the uncertainties of indirect comparisons of small series from single institutions.

b. Do the experts consider the definition of CR in SAA as standardized such that CR rates in SAA in clinical practice can be compared to the CR rates of historical controls proposed by the applicant?

The criteria for adjudicating partial or "complete" response across studies are often slightly different but the differences are of negligible clinical importance. Response and other clinical outcomes (e.g., transfusion independence, normal function) are generally clinically important regardless of the precise definition. However, where the primary outcome is defined by CR, the variable criteria may impact on the reported success of a therapy. Thus, small changes in adjudication criteria may add significant uncertainty to the historical comparisons presented.

c. Is the standard of care (including supportive care such as e.g. use of G-CSF and antimicrobials) for SAA patients comparable across regions (US and EU)?

There is no single internationally agreed standard of care (see answer to question 1a), and this applies to supportive care as well. The standards in terms of supportive care are expected to be very heterogeneous and likely vary from hospital to hospital. However, these variations are not expected to add significant uncertainties to the historical comparisons presented.

d. **Are observed effects (in terms of CR, transfusion requirements for platelets and red blood cells, supportive treatments, hospitalisation and quality of life) in the pivotal study of clinical relevance?**

Response and other clinical outcomes are generally clinically important regardless of the precise definition. The observed effects, if associated to the product (an association that some experts considered unproven), were considered clinically relevant. The experts noted that Quality of Life data were missing.

e. Do the experts agree that reaching complete response (and/or overall response) can be considered as a prognostic factor/ surrogate for a favourable long-term outcome?

The experts agreed that failure to respond is associated with very poor outcome in the absence of rescue treatments and response is associated with improvement in survival. Therefore, the outcomes studied showing improvement in complete response and/or overall response are considered clinically important.

f. Is the safety profile of the proposed treatment regimen acceptable for the intended patient population?

The safety profile of the proposed treatment regimen appears to be acceptable in the short term. However, long-term data (e.g., 15 years of follow-up) are needed to assess the risk of clonal evolution.

2. As younger age predicts a more favourable outcome of IST, the experts are asked if the demographics of the AUS01T population (median age 26.5 years; in cohort 3+extension 29% were <18, 55% were 18-64 and 16% were ≥65 years of age) can be considered representative for SAA patients seen in the clinical setting.

The population included based on median age was slightly younger than expected. However, given that the effect appeared to be lower in younger patients, there are no concerns about selection bias in terms of a younger population.

Furthermore, despite the slightly younger population, there are no concerns in terms of generalisability to the target indication.

3. **Could results from RACE add substantial information to support an extension of indication?**

   From the point of the design of the study, given the randomized add-on design, the RACE study (given sufficient follow-up for safety) is expected to be able to provide a direct estimate of the efficacy and safety of eltrombopag used in combination with antithymocyte globulin and cyclosporine compared to antithymocyte globulin and cyclosporine, in the adult population.

4. **Do the experts share the view of the applicant that the use of eltrombopag in SAA has shifted to first line in clinical practise already? What impact will the claimed improvement in clinical efficacy of first line eltrombopag + IST have on the only curative treatment (i.e. allogeneic stem cell transplantation) in SAA?**

   Although practices including off-label use vary, currently there is no widespread off-label use of eltrombopag in first-line treatment due to various reasons, e.g. access (including pricing and reimbursement).

   There is no concern that a potential change in practice would hinder or somehow shift the practice against stem-cell transplantation, which, if possible, remains the only curative option. However, it is important that eltrombopag treatment is initiated by haematologists expert in the management of SAA.

5. **What is the experts´ view on extrapolation from adults to the paediatric population, and specifically on the inclusion of adolescents from 12-17 years (n=13), children from 6-11 years (n=11) and infants aged 2-5 years (n=1) in the indication?**

   All members agreed that the benefits have not been established in children and adolescents due to apparent lack of a relevant clinical effect in study NIH AUS01T. Adequate evidence of benefit in this population should be available, at least from an externally controlled trial looking at response rate, before extrapolation on the basis of PK/PD data can be considered.

