EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2015
EMA/CHMP/598426/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: REVOLADE

International non-proprietary name: ELTROMBOPAG / ELTROMBOPAG OLAMINE

Procedure No. EMEA/H/C/001110/II/0020

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
AUC	Area under the curve
CBC	Complete blood count
CI	Confidence interval
CR	Complete haematologic response
CsA	Cyclosporine A
CSR	Clinical study report
EPO	Erythropoietin
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
hATG	Horse anti-thymocyte globulin
HCV	Hepatitis C virus
HSPC	Haematopoietic stem and progenitor cells
HSCT	Haematopoietic stem cell transplant
IND	Investigational new drug
ISS	Integrated Summary of Safety
IST	Immunosuppressive therapy
ITP	Immune thrombocytopaenic purpura
MDS	Myelodysplastic syndrome
NHLBI	National Heart Lung Blood Institute
NIH	National Institutes of Health
PR	Partial haematologic response
rATG	Rabbit ATG
RBC	Red blood cell
SAA	Severe aplastic anaemia
SAE	Serious adverse event
TPO	Thrombopoietin
TPO-R	TPO receptor
ULN	Upper limit or normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 11 November 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name:**
REVOLADE	ELTROMBOPAG / ELTROMBOPAG OLAMINE

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, II and IIIB

The Marketing authorisation holder (MAH) applied for a new indication in the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy. Consequently the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC. The package leaflet is proposed to be updated accordingly. In addition, the MAH proposed to correct the acronym used for full blood counts (FBC) in the SmPC, Annex II and PL.

The variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included the EMA Decisions P/0307/2012; P/312/2011 and P/0262/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0262/2014 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 MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Greg Markey

Timetable	Actual dates
Submission date	11 November 2014
Start of procedure:	28 November 2014
PRAC Rapporteur Assessment Report	3 February 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 February 2015
CHMP Rapporteur Assessment Report	16 February 2015
CHMP Co-Rapp Assessment Report	16 February 2015
CXMP comments	20 February 2015
Rapporteurs Revised Assessment Report	20 February 2015
Request for supplementary information (RSI)	26 February 2015
Re-start of the procedure	26 April 2015
PRAC Rapporteur Assessment Report on the MAH's responses	25 May 2015
CHMP Rapporteur and Co-Rapp Assessment Report on the MAH's responses	26 May 2015
Committees comments on PRAC Rapp Advice	4 June 2015
PRAC Rapporteur Updated Assessment Report	n/a
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	11 June 2015
CHMP Rapporteurs updated Assessment Report	19 June 2015
2nd Request for supplementary information (RSI)	25 June 2015
Re-start of the procedure	2 July 2015
Joint Rapporteurs updated Assessment Report on the MAH's responses	6 July 2015
Committees comments on updated Assessment Report	13 July 2015
Rapporteurs' revised Assessment Report	16 July 2015
CHMP Opinion	23 July 2015

2. Scientific discussion

2.1. Introduction

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. Its diagnosis is of exclusion, exhibiting hypocellular bone marrow (<25%) and pancytopenia (with at least 2 of the following: absolute neutrophil count (ANC) <0.5 Gi/L; platelet counts <20 Gi/L; reticulocytes <20 Gi/L). Aplastic anaemia affects approximately 2 out of every 1 million people in Western countries. Historically, SAA was an almost uniformly fatal diagnosis due to infection or haemorrhage resulting from prolonged pancytopenia. Outcomes in patients with SAA have improved dramatically due to definitive treatment with either intensive immunosuppressive therapy (IST) with anti-thymocyte globulin and cyclosporine (ATG/CsA), or haematopoietic stem cell transplantation (HSCT). Observed haematologic responses with these treatments led to substantial improvements of survival rates for patients with SAA.

No therapies are currently approved for the treatment of SAA patients in the European Union, but the standard treatment regimen for treatment-naïve SAA is ATG/CsA. Since the establishment of IST as a standard treatment for SAA, no subsequent improvements in treatment have been identified. Intensification of primary IST for treatment-naïve cases with agents more immunosuppressive than hATG, including rabbit ATG, alemtuzumab, or high dose cyclophosphamide, have not been successful. Addition of sirolimus or mycophenolate to hATG/CsA has not improved response rates.

No established standard of care exists for SAA patients with an insufficient response to IST who lack a matched related donor for HSCT, other than transfusion support and treatment of infections. Alternative donor transplantation (matched unrelated donors) can be effective in selected patients with SAA, but there are issues of donor availability, cost, and treatment-related mortality and morbidity. To date, outcomes following umbilical cord transplant have been dismal in patients with bone marrow failure syndromes. Cord and haploidentical transplants are not recommended outside of clinical trials.

A second course of IST salvages in some SAA patients who were unresponsive to initial IST could induce haematologic responses in approximately 21% to 37% of patients. A third course of IST has been shown to be ineffective in patients unresponsive to previous IST.

Growth factors such as erythropoietin and granulocyte colony stimulating factor have not been shown to improve response rates. Androgens have not demonstrated efficacy in combination with IST, but a small proportion of IST-refractory patients may respond to androgens based on anecdotal evidence. Despite significant improvements in standard supportive care treatments (particularly antifungal antimicrobials and other antibiotics), approximately 40% of IST-refractory SAA patients die of bleeding or infection within 5 years of diagnosis. Consequently, such patients have a high unmet medical need, and outcomes remain unsatisfactory. New treatment options are needed for patients with an insufficient response to IST.

Eltrombopag is a novel, small molecule, non-peptide, orally active thrombopoietin receptor (TPO-R) agonist that functions in a similar manner to endogenous thrombopoietin (TPO), the main cytokine involved in regulation of megakaryopoiesis and platelet production.

REVOLADE contains eltrombopag as eltrombopag olamine, the bismonoethanolamine salt of the free acid eltrombopag; and is presented as 25, 50, or 75 mg tablet, indicated for:

- adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).
- second line treatment for adult non-splenectomised patients where surgery is contraindicated.
- 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.

This MAH applied for the following new indication:

"REVOLADE is indicated for the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy".

Following the review, the indication agreed with the CHMP was:

"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)"

The recommended starting dose of eltrombopag is 50 mg once daily, to be adjusted in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥ 50,000/µl. A dose of 150 mg daily should not be exceeded (see SmPC section 4.2). For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily. The treatment should not be initiated when the patients have existing cytogenetic abnormalities of chromosome 7 (see SmPC section 4.2).

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

The original ERA for eltrombopag identified a measured partition coefficient (noctanol/ water) for this molecule, at pH 7, of greater than 4.5. On the basis of this observation and as a part of the approval, the MAH agreed to undertake, as a follow-up measure, a staged Persistent Bio-accumulative Toxicity (PBT) assessment of eltrombopag in a stepwise manner in accordance with EU guidelines (FUM001). Accordingly, a bioconcentration study: Flow-through fish test (OECD 305) was performed and an updated version of the original ERA on the impact of eltrombopag tablets on the environment was submitted.