Discussion and overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the ad hoc expert group. The CHMP assessment of the key points discussed in the detailed grounds for re-examination submitted is summarised as follows:

- Unmet medical need for SAA patients remains high despite IST treatment and with no drug currently approved in EU for this disease

The MAH stresses the unmet medical need in the treatment of SAA and the importance of increasing the speed and quality of haematologic recovery for treatment-naïve patients with SAA. This is acknowledged since only about one third of patients are suitable for HSCT and not all patients respond to IST (h-AST and CsA), the present standard of care for transplant ineligible patients. Availability of a treatment reducing the overall burden of disease (e.g. reducing transfusion needs or lowering the impact of IST) would be of special interest to health care professionals and patients. However, the unmet medical need

has not been part of the grounds for refusal; the grounds are mainly addressing the efficacy and safety of eltrombopag in the proposed first line of treatment/new treatment regimen.

In conclusion, this key point does not resolve the existing grounds for refusal.

- The current standard of care in SAA is shifting worldwide to use eltrombopag in combination with IST for the first-line treatment of SAA

Scientific literature indeed points to an effect of eltrombopag not only on megakaryocyte stimulation and platelet production, but also in stem cell proliferation and maintenance. Yet again, the therapeutic rationale was not refuted in the original procedure and it is not regarded as part of the CHMP´s ground for refusal; it remains the applicant's choice to select and investigate a treatment regimen and the applicant's responsibility to provide robust data to substantiate the intended label claim.

- Significant and robust improvement in CR rate observed in a well-designed study AUS01T by the NIH, as compared to matched historical controls; and the responses in AUS01T (CR and OR) also compare favourably to a broader pool of historical trials conducted worldwide, which supports the generalizability of AUS01T findings

The MAH argued to have provided "compelling results from a well conducted study" referring to the pivotal trial AUS01T, which was the basis of the initial type II variation submission.

However, as outlined throughout several RSI´s in the initial procedure and in the grounds for refusal, the major drawback of study AUS01T is the non-controlled, non-randomized combination study design that results in major uncertainties on the reliability of the interpretation of the study results. Direct comparison of the results obtained in AUS01T with responses to first line immunosuppressive (IS) treatment is not possible. The claimed difference in CR at 6 months compared with historically reported CR rates with IST cannot be robustly established, due to the heterogeneity of CR rates reported in the literature.

Study AUS01T was an uncontrolled study and study outcomes were compared with historical data to provide a reference range for the efficacy and safety endpoints. The MAH reports the rationale and procedure behind the selection of studies deemed suitable as historical control.

With regards to the selection of the historical controls; in the first attempt, the selection criteria were more stringent to assure comparability of treatment concerning the regimen, treatments, dose and duration of treatment, resulting in overall 4 studies that could be compared to the study outcomes of study AUS01T.

The selection criteria were as follows:

1. IST-naïve patients included in the trial
2. IST consisting of h-ATG+CsA for at least one arm
3. Definition of complete and/or overall responses based on the same criteria as in AUS01T and response rate at Month 6 reported
4. IST regimen comparable to AUS01T in terms of drugs doses and durations

From this comparison, it appeared that the rate of the observed complete, partial and overall haematological responses might indeed support a claim towards increased efficacy. However, several uncertainties apply: The selected 4 trials were all conducted by the NIH (National Institutes of Health), which is incidentally also the sponsor of AUS01T, the pivotal trial for this application. This hampers the

external validity of the overall comparison. Further, a selection bias cannot be ruled out, e.g. that only SAA patients with a high probability of achieving a response might have been asked to participate in the trial. This notion is supported by the fact that the age distribution of subjects in AUS01T differs significantly from that of comparable trials in a treatment naïve population (e.g. Assi, 2018). Thus, substantial doubt remains about the reliability of such a single centre comparison and the external validity of the obtained pivotal data.

The applicant has recognized the lack of variability in the pool of historical controls as one major drawback and widened the selection criteria for study inclusion for additional analyses.