Further PBT assessment with eltrombopag, was submitted in the context of a Type II variation to introduce the HCV indication in November 2011. The post-authorization commitments of the HCV submission included the conduct of Phase II Tier A Aquatic studies [Aerobic Transformation in Aquatic Sediments system (OECD 308), Daphnia sp. reproduction test (OECD 211), and Fish, early life stage toxicity test (OECD 210)] in addition to the following Phase II Tier B terrestrial fate and effect studies:

- Aerobic Transformation in Soil (OECD 307)
- Soil Microorganisms, Nitrogen Transformation Test (OECD 216)
- Terrestrial Plants, Growth Test (OECD 208)
- Earthworm, Acute Toxicity Test (OECD 207)
- Collembola Reproduction (ISO 11267)

- Sediment – Water Chironomid (OECD 218/219)

In this submission, eltrombopag was initially investigated for determination of activated sludge sorption isotherm, 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 the physico-chemical characteristics of eltrombopag that contributed to the failure of this study suggested a theoretical Koc value for eltrombopag of greater than 10,000 L/kg thereby triggering the need for a Phase II Tier B analysis in soil. Furthermore, a QSAR (PCKOC) evaluation of eltrombopag predicts that Koc will be significantly greater than 10,000 (Log Koc = 5.66).

Moreover, animal studies used to investigate the absorption, distribution, metabolism and elimination of eltrombopag, (as part of the original MAA) reveal that it is predominantly excreted in faeces which suggests that adsorption to organic material is a characteristic of this substance. However, despite these considerations, the MAH has re-conducted an adsorption - desorption study using the batch equilibrium method (OECD 106) in the context of MEA 00X; the results of this study and its implications, will be provided as part of an updated ERA (across indications).

In conclusion, the remaining components of the eltrombopag tablets product, including packaging, are already introduced into the environment from a variety of sources in much greater quantity. Therefore, introducing these components into the environment as a result of the use of this product is not expected to result in adverse environmental effects.

The measured octanol/water partition coefficient for eltrombopag is greater than 4.5, at pH7 (measured partition coefficient of 4.52 at pH7). On the basis of this observation a staged Persistent Bio-accumulative Toxicity (PBT) assessment of eltrombopag was initiated in a stepwise manner in accordance with EU guidelines and a bioconcentration: flow-through study in fish (OECD 305) has, therefore, been conducted.
Eltrombopag olamine was shown not to significantly accumulate in fish tissue at test concentrations between 7 and 71 times the predicted “worst case” PEC for eltrombopag (0.35 µg/L). In this study, at the end of the 10 day depuration period, 88% and 85% of eltrombopag olamine was eliminated from the fish tissues at each concentration, respectively. Based on this information the biological half-life for eltrombopag is considered to be between 3 and 10 days. Thus, although, on the basis of the results from this study it can be concluded that, on the basis of P (Persistence) criteria, eltrombopag is persistent, it does not fulfil the criteria for bioaccumulation as defined in the EU Testing Guidelines and therefore it can be concluded that eltrombopag does not fulfil the criteria to be considered a PBT/vPvB (i.e. Persistent/Bioaccumulative/Toxic or very Persistent/very Bioaccumulative) substance as set out in the guidance.
According to current guidance, the fate of the drug substance, eltrombopag requires further consideration. Following use of eltrombopag tablets, all components derived from the drug substance will be released into waste water systems. An updated assessment should contain calculations of the $PEC_{SURFACEWATER}$ as the sum all of each indication for eltrombopag and will evaluate the predicted environmental exposure in the light of the observed no effect concentrations defined in the new studies.

2.2.2. Conclusion on the non-clinical aspects

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

The Applicant will provide an updated Environmental Risk Assessment and address all authorised indications for eltrombopag tablets. The updated assessment will contain calculations of the $PEC_{SURFACEWATER}$ as the sum all of each indication for eltrombopag and will evaluate the predicted environmental exposure in the light of the observed no effect concentrations defined in the new studies.

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 1: Overview of studies supportive the application for eltrombopag in SAA

	ELT112523 (Pivotal)	**ELT116826 (Supportive)**	**ELT116643 (Supportive)**
Study design	Phase II Open label, non-randomised, single arm, single centre	Phase II Open label, non-randomised, single arm, single centre	Phase I/II Open label, non-randomised, single arm, single centre
Population	Patients 12 years of age or older with SAA and insufficient response to IST	Patients 2 years of age or older with SAA and insufficient response to IST	Patients 2 years of age or older with treatment naïve SAA
Treatments	Eltrombopag regimen: 50 mg once daily (25 mg once daily for east Asian patients), increased by 25 mg daily every 2 weeks based on platelet counts – to a maximum of 150 mg daily (75 mg for east Asian patients)	Eltrombopag regimen: 150 mg once daily (lower starting doses based upon age and ethnicity)	Eltrombopag +hATG/CaA: Eltrombopag regimen: 150 mg once daily starting on day 14 (lower starting doses based upon age and ethnicity) hATG/CaA regimen: Administered according to standard of care of the NIH.
Number of pts	N=44 (entered) – 43 pts treated	N=15 entered 60 planned / 15 treated	N=47 entered 62 planned / 44 treated

	ELT112523 (Pivotal)	ELT116826 (Supportive)	ELT116643 (Supportive)
Status	completed	ongoing	ongoing
Data cut-off	09.05.2014	31.03.2014	31.03.2014

2.3.2. Pharmacokinetics

No clinical pharmacology/pharmacokinetic data in the severe aplastic anaemia population were submitted with this application.

Results from clinical pharmacology studies were provided in the original MAA to support eltrombopag use in adult patients with chronic idiopathic thrombocytopaenic purpura. No additional clinical pharmacology studies were completed for this application, with the exception of the following information from the supportive study ELT116643.

Preliminary pharmacokinetic (PK) results from Cohort 1 of supportive Study ELT116643 have become available. In Cohort 1 of Study ELT116643, a PK sample for plasma concentrations of eltrombopag was taken from 23 subjects at the 3 month visit; PK is not being performed in Cohort 2 of the study. Thirteen (57%) subjects were female, 2 (9%) were elderly, and 3 (13%) were adolescents. Steady state eltrombopag geometric mean PK parameters for the 150 mg daily dose in these 23 subjects were Cmax 35.0 µg/mL (50%) and AUC(0-∞) 693.7 µg.h/mL (43%).

2.3.3. Pharmacodynamics

No new PD data in the severe aplastic anaemia population were included in the submission.

2.3.4. Discussion on clinical pharmacology

No new relevant studies have been submitted with this application but some information is derived from a supportive study Study ELT116643 which evaluates the efficacy of eltrombopag in combination with a common immunosuppressive regimen for the treatment of naïve SAA subjects (ATG/CsA).