The inclusion criteria here were as follows:

1. IST-naïve patients included in the trial

2. Treatment with:

    a. IST consisting of h-ATG or h-ALG (Lymphoglobulin) + CsA for at least one arm, regardless of the doses and durations

    b. Additional treatment(s) on top of h-ATG/h-ALG + CsA were allowed (e.g., growth factors, other immunosuppressive agents)

3. Definition of complete and/or overall responses based on the same parameters irrespective of the threshold considered

4. CR rate and/or OR rate at Month 6 or best CR rate and/or OR rate within 6 months or longer, reported.

Under these widened criteria, 13 publications including studies from other sites and countries on top of the initially selected 4 trials were applicable for inclusion.

The MAH conducted additional analyses for both CR and OR rates, using random effects meta-analyses due to high heterogeneity between studies. This approach is methodologically appropriate to address the situation and results seem to be comparable to the analysis of the initial 4 studies. However, the widening of the inclusion criteria introduced large heterogeneity of the responses rates. This fully reflects the CHMP´s concern raised in the grounds for refusal on the comparison to historical data, i.e. that differences in the characteristics/risk factors of the study populations and in the setup of the studies, unknown or known (such as variations in doses and treatments for IST and slight differences in the definition/timing of the primary endpoint), make indirect comparisons very unreliable.

In this respect, it does not help that study AUS01T compares favourably against the mean of a set of historical trials in the comparisons presented by the MAH. Rather than how AUS01T compares against the mean of other trials, the key question is, in which region the response rate of the patients included in AUS01T would lie without add-on eltrombopag treatment. This, however, is difficult to conclude on, as the range of CR in historical studies is extremely wide.

As can be seen from Figure 3-4 for the historical studies included, the rate for CR ranged between 3% and 60%, with most studies showing a CR rate between 10% to 30%. However, some important sources, e.g. the rather large number of EBMT patients/data reported by Bacigalupo, showing higher response rates, should not be ignored. Therefore, it remains difficult to define where exactly the threshold for a meaningful comparison should be set, considering the heterogeneity of the CR rates reported in these studies (3%-60%). This is however deemed essential in order to conclude that the observed response rates are indeed compelling.

Despite the fact that the widened inclusion criteria indeed provided more studies for comparison, the trends observed pointing towards efficacy in these sensitivity analyses need to be kept in perspective. The additional studies could not solve the major drawback of uncontrolled data per se, but rather

introduced more heterogeneity, instead of rendering a comparison less difficult. The analyses conducted still do not outweigh the necessity for a valid internal comparator demonstrating superior efficacy of the new treatment regimen compared to current standard of treatment with IST. Compelling evidence of superior benefit is necessary to avoid an increased treatment burden in an already highly vulnerable and heavily treated patient population. Additionally, eltrombopag is used as an effective rescue treatment in relapsed and resistant patients and it is not clear if first line use will blunt the response to subsequent rescue treatment.

Overall, no significant new information changing the grounds for refusal has been provided that could overcome the uncertainty whether historical data could compensate for the lack of a comparative study (eltrombopag + IST versus IST alone). Therefore, the concern raised in the grounds for refusal on the lack of robustness and the indirect comparison remains.

Another open question was the uncertainty with regard to the contribution of eltrombopag to the duration of the haematological response. In cohort 3 of the AUS01T study, the treatment regimen intended for marketing authorization (eltrombopag + IST for 6 months) was administered. But after the initial 6 months of treatment, a maintenance dose of CsA was introduced for 24 months; it was not entirely clear whether/how much eltrombopag contributed to the overall long-term effect in terms of response and relapse rates.

The MAH concludes that the long-term responses are "*likely due to eltrombopag combined with IST during the first 6 months of treatment and not a function of CsA maintenance alone*". The rationale for this statement seems largely based on 6 patients, who did not receive CsA maintenance but still improved to CR at a later time point. However, if this long-term positive effect is actually based on the addition of eltrombopag or the standard IST alone remains unclear, especially considering the very limited sample size of 6 patients showing improvements beyond 6 months. Furthermore, 3 of these patients were from cohort 1, receiving eltrombopag from D14 to 6 months, and 3 from cohort 2, receiving eltrombopag only from D14 to month 3. Additionally, the provided argumentation does not answer questions regarding the relapse rates, which are also of high interest for long-term outcomes.

In conclusion, the responses to these key points do not resolve the existing grounds for refusal.