The observed eltrombopag exposure in these 23 SAA subjects was 2 to 3 times higher than that observed in healthy subjects or patients with chronic ITP. The higher eltrombopag exposure may be due to a possible drug-drug interaction between eltrombopag and CsA. Published studies have shown CsA inhibits drug transporters such as organic anion transporting polypeptide and breast cancer resistance protein (BCRP), thereby potentially impacting plasma levels of substrates of these transporters and eltrombopag is a substrate of BCRP (Gupta, 2006). The MAH is planning to conduct a drug-drug interaction study in healthy volunteers to further evaluate the potential for a PK drug interaction between CsA and eltrombopag, however, as concomitant use of eltrombopag with CsA is not expected in refractory SAA, such DDI study is not required under the scope of this extension of indication.

Current PK/PD information is considered sufficient to support the new indication.

2.3.5. Conclusions on clinical pharmacology

Current knowledge of the clinical pharmacology of eltrombopag can be applied in the SAA population.

The information in the SmPC is considered sufficient to cover the extension of the indication.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No formal dose response studies have been conducted for the current application.

2.4.2. Main study

Title of Study: Pivotal Study ELT112523

Methods

ELT112523 was an open-label, single centre, non-randomized, single-arm, Phase II, dose modification study to assess the safety and efficacy of eltrombopag in subjects with SAA and an insufficient response to IST. This was an investigator-sponsored study conducted by the NIH.

Study participants

Inclusion criteria were:

- Patients' age ≥12 years old with
- diagnosis of SAA, with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/cyclosporine
- platelet count ≤30Gi/L.

Exclusion criteria were:

- diagnosis of Fanconi anaemia,
- infection not adequately responding to appropriate therapy,
- PNH clone size in neutrophils of ≥50%,
- liver and/or renal impairment, (Creatinine > 2.5 Bilirubin > 2.0 SGOT or SGPT > 2 times the upper limit of normal)
- HIV positivity
- Hypersensitivity to eltrombopag or its components
- Female subjects who are nursing or pregnant or are unwilling to take oral contraceptives or refrain from pregnancy if of childbearing potential
- History of malignancy other than localized tumours diagnosed more than one year previously and treated surgically with curative intent (for instance squamous cell or other skin cancers, stage 1 breast cancer, cervical carcinoma in situ, etc)
- Unable to understand the investigational nature of the study or give informed consent
- History of congestive heart failure, arrhythmia, arterial or venous thrombosis (not excluding line thrombosis) within the last 1 year, or myocardial infarction within 3 months before enrollment

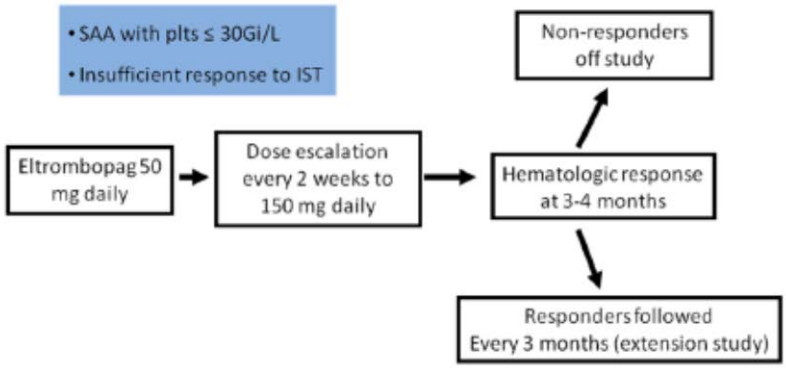
- ECOG Performance Status of 3 or greater
- Treatment with horse or rabbit ATG or Campath within 6 months of study entry. Concurrent stable treatment with cyclosporine or G-CSF is permitted.

Treatments

The starting dose of eltrombopag was 50 mg daily (25 mg for East Asian subjects), and the dose was increased by 25 mg daily every 2 weeks based on platelet counts to a maximum of 150 mg daily (75 mg for East Asian subjects). The dose of eltrombopag during extended access was at the lowest dosage that maintained a stable platelet count until subjects met off-study criteria, or the study was closed. Subjects who could not tolerate study medication or did not respond by the Primary Response Assessment were discontinued from eltrombopag.

For subjects who entered the extension, eltrombopag was tapered in subjects who achieved tri-lineage haematopoiesis (defined as platelets >50 Gi/L, haemoglobin [Hgb] >10 g/dL in the absence of RBC transfusions, and ANC >1 Gi/L for more than 8 weeks). The dose of eltrombopag was decreased to 75 mg/day for non-East Asians; or to 25 mg/day for East Asians. After 8 weeks at this dose if platelet, haemoglobin and neutrophil counts remained above these thresholds, treatment with eltrombopag was stopped.

Figure 1 ELT112523 Study Schematic



Objectives

The primary objective was to assess the safety and efficacy of the oral thrombopoietin receptor agonist (TPO-R) eltrombopag in SAA subjects with immunosuppressive therapy refractory thrombocytopenia.

Outcomes/endpoints

The primary efficacy endpoint was investigator-assessed haematologic response at the Primary Response Assessment (week 12 or 16 visit). Haematologic response was defined as meeting 1 or more of the following criteria:

- Platelet count increase to 20 Gi/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks;

- Haemoglobin increase by >1.5 g/dL for subjects with pre-treatment haemoglobin <9 g/dL, or a reduction in the units of RBC transfusions by at least 4 for 8 consecutive weeks, compared with the 8 weeks pre-treatment;
- ANC increase of 100% (for pre-treatment levels <0.5 Gi/L), or an ANC increase >0.5 Gi/L.

Subjects with evidence of response at 12 weeks could continue eltrombopag for an additional 4 weeks to ensure response prior to being consented for entry into the extended access part of the study. Responding subjects were eligible to enter an extended treatment portion of the trial.

Assessment of response in patients with SAA relies on haematologic improvements in blood counts. Patients who no longer meet the criteria for SAA, or who become red cell or platelet transfusion independent, have achieved a clinically meaningful response to treatment.

Other efficacy assessments evaluated in ELT112523 included:

- Best lineage response (i.e., uni-lineage, bi-lineage or tri-lineage) was determined to assess whether response to eltrombopag improved over time after continued treatment;
- Response at each subject's last assessment (as of the data cut-off date) was examined to assess maintenance of effect over time during the extension;
- Duration of response and maintenance of response after discontinuation of eltrombopag were assessed to evaluate durability of response;
- Transfusion independence for both platelets and RBC was assessed by shift from baseline transfusion dependence to independence, and the maximum duration of transfusion independence (via summary statistics);
- Bone marrow cellularity and haematopoiesis were evaluated to assess reconstitution of the bone marrow; and
- Health-related quality of life was measured at baseline and 12 to 16 weeks after baseline.