- Safety profile of eltrombopag in first-line SAA is in line with the known safety profile in the other approved indications, with no new safety signals identified

The CHMP considered that the grounds for refusal outlined in section 4 cover mainly the lack of a valid internal comparator in the pivotal study AUS01T. Interpretation of study results is thus hampered and major uncertainties on the reliability of the obtained efficacy and safety data question the role of eltrombopag in first-line therapy of SAA patients.

The MAH elaborates on the safety profile of eltrombopag when added on top of first line IST. This was part of the grounds of refusal since a major uncertainty existed in the initial submission whether unfavourable effects may be introduced if eltrombopag is added on top of IST.

The MAH reconfirms that from the data set available no new safety signals became apparent, with a well-known safety profile of eltrombopag and the standard immunosuppressive therapy (IST) treatment regimens (h-ATG and CsA). Overall, bleeding events and thromboembolic events seem to be rare in all 3 cohorts in study AUS01T. Seven deaths occurred, but were considered unrelated to study medication. No events of recurrent thrombocytopenia, bone marrow fibrosis or hematologic malignancies were reported. These findings indicate that the safety profile observed in study AUS01T is consistent with the expected safety profile for subjects with SAA.

However, uncertainty remains regarding the risk of emergence of clonal evolution, a serious complication of aplastic anaemia. Although clonal cytogenetic evolution does not seem to be higher in study AUS01T compared with historical data (in fact even lower than the reported values for the treatment with IST alone), it cannot be ruled out yet that eltrombopag as a component of the triple therapy (h-ATG + CsA + eltrombopag) may contribute to or enhance clonal aberrations. Studies AUS28T and Study AUS18T provide supportive data on the development of cytogenetic abnormalities for eltrombopag alone, but not for the on top treatment regimen. Recent literature raises concern of a possible link between eltrombopag in addition to IST treatment and cytogenetic clonal evolution (Winkler et al. 2019). rSAA subjects were treated in 2 consecutive eltrombopag studies. Clonal evolution was almost always an early event: 13 (87%) of 15 occurred within 6 months of EPAG initiation, including all with chromosome 7 abnormalities. The authors conclude that the striking kinetics of these events in relation to EPAG treatment may suggest a direct link.

Conclusion

In the provided discussion, the MAH addresses several aspects, such as a justification for the selected treatment regimen of eltrombopag on top of standard IST and the unmet medical need in the treatment of SAA. The reduction of the transfusion burden as a clinical readout of the haematological response is also discussed. However, these issues are not primarily part of the grounds for refusal and the discussion provided is regarded only as supportive.

Following the concerns raised in the course of the initial type II assessment procedure, the MAH in the re-examination limited the indication regarding paediatric patients to an age of 12-17 years. SAA mainly peaks in patients aged 15 to 25 years old and those over 60. Data generated so far seem to indicate favourable response rates in children aged 12 years and above. If the uncertainties, which are part of the grounds for refusal and currently question the role of eltrombopag as first line therapy on top of standard IST, are resolved, a label for the paediatric subpopulation aged 12-17 years may be considered.

The major and crucial concern remains the lack of a valid internal comparator to establish superior efficacy of the new treatment regimen compared with the current standard of treatment, IST. In this context, the applicant carried out additional analyses with widened inclusion criteria in order to provide more studies for comparison serving as historical control. Under these widened criteria, it is acknowledged that trends are observed indicating efficacy of the tested triple regimen. However, this approach did not solve the major drawback of uncontrolled data per se, but rather introduced heterogeneity for the comparison to be made against a wide range of historical response rates.

Overall, the historical data presented are insufficient to compensate for the lack of a comparative study (eltrombopag + IST versus IST alone).

As for the safety,the major uncertainty with regard to the risk of emergence of clonal aberrations, a serious complication of aplastic anaemia, remains. Recent literature raises the concern of a possible link between eltrombopag addition to IST treatment and cytogenetic clonal evolution in the refractory SAA setting (Winkler et al. 2019).

In conclusion, the lack of a direct comparison versus the current standard of care IST, severely limits interpretation of the magnitude of clinical benefit.

Risk Management Plan

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

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

6. Benefit-risk balance

Therapeutic Context

Disease or condition

The MAH initially applied for an extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia for Revolade in combination with standard immunosuppressive therapy. During the procedure the MAH changed the proposed indication to adult and paediatric patients aged 12 years and above.