All subjects were to be evaluated at the NIH at baseline, weeks 5, 9 and 13 (labelled 12 week assessment in the reporting analysis plan). Responding patients who entered the extension were monitored at the NIH every 3 months. After discontinuation, subjects completed FU visits at week 4 and 6 months.

Sample size

In the original Protocol, the Two-Stage Minimax Design with a response probability of 10% or less to terminate the treatment and the hypothesized actual response probability of 30% or more. The sample size is determined by testing the null hypothesis H0: $p \leq 10\%$ versus the alternative H1: $p \geq 30\%$ at a significance level of 0.05 and a power of 0.8. At the first stage, 15 subjects will be accrued and the null hypothesis will be accepted if no more than 1 subject responds to the treatment within 3 months. If 2 or more subjects respond to the treatment within 3 months at the first stage, then an additional 10 subjects will be accrued, bringing the total number of subjects to n=25. The null hypothesis of $p \leq 10\%$ will be accepted if the total number of responders within 3 months is 5 or less. By 2 subsequent protocol amendments the sample size was increased to 50 patients (Cohort 1).

Randomisation

The study was non-randomised.

Blinding (masking)

The study was open label.

Statistical methods

Study ELT112523 was originally designed as a two-stage study with a maximum of 25 subjects to test the null hypothesis that the response rate with this treatment was no greater than 10%. The null hypothesis of p≤10% was to be rejected if the total number of responders out of 25 subjects within 12 weeks was 6 or more: 11 subjects were determined to have responded, so that the objective of the design was met and the null hypothesis rejected for this part of the study.

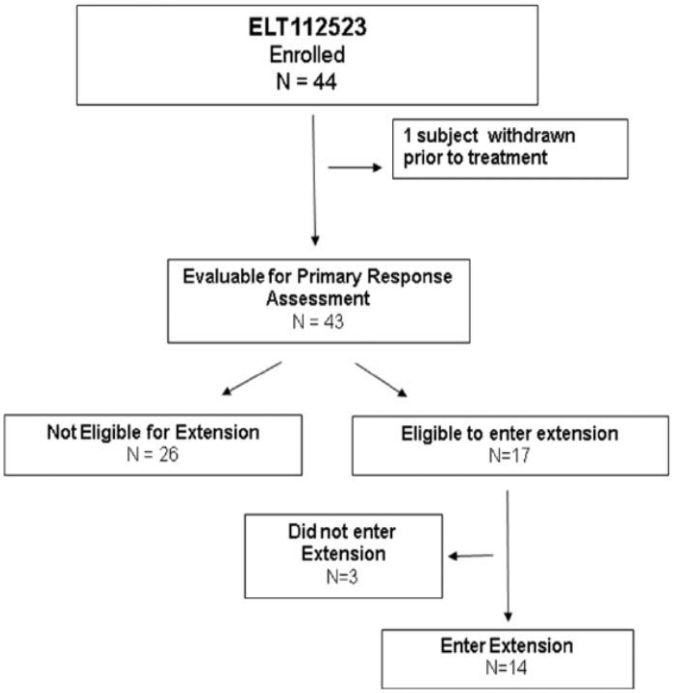
The primary population for all analyses was comprised of all subjects enrolled into the study who received at least 1 dose of study treatment. The probability of a haematologic response is summarized in the ELT112523 clinical study report (CSR) using point estimates and 95% Klopper-Pearson confidence intervals. The analyses were not adjusted for the original 2-stage design or subsequent increase in sample size. Subjects could respond according to 1 or more of 3 criteria: platelets (platelet counts and/or platelet transfusions), red cells (Hgb level and/or RBC transfusions), and ANC.

For subjects who discontinue the study drug prematurely (before 3 months), Platelet count measurement will be attempted even if a subject discontinues study drug. Subjects who withdraw from the study for reasons other than lack of efficacy or toxicity (rendering platelet count missing) may be replaced. All other subjects should be evaluable for efficacy. Based on the assumed drop-out rate of 15-20% and the goal of having 25 evaluable subjects, 5 additional subjects may be enrolled.

Results

Participant flow

Figure 2 Subject Disposition (All Subjects)



The study was designed to allow continued eltrombopag treatment in responding subjects and discontinuation of eltrombopag in non-responding subjects. Subjects with no response to eltrombopag treatment by the Primary Response Assessment were to discontinue treatment. Responders were allowed to enter an extended treatment portion of the study where they were allowed to taper off eltrombopag based upon tri-lineage peripheral blood counts above pre-defined thresholds (defined as platelets >50 Gi/L, Hgb >10 g/dL in the absence of RBC transfusion, and ANC >1 Gi/L for more than 8 weeks).

Of the 26 subjects who did not meet response criteria, 22 discontinued treatment as per protocol (i.e., 'completed scheduled treatment period'). The remaining 4 non responding subjects discontinued treatment at or prior to the Primary Response Assessment due to 'lost to follow-up' (1 subject), 'withdrew consent' (1 subject) and due to an adverse event (AE; 2 subjects).

Table 2 Summary of Subject Status and Reason for Study Withdrawal (Study ELT112523; Safety Population)

	Eltrombopag (N=43)
Subject Status, n (%)	
Ongoing in Study	10 (23)
Completed	7 (16)
Died	6 (14)
Withdrawn from Study	20 (47)
Primary reason for study withdrawal[a], n (%)	
Subject reached protocol defined study withdrawal criteria[b]	14 (33)
Adverse event	2 (5)
Withdrew consent	2 (5)
Lost to follow-up	1 (2)
Lack of efficacy	1 (2)

Data Source: m5.3.5.2 ELT112523 CSR Section 5.2
a. Subjects can have only 1 primary reason for withdrawal.
b. Referred to other therapies or transplant, had a cytogenetic abnormality detected or had evidence of dysplasia.

Of the 17 subjects with a response, 3 subjects did not enter the extended treatment phase either due to an AE (2 subjects) or due to investigator discretion (1 subject). Of the remaining 14 subjects who entered the extension phase, 4 subjects remain ongoing in treatment, 5 subjects met protocol defined

criteria for tri-lineage haematopoiesis and tapered off eltrombopag, and 5 subjects discontinued treatment during the extension due to either an AE (1 subject), detection of a cytogenetic abnormality (2 subjects) or lack of efficacy (2 subjects).

Subjects were discontinued from treatment with eltrombopag if no response was observed after 16 weeks. Subjects were discontinued from treatment with eltrombopag if no haematologic response has been observed after 16 weeks or upon detection of new cytogenetic abnormalities.

Recruitment

As of the clinical cut-off date of 09 May 2014, 44 subjects had been enrolled in the study.

Conduct of the study

The original protocol was planned to enrol and treat 25 subjects (Cohort 1).

The protocol was amended 20 April 2012 to increase enrolment from 25 to a maximum of 45 subjects, and to allow subjects with tri-lineage haematopoiesis to taper off eltrombopag.

The protocol was amended 05 February 2013 to increase enrolment to a maximum of 50 subjects, and to allow subjects with tri-lineage haematopoiesis to taper off eltrombopag. Subjects enrolled under these amendments are referred to as Cohort 2.

The pivotal study did not reach the target enrolment of 50 subjects because the NIH decided to stop enrolling in the ELT112523 study when their second refractory study (ELT116826), opened. The NIH's rationale for this decision was that the pivotal study had a long period of escalation to the effective dose of 150 mg and a short duration of treatment at the effective dose prior to response assessment. The NIH considered the dosing and administration of eltrombopag in ELT116826 (starting dose of 150 mg and 6 month duration of treatment) likely to be more effective than the dosing and administration of eltrombopag in ELT112523. Therefore, once ELT116826 was opened the NIH closed enrolment in the pivotal study.

Baseline data

All subjects enrolled in the study were platelet transfusion dependent, or had untransfused platelet counts ≤30 Gi/L at baseline. The majority of subjects had bi-lineage or tri-lineage cytopenias at baseline and were both platelet and RBC transfusion dependent. All subjects had an insufficient response to prior intensive immunosuppressive therapy (including hATG, rabbit ATG, alemtuzumab and cyclophosphamide).

The median age was 45 years and the majority of subjects were between the ages of 18 and 64 years (63%) (Table 3). Two subjects were 17 years old at entry into the study. No subjects were over 85 years of age. A majority of subjects were male (56%) and the most common race was White (47%).

Table 3 Baseline Demographic Characteristics (Study ELT112523; Safety Population)

	Eltrombopag (N=43)
Age (yrs)	
Mean (SD)	45.5 (19.82)
Median (min-max)	45.0 (17-77)
Age group (yrs), n (%)	
<18	2 (5)
18 - 64	27 (63)
65 - 74	12 (28)
≥75	2 (5)
Sex, n (%)	
Female	19 (44)
Male	24 (56)
Race/Ethnicity, n (%)[a]	
White	20 (47)
Black	13 (30)
Hispanic	9 (21)
Asian	1 (2)

Data Source: m5.3.5.2 ELT112523 CSR Section 5.5.1
Abbreviations: SD=Standard Deviation
a. Categories NIH used to capture race/ethnicity.

The median time since diagnosis of SAA until screening was 31 months (range: 10-190 months) (Table 4). All subjects met criteria for diagnosis of SAA and the baseline median values for ANC, platelets, haemoglobin and reticulocytes were indicative of the pancytopenic SAA patient population (Table 4) despite inclusion of laboratory values from patients recently transfused. At baseline, 91% of subjects were platelet transfusion-dependent and 86% were RBC transfusion-dependent. Subjects received a median of 4 platelet transfusions and 4 RBC transfusions in the 4 weeks prior to entry into the study.

The majority of subjects, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 subjects had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens.

Table 4 Disease Characteristics at Screening (Study ELT112523; Safety Population)

	Eltrombopag (N=43)
Time Since Diagnosis (Months)	
Median (min-max)	30.9 (10-190)
Transfused at Referral - Platelets, n (%)	
Yes	39 (91)
Number of Platelet Transfusions per Month at Referral, n (%)	n=39
Median (min-max)	4.0 (1-9)
Transfused at Referral - RBC, n (%)	
Yes	37 (86)
Number of RBC Transfusions per 8 Weeks at Referral	n=37
Median (min-max)	4.0 (1-17)
Transfused at Referral - Platelet & RBC, n (%)	
Yes	35 (81)
Karyotype, n (%)	n=42
Normal	38 (88)
Abnormal	3 (7)
Insufficient metaphases	1 (2)
Baseline Labs, n (%)	n=43
Neutropenia (<0.5 Gi/L)	18 (42)
Thrombocytopenia (<20 Gi/L)	18 (42)
Anaemia (<10 g/dL)	35 (81)
Baseline Median Lab Values	
ANC, Gi/L	0.58 (0.07-2.81)
Platelets, Gi/L	20 (6-90)
Haemoglobin, g/dL	8.4 (6.6-13.8)
Reticulocytes, Gi/L	24.3 (1.7-96.9)

Data Source: m5.3.5.2 ELT112523 CSR Section 5.5.2

All patients enrolled in the study received at least 1 prior ATG based intensive immunosuppressive therapy; either horse (95%) or rabbit ATG (58%) were the most common (Table 5). Other ISTs received by subjects in this study were alemtuzumab and cyclophosphamide. In addition, 93% of subjects received other medications for the treatment of their SAA. Androgens were administered as prior treatment to 37% of subjects. The remaining other medications previously received for SAA included non-intensive immunosuppressive agents (cyclosporine, tacrolimus, sirolimus, rituximab, daciluzumab, steroids, immunoglobulins), supportive care agents (GM-CSF, Neupogen, Procrit and Nplate) and methotrexate.

Table 5 **Summary of Prior Intensive Immunosuppressive Therapies and Other Medications for Aplastic Anaemia (Study ELT112523; Safety Population)**

	Eltrombopag (N=43)
Any medication, n (%)	**43 (100)**
Prior IST Medications	43 (100)
Horse ATG Based regimen	41 (95)
Rabbit ATG Based regimen	25 (58)
Alemtuzumab	15 (35)
Cyclophosphamide	6 (14)
Other[a]	1 (2)
Other Medications for SAA	40 (93)
Androgens (e.g., danazol)	16 (37)
Other[b]	34 (79)

Data Source: m5.3.5.2 ELT112523 CSR Section 5.6.1

a. ATG (non-specified)

b. Non-intensive immunosuppressive agents (cyclosporine, steroids [prednisone, corticosteroids, nandrolone], daciluzumab, mycophenolate, tacrolimus, rituximab, sirolimus and immunoglobulins [IVIG and WINRHO]), supportive care agents (GM-CSF, Neupogen, Nplate, Procrit) and methotrexate.

Subjects were heavily pretreated, with 84% having received at least 2 prior ISTs and more than 30% of subjects having received at least 3 prior immunosuppressive regimens (Table 6).

Table 6 **Summary of Number of Prior Immunosuppressive Therapies (Study ELT112523; Safety Population)**

	Eltrombopag: (N=43)
Number of Prior Immunosuppressive Therapies, n (%)	
≥ 1	43 (100)
≥ 2	36 (84)
≥ 3	14 (33)
≥ 4	3 (7)

Data Source: m5.3.5.2 ELT112523 CSR Section 5.6.1

Numbers analysed

Of the 43 subjects who received eltrombopag, 40 (93%) were escalated to the maximum dose of eltrombopag 150 mg. Three subjects who did not receive the maximum dose of 150 mg received a maximum dose of 125 mg. All 3 subjects had AEs leading to treatment discontinuation or dose modifications. Given the design of the study, in which subjects who did not meet response criteria were discontinued from treatment after 3 months, the median time on treatment was 3.6 months. Nine subjects received eltrombopag for more than 12 months, with a maximum duration of 39 months.