Available therapies and unmet medical need

The only curative treatment is haematopoietic stem cell transplantation (HSCT). However, immunosuppressant therapy (IST) with ATG/CsA has changed the prognosis of the disease in patients who are not candidates for HSCT. First line therapy is selected according to the age of the patient, which correlates with ability to tolerate HSCT, the severity of the disease and the availability of an appropriate donor (basically a fully HLA-matched family member). The treatment must balance the relative toxicities and long-term efficacy of the therapies, which differ over time (i.e. higher up-front mortality but greater chance of cure with HSCT), and according to patient age. Published prospective long-term studies show that standard initial IST (horse ATG and CsA) achieve haematological recovery in 60-70% and excellent long-term survival among responders. The medical need for a treatment that can significantly increase the rate of responders and decrease relapse rate, together with an acceptable safety profile, remains high, considering the severity of the disease, but also the overall burden associated with IST as current standard of care.

Main clinical studies

For this indication no specific dose finding studies for adults or children have been performed. The proposed dose is based on results from refractory SAA study (AUS28T), the exposure observed for paediatric and adult ITP patients *vs.* paediatric SAA patients as well as the PK/PD results and the safety profile obtained from the AUS01T updated cut-off (28-Feb-2018).

The main evidence of efficacy of eltrombopag in treatment-naïve patients with SAA comes from study AUS01T, a phase I/II, non-randomized, single-arm, single-centre study evaluating the efficacy and safety of eltrombopag treatment, in combination with the regimen of h-ATG and CsA, in immunosuppressive therapy-naïve subjects with SAA. This study followed an adaptive design such as commonly used in phase I/II single arm trials to assess response rate at an interim time point and allow early termination of a cohort if efficacy is not shown.

Complete response rate at Month 6 was the primary endpoint and it was defined as absolute neutrophil count >1×103/ µL, and platelet count >100×103/ µL, and Hgb>10 g/dL.

Overall, the pivotal study included treatment-naïve patients with SAA who were in principle not candidates for HSCT. In total, 30 patients were included in cohort 1 and 31 in cohort 2 and 3, respectively. In addition, the extension cohort was added to recruit more subjects with the same dosing regimen as Cohort 3, and collect more data for the analysis of the secondary endpoints within the target regimen.

Favourable effects

Complete response (CR), the primary endpoint, was observed in 33.3%, 25.8% and 58.1% of subjects in cohort 1, cohort 2 and cohort 3, respectively (FAS population) at month 6 of treatment. When cohort 3 and the extension cohort were pooled (cut-off 28 Feb-2018), CR was observed in 43.7% of patients at month 6.

More than 75% of the whole population achieved an OR (PR or CR) at month 3 (76.7%, 77.4%, 87.1% and 79.6%, for Cohort 1, 2, 3 and 3+extension, respectively) and improved at month 6 (80%, 87.1%, 93.51% and 84.8%, for Cohort 1, 2, 3 and 3+extension, respectively). Updated results were provided with a cut-off of February 2018. The MAH concludes that eltrombopag has a durable effect since 50% of patients achieved a complete response at any time, and 83.1% of them still responded at month 18. Among the patients with overall response during the study (76.1%), 72.9% of patients still responded 18 months later.

Provided comparisons versus historical controls seem to suggest that the triple combination might have better efficacy over h-ATG+CsA alone in terms of CR at month 6. In addition, the evaluation of the reported haematological response, as reported for re-examination, seems to indicate less transfusions and longer transfusion free intervals hinting towards a clinical benefit for treatment responders, with even better results for patients achieving CR than PR.

Uncertainties and limitations about favourable effects

Study AUS01T is a small, uncontrolled phase I/II study, in which 93 patients were included in3 consecutive cohorts. Although conducting a randomized controlled trial in this clinical setting may be challenging, performance of a controlled trial would have been crucial to assess the efficacy results in a robust way. In fact, a randomised study comparing hATG+CsA vs hATG+CsA+Eltrombopag for SAA (the RACE study) sponsored by European Group for Blood and Marrow Transplantation (with Novartis and Pfizer as collaborators) is ongoing since 2014, thus showing that a comparative study to support the first line indication in SAA patients would have been feasible.

The absence of a comparator is the main limitation for assessment of the additive effect of eltrombopag to IST. In the comparison versus historical controls, the MAH has made an effort to match patients to assure comparability of the groups. However, using external comparators has important limitations since in the absence of randomisation it is not possible to control all prognostic factors and unknown confounders that can have an impact on the results. This limitation also holds true for the enlarged pool of historical comparator studies in the scope of the analysis presented for re-examination. Less stringent criteria for study inclusion were applied in order to extend the original pool of four studies with an additional 13 studies from other sites and countries. However, the trends pointing towards efficacy in these sensitivity analyses need to be kept in perspective: this approach does not solve the major drawback of uncontrolled data per se, but rather confirms CHMP´s concern. The range of responses (CR rates) is very broad, reaching from 3% to 60%, and this heterogeneity makes a comparison very difficult and poses an additional uncertainty per se.

The maintenance of the effect beyond 6 months is not demonstrated as a decline in OR is observed at month 12 for patients on all cohorts. The MAH has provided updated results (cut-off of February 2018) showing that 83.1% of patients who achieved a CR at any time of the study and 72.9% of those with OR during the study still responded 18 months later, but it should be considered that patients did not receive eltrombopag beyond month 6 while they remained on CsA for the whole follow-up period. Therefore, the prolonged effect is likely to be related to the continuous administration of CsA.

Unfavourable effects

The safety profile of Revolade in the claimed indication is mainly based on the results of Study AUS01T that evaluated the safety and efficacy of eltrombopag in combination with h-ATG and CsA in subjects with SAA, who had not received prior IST. Safety data from the clinical development in the other indications is also available as well as data from the post-marketing experience.

Overall, the safety and tolerability of eltrombopag in treatment-naive SAA patients appears consistent with what was shown in previous indications; no new or unexpected findings have been identified. Most of the AE and SAE identified are related to the underlying condition and are manageable in clinical practice.

In study AUS01T the most common AEs (regardless of causal relationship to study drug) observed with an incidence of ≥10% were febrile neutropenia, ALT/AST increase (known to occur with eltrombopag, h-ATG and CsA), blood bilirubin increase and serum sickness (attributable to h-ATG). No deaths related to study treatment were reported. Few AEs led to treatment discontinuation: Of 6, 1 AE of encephalopathy (leading to the on-treatment death as above), 4 AEs of rash, and 1 AE of colitis. Most of the AEs requiring dose interruption/adjustment (17 subjects) were increased ALT and AST. Regarding the adverse events of special interest already described, no events of recurrence of thrombocytopenia, bone marrow fibrosis, or haematologic malignancies were reported. Renal events, thromboembolic events and bleeding events were rare in all cohorts, and none of these events led to treatment discontinuation or to dose interruption/adjustment.

A serious complication of AA is its evolution to clonal haematologic diseases such as myelodysplasia and leukemia, which is usually associated with the appearance of cytogenetic abnormalities in bone marrow cells. In Study AUS01T, clonal cytogenetic evolution occurred in 9 of 123 (7%) subjects, which is not higher compared with historical data; 5 events of clonal evolution occurred within 6.1 months of starting treatment, 4 of which had abnormalities in chromosome 7. These observations are consistent with what has been reported in the studies in refractory SAA subjects who received eltrombopag alone (Study US18T and Study US28T).

Uncertainties and limitations about unfavourable effects

The assessment of safety of eltrombopag in this population is hampered by the severity of the underlying condition, the lack of a control arm and the overall limited database. Although the safety profile seems similar to that observed for the refractory SAA indication, the lack of a comparator prevents from ascertaining which adverse events are related to the addition of eltrombopag.

A final conclusion about the early onset of cytogenetic abnormalities with eltrombopag relative to immunosuppressant treatment cannot be reached until more data in a higher number of patients with a long-term follow-up is available. Such a risk is further highlighted by recent literature reporting a possible relationship between exposure to eltrombopag and increased rates of cytogenetic clonal evolution (Winkler et al. 2019).