Outcomes and estimation

Primary endpoint

Haematologic response was achieved in 17 subjects (40%) in at least 1 lineage (95% CI: 25-56%). One subject had a tri-lineage response, 3 subjects had bi-lineage responses, and the remaining 13 had a uni-lineage response. The majority of responders (65%) met platelet response criteria, followed by ANC and haemoglobin response criteria (47% and 18%, respectively) (Table 9).

The prior treatment history of responders was similar to the overall population in the study with 84% having received at least 2 IST prior to entry into the study. Baseline disease characteristics were similar between responders and non-responders. In summary, treatment with eltrombopag produced a 40% response rate in the heavily pretreated patient population, where no established standard of care exists.

Table 9 Summary of Lineage Characteristics of Haematologic Response (Study ELT112523; Safety Population)

	Primary Response Assessment	Best Response Observed	Response at Last Assessment
	Eltrombopag (N=17)	Eltrombopag (N=17)	Eltrombopag (N=17)
Response Criteria: Response Due To, n (%)			
Unilineage	13 (76)	8 (47)	5 (29)
Multilineage	4 (24)	9 (53)	9 (53)
Bilineage	3 (18)[a]	4 (24)	4 (24)
Trilineage	1 (6)	5 (29)	5 (29)
Relapsed by Last Assessment			3 (18)
Response By Lineages[b], n (%)			
Platelet	11 (65)	12 (71)	12 (71)
Haemoglobin	3 (18)	8 (47)	6 (35)
Neutrophils	8 (47)	11 (65)	10 (59)

Data Source: m5.3.5.2 ELT112523 CSR Section 6.2.1

a. Subject 1 responded according to ANC criteria at Week 12, and then had a Week 16 visit at which he responded according to ANC and platelet criteria.

b. Subjects could be counted as a response according to more than 1 criteria.

Responders were allowed to continue eltrombopag in the extended treatment portion of the study. Fourteen of the 17 responders entered into the extension phase. As of the clinical cut-off date, 10 responders (65%) were ongoing in the study and continued to maintain a response.

Secondary endpoints

Best Response: Best response during the study (defined as the best lineage response, i.e., uni-lineage, bi-lineage or tri-lineage, observed during the assessment phase) was determined to assess whether response to eltrombopag improved over time after continued treatment.

Of the 14 subjects who entered the extension phase of the trial, 7 subjects had improvements in more than 1 lineage following continuation of treatment in the extension:

- 5 subjects with uni-lineage response improved to multi-lineage response (bi-lineage or tri-lineage).
- 2 subjects with bi-lineage response improved to tri-lineage response

At the time of their best response, a total of 5 subjects had tri-lineage responses and 4 additional subjects had bi-lineage response. Three of the 4 bi-lineage responders also had improvements in haemoglobin >1.5 g/dL; however, as their baseline haemoglobin was above 9 g/dL they are not counted as having an erythroid response. The remaining 8 subjects had a uni-lineage best response.

Last Response

Response at each subject's last assessment (Last Response) was examined to assess maintenance of effect over time during continued treatment. For 14 of 17 subjects, including all 9 tri-lineage and bi-lineage responders, the last response assessed was the same as the best response. The remaining 3 subjects relapsed at the Month 3 Extension visit.

Duration of Response

Duration of response was assessed for subjects who met the haematologic response criteria at the Primary Response Assessment and had at least 2 response assessments. Of the 17 subjects who responded, 2 subjects did not have at least 2 response assessments and were not evaluable for response duration. Fifteen responders evaluable for assessment of response duration had a median duration of investigator-assessed response of 12.0 month.

Ten of the 15 responders were ongoing in the extension portion of the study and therefore their duration of response was censored at the last response assessment. At the last response assessment, the median duration of response for these subjects was 32.9 months (range: 11.0 to 54.8 months). The remaining 5 subjects stopped treatment in the extension and are no longer being followed for efficacy (1 subject due to an AE, 1 subject due to a cytogenetic change and 3 subjects due to relapse).

Transfusion Independence

Baseline platelet and RBC transfusion dependence was defined as the subject receiving at least 1 transfusion in the month prior to the first dose of eltrombopag. Post-baseline transfusion independence was achieved if subjects who were transfusion dependent at baseline became transfusion free for a period of at least 28 (platelets) and 56 days (RBCs). The time period for assessment of transfusion independence was anytime during the treatment period and during 4 weeks of the follow-up or the last visit, whichever occurred first.

Platelet Transfusion Independence: Of the 39 subjects who were platelet transfusion dependent at baseline, 59% (23 subjects) became platelet transfusion independent during the study. The 4 subjects who were platelet transfusion independent at baseline remained platelet transfusion independent during the study. The longest platelet transfusion free period for the entire treated population was 33 days (median). The longest platelet transfusion free period for non-responders was similar (median of 27 days). The longest platelet transfusion free period for responders was 287 days (median). All responders had received at least 1 platelet transfusion in the month prior to study entry, with the exception of 2 subjects.

RBC Transfusion Independence: Of the 37 subjects who were RBC transfusion dependent at baseline, 27% (10 subjects) became RBC transfusion independent during the study. Of the 43 subjects treated in the study, 6 subjects (4 responders, 2 non-responders) were RBC transfusions independent at baseline. All 6 subjects remained RBC transfusion independent during the study. Thirty-seven of the 43 subjects in the study received at least 1 RBC transfusion in the month prior to study entry. The longest RBC transfusion free period for the entire study population was 32 days (median). The longest RBC transfusion free period for non-responders was similar (median of 29 days). The longest RBC transfusion free period for responders was 266 days (median). All responders had received at least 1 RBC transfusion in the month prior to study entry, with the exception of 4 subjects. Seven of the 17 responding subjects met haemoglobin and/or RBC transfusion independence criteria for response.

Maintenance of Response after Discontinuation of Eltrombopag

As of the clinical cut-off date, 7 subjects that discontinued eltrombopag had maintained a response.

Reconstitution of Haematopoiesis

Bone marrow examinations were performed during screening, at the Primary Response Assessment and every 6 months thereafter. Restoration of bone marrow cellularity and tri-lineage haematopoiesis was shown in a proportion of responders.

Health Outcomes

Health outcome measures were summarized and analyzed as specified by the developers of the Medical Outcomes Trust for the Short Form-36 item (SF-36) V2 instrument. Descriptive health outcomes results were presented at baseline, post-baseline, and change from baseline. At baseline, subjects reported slight to modest impairment in all eight dimensions of HRQoL as well as in physical and mental health component scores.