Effects Table

Table 6-1: Effects Table for Revolade in SAA naïve patients in association with IST treatment (data cut-off: 28/February/2018).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
CR	Complete response rate at 6 months as absolute neutrophil count>1x10^3/µl, platelet count >100x10^3/µl and Hb>10 g/dl	%	43.7%	20.0% 11.9% 25.0%	26.9%(14.6;39.3)[1] 28.4%(13.0;43.7)[1] 27.1%(11.7;42.5)[1]	Scheinberg et al 2011. Scheinberg et al 2009. Tisdale et al 2000.
OR	(PR+CR) at month 6. PR as equivalent to at least 2 of the 3 criteria of absolute neutrophil count > 500/µL, Platelet count > 20x10^3/µL and reticulocyte count > 60x10^3/µL	%	79.3%	68.3% 61.9% 61.5%56.3%	16.3%(5.8;26.7)[1] 10.4%(-3.4;24.3)[1] 9.9%(-2.4;22.1)[1]	Scheinberg et al 2011. Scheinberg et al 2009. Rosenfeld et al 2003. Tisdale et al 2000.
Unfavourable Effects						
Febrile neutropenia		%	6.5%	[2]		
ALT/AST increase		%	28.3% /17.4%	[2]		
Blood bilirubin increase		%	16.3%	[2]		
Serum sickness		%	6.5%	[2]		
Clonal disease		%	7%	[2]		

OR=Overall response; PR= partial responses.

[1] Indirect comparisons to pooled historical controls using fixed effects model, propensity scores matching and IPTW propensity scores, respectively.

[2] Data presented in publication from the historical studies appears similar to AUS01T study.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

The lack of a direct comparison versus the current standard of care IST, severely limits interpretation of the magnitude of clinical benefit. Haematological response in the AUS01T study was compared with results from historical studies that used standard IST. Comparative results seem promising, but the limitations of such comparisons are well known, preventing drawing sound conclusions.

The reported safety profile of eltrombopag is similar to the already known safety profile in the refractory/relapsed population. Nevertheless, the lack of a comparator arm makes it difficult to ascertain which adverse events are related to the addition of eltrombopag to standard treatment. From the available data set, no new safety signals became apparent. However, the risk of emergence of clonal aberrations, a serious complication of aplastic anaemia, remains a major uncertainty warranting a dedicated follow-up study to address this risk.

Balance of benefits and risks

The effect of eltrombopag on top of IST for the first line treatment in SAA patients looks encouraging in terms of CR and OR, but it is difficult to interpret due to the lack of a comparator arm in the pivotal clinical trial. The use of external cohorts for comparison with standard IST suggests a favourable response when adding eltrombopag to IST, but such comparisons have well known limitations. In the comparison including only NIH based studies, external validity is questioned and selection bias cannot be excluded. The approach of using an extended historical study pool based on widened criteria for study selection tried to overcome these limitations. However, it could not solve the major drawback of uncontrolled data per se, but rather introduced more heterogeneity.

From a safety point of view, no unexpected findings have been identified, but due to the absence of a comparator in study AUS01T it is difficult to assess the contribution of eltrombopag to the safety profile of the triple combination in this setting. No safety advantage, such as e.g. a lower dose of immunosuppressive drugs, comes with the first line eltrombopag regimen, and while the AE profile in AUS01T seems similar to what is known from the approved indication, concerns about the potential of clonal evolution with eltrombopag need to be followed up.

Additional considerations on the benefit-risk balance

Not applicable.

Conclusions

The overall B/R of Revolade is negative.

7. Recommendations following re-examination

Final outcome

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion considers the following variation not acceptable and therefore does not recommend by a majority of 28 out of 30, the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia for Revolade in combination with standard immunosuppressive therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 50 has also been updated.

During the initial application, the MAH changed the proposed indication to adult and paediatric patients aged 12 years and above.

Grounds for refusal:

- The efficacy and safety data of eltrombopag on top of standard of care as first line treatment of patients with severe aplastic anemia has not been sufficiently demonstrated. The submitted data, based on study NIH AUS01T, do not allow a reliable and valid assessment of the benefit of Revolade when added to the standard of care (SOC) due to the lack of a robust comparison against established treatment. The indirect comparison with historical data cannot overcome this deficiency.