No changes at all were reported in HRQoL scores.

Ancillary analyses

Additional comparisons of results were performed for demographics, the number of prior IST therapies and by cohort for the ELT112523 study. No apparent differences in response to eltrombopag were noted; albeit these comparisons were limited by the small numbers of subjects.

Subpopulations of age, sex and race in ELT112523 are summarized below: Response rate was compared by gender: 11/24 (46%) males and 6/19 (32%) females responded to treatment with eltrombopag; Comparisons of response by age were not performed because of the small numbers of subjects <18 years or >65 years. Comparisons of response by race were not performed due to the small number of subjects in each category.

The response rate was similar when examined by the number of prior IST received: 1 prior IST, 3/7 (43%); 2 prior IST, 8/22 (36%); 3 prior IST 5/11 (45%); and 4 prior IST 1/3 (33%).

The response observed in Cohort 1 and Cohort 2 was similar: Cohort 1: 11/25 subjects (44%); Cohort 2 6/18 (33%).

In addition, given the close relationship between transfusions and platelet/RBC counts, the number of patients who achieved a response based on increments in platelet and haemoglobin values above the established threshold and those who reached a response based on transfusions criteria has been clarified. A total of 11 subjects met the platelet response criteria, 8 of the 11 subjects met the criteria by having 'stable platelet counts with transfusion independence for a minimum of 8 weeks' at the Primary Response Assessment. Seven of the 8 subjects have not required a subsequent platelet transfusion (1 subject had a single platelet transfusion after platelet response and has subsequently been platelet transfusion independent for >250 days). The remaining 3 subjects met the platelet response criteria by having 'platelet count increases of at least 20Gi/L above baseline'; none of these 3 subjects had platelet transfusions within 3 months prior to meeting platelet count response criteria. A total of 3 subjects met the erythroid response criteria at the Primary Response Assessment, one had 'an increase in haemoglobin by >1.5 g/dL over baseline <9g/dL' and 2 had an 'absolute reduction of at least 4 RBC transfusions for 8 consecutive weeks, compared to the number of transfusions in the 8 weeks pre-treatment'. The 2 subjects who met the reduction in RBC transfusion requirements relapsed at the Month 3 Extension visit.

Regarding the maintenance of the effect after treatment discontinuation, as of January 2015 cut-off date, 7 subjects that discontinued eltrombopag had maintained a response, 5 correspond to those reaching a tri-lineage hematologic response who were able to taper off (plus 1 additional case not previously reported) and stop eltrombopag.

Summary of main study

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

Summary of efficacy for trial ELT112523

Title: A pilot Study of a Thrombopoietin-receptor Agonist (TPO-R agonist), Eltrombopag, in Aplastic Anaemia Patients with Immunosuppressive-therapy Refractory Thrombocytopenia			
Study identifier	ELT112523		
Design	open-label, single centre, non-randomized, single-arm, Phase II, dose modification study to assess the safety and efficacy of eltrombopag in subjects with SAA and an insufficient response to IST.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		haematologic response at 3-4 months N/A Monitoring every 3 months until criteria met or reasons for discontinuation
Hypothesis	null hypothesis: response rate with this treatment was no greater than 10%. The null hypothesis of p≤10% was to be rejected if the total number of responders out of 25 subjects within 12 weeks was 6 or more: 11 subjects were determined to have responded, so that the objective of the design was met and the null hypothesis rejected		
Treatment groups	eltrombopag		
Endpoints and definitions	Primary Efficacy Endpoint	Haematologic response	Haematologic response was defined as meeting 1 or more of the following criteria: • Platelet count increase to 20 Gi/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks; • Haemoglobin increase by >1.5 g/dL for subjects with pre-treatment haemoglobin <9 g/dL, or a reduction in the units of RBC transfusions by at least 4 for 8 consecutive weeks, compared with the 8 weeks pre-treatment; • ANC increase of 100% (for pre-treatment levels <0.5 Gi/L), or an ANC increase >0.5 Gi/L.
	Secondary	Best Response	Best response defined as the best lineage response, i.e., uni-lineage, bi-lineage or tri-lineage, observed during the assessment phase

	Secondary	Last Response; Duration of Response	Last Response; Response at each subject's last assessment (Last Response) was examined to assess maintenance of effect over time during continued treatment. For 14 of 17 subjects, including all 9 tri-lineage and bi-lineage responders, the last response assessed was the same as the best response. The remaining 3 subjects relapsed at the Month 3 Extension visit. Duration of haematological responses at 3 months, 12 months and yearly thereafter
Database lock	clinical cut-off 09 May 2014		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description		
descriptive statistics and estimate variability	Treatment group	eltrombopag
	Number of subject	43
	Response at w12, n (%)	17 (40%)
	(95%CI)	(25, 56)
Notes		
Analysis description	**Secondary analysis based on 17 out of 43 responders** Of the 14 subjects who entered the extension phase of the trial, 7 subjects had improvements in more than 1 lineage following continuation of treatment in the extension:5 subjects with uni-lineage response improved to multi-lineage response (bi-lineage or tri-lineage); 2 subjects with bi-lineage response improved to tri-lineage response	

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analyses and/or meta-analysis have been presented.

Clinical studies in special populations

There are no new specific studies in special populations.

The main study included two 17 years old subjects and 14 (32%) elderly patients, two were over 75 years old. Study ELT116826 has included 3 adolescents and 1 elderly subject (65-69 year old). Study ELT116843 has included 7 adolescents up to date.

Across the 3 SAA studies (ELT112523, ELT116826 and ELT116643) a discussion of the efficacy and safety results in the subset of paediatric populations was presented:

Children and Adolescents

At the time of enrolment, a total of 18 (13%) of the 134 SAA subjects enrolled in the SAA dataset are less than 18 years of age (Table **x**). The majority (12 subjects) were enrolled in the treatment naïve study (ELT116643), which is not the subject of the current application; 6 subjects (all between the ages of 12 and 17) had an insufficient response to immunosuppressive therapy and were enrolled in ELT112523 and ELT116826.

Table 1 Overall Number of Paediatric SAA Subjects Exposed to Eltrombopag by Study and Age Group

	Age 2-5, n (%)	Age 6-11, n (%)	Age 12-17, n (%)	Total Paediatric Subjects, n (%)
Non controlled trials, Total N=134[a]	**1 (1)**	**1 (1)**	**16 (12)**	**18 (13)**
ELT112523, N=43	0	0	2 (5)	2 (5)
ELT116826, N=28	0	0	4(14)	4 (14)
ELT116643, N=63[a]	1 (2)	1 (2)	10 (16)	12 19)

a. One adult subject received treatment with hATG/CsA but did not receive eltrombopag due to the detection of a cytogenetic abnormality on the baseline bone marrow aspirate.

Table 2 Overall Response and Safety Profile of Paediatric SAA Subjects by Study

	Responders[a], n (%)	SAEs, n (%)	Cytogenetic Abnormality, n (%)	MDS/AML , n (%)
ELT112523, N=2	0	1 (50)	1 (50)	1 (50)
ELT116826, N=4	3 (75)	1 (25)	0	0
Total paediatric subjects with an insufficient response to prior therapy (ELT112523 and ELT116826) N=6	**3 (50)**	**2 (33)**	**1 (17)**	**1 (17)**
ELT116643, N=12	9 (75)[b]	7 (58)	0	0

a. Responders at the 3 month and/or 6 month response assessment.
b. One subject has not reached the 3-month response evaluation

Elderly

As of the 14 January 2015 clinical cut-off date, a total of 24 (18%) of the 134 subjects in the SAA eltrombopag dataset are aged 65 or above (Table 4). The majority of subjects (22 subjects) fall into the 65-74 age category. No subjects aged 85 or older have been enrolled, and 2 subjects between 75 and 84 have been enrolled.

Table 4 Overall Number of Elderly SAA Subjects Exposed to Eltrombopag by Study and Age Group

	Age 65-74, n (%)	Age 75-84, n (%)	Age 85+, n (%)	Total Elderly Subjects , n (%)
Non controlled trials, Total, N=134[a]	**22 (16)**	**2 (1)**	**0**	**24 (18)**
ELT112523, N=43	12 (28)	2 (5)	0	14 (33)
ELT116826, N=28	3 (11)	0	0	3 (11)
ELT116643, N=63[a]	7 (11)	0	0	7 (11)

a. One adult, non-elderly subject received treatment with hATG/CsA but did not receive eltrombopag due to the detection of a cytogenetic abnormality on the baseline bone marrow aspirate.

Table 5 Overall Response and Safety Profile of Elderly SAA Subjects by Study

	Responder[a] n (%)	SAEs n (%)	Cytogenetic Abnormality n (%)	MDS/AML n (%)
ELT112523, N=14	6 (43)	7 (50)	2 (14)	1 (7)
ELT116826, N=3	1 (33)[a]	0	0	0
Total elderly subjects with an insufficient response to prior therapy (ELT112523 and ELT116826) N=17	**7 (41)[a]**	**7 (41)**	**2 (12)**	**1 (6)**
ELT116643, N=7	5 (71)[a]	5 (71)	1 (14)	0

a. Responders at the 3 month and/or 6 month response assessment
b. One subject has not yet reached the 3 month response assessment and is not evaluable for response yet.

Supportive study(ies)

Study ELT116826

Study Design

ELT116826 is an ongoing, open-label, non-randomized, single-arm, Phase II, single centre study to evaluate the safety and efficacy of eltrombopag in subjects aged 2 and above with refractory SAA. This was an investigator-sponsored study conducted by the NIH. The investigators at the NIH designed this study as a non-randomized, single-arm study due to ethical and practical concerns regarding enrolling subjects into a randomized study given the results of ELT112523 and the lack of alternative treatment options for this patient population. The starting daily dose of eltrombopag was 150 mg, with dose adjustment for East Asian and children. The dose of eltrombopag 150 mg dose was chosen for this trial based on the results seen in the pivotal study ELT112523, where nearly all subjects required escalation to 150 mg to achieve haematologic response. During the extension protocol the same dose adjustments as for Study 23 were included.

The planned enrolment was 60 subjects to have 49 subjects evaluable for response at 6 months. Subjects who could not tolerate the medication or did not respond by 24 weeks discontinued eltrombopag. Responding subjects were eligible to enter an extended treatment portion of the study. The dose of eltrombopag during the extended access was the lowest dosage that maintained stable platelet counts. This study is ongoing and data are included up to clinical cut-off 31 March 2014.

The primary endpoint of the study was haematologic response (platelet count, erythroid or neutrophil) at 6 months (24 weeks). Haematological response is defined as:

-Platelet count increases to 20 Gi/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks;

-Haemoglobin increase by >1.5 g/dL (for subjects with pre-treatment haemoglobin <9 g/dL), or a reduction in the units of red blood cell transfusion by at least 4 of 8 consecutive weeks pre-treatment;

-Absolute neutrophil count increase of 100% (for pre-treatment levels <0.5 Gi/L), or an ANC increase >0.5 Gi/L.

Secondary endpoints included duration of response (haematological responses at 3 months, 12 months and yearly thereafter), relapse, and progression to clonal haematopoiesis (PNH evolution, cytogenetic abnormalities in bone marrow, myelodysplasia by morphology, or acute leukaemia), survival, and health-related quality of life.

The planned analysis included descriptive statistics on the proportion of responders (% subjects with treatment response).

Results

As of the clinical cut-off date of 31 March 2014, 15 of the planned 60 subjects have been enrolled. Five subjects have completed 6 months of treatment and are evaluable for the 6 month primary response assessment; 4 of the 5 subjects have entered the extension phase of the study. Eight subjects are ongoing with <6 months on treatment. The remaining 2 subjects discontinued treatment at the 3 month assessment due to detection of a cytogenetic abnormality. Median age of subjects was 46 years (14, 69), with 3 subjects being in the 12-17 year range. Median baseline lab values were 0.53 –Gi/L for neutrophils, 11 Gi/L for platelets, 34.7 Gi/L for reticulocytes and 8.6g/dL for haemoglobin.

At the 31 March 2014 clinical cut-off date, 11 and 6 subjects, respectively, were evaluable or had discontinued treatment at the 3 and 6 month response assessments. At the 3 month assessment 4 of 11 (36%) evaluable subjects met the haematologic response criteria in at least 1 lineage. At the 6 month assessment (primary response assessment), 4 of 6 (67%) evaluable subjects met the haematologic response criteria in at least 1 lineage. As of the clinical cut-off date, 2 of the 4 subjects with a response at the 3 month assessment were evaluable and had maintained their response at 6 months. The remaining 2 subjects had not had their 6 month assessment as of the clinical cut-off date.

Table 14 3 and 6 Month Response Assessments (ELT116826)

Haematologic Response, n (%)	3 Month N=11	6 Month N=6
Response	**4 (36)**	**4 (67)**
Response Criteria; Response Due to, n (%)		
Unilineage	2 (50)	2 (50)
Multilineage	2 (50)	2 (50)
Bilineage	2	2
Trilineage	0	0

Data Source: m5.3.5.2 ELT116826 Short Study Summary

Updated results (cut-off date March 2015)

Based upon the 14 January 2015 clinical cut-off date, a total of 16 subjects have completed 6 months of treatment with eltrombopag. Five additional subjects were withdrawn from treatment with eltrombopag prior to completing 6 months of treatment, but are included in the number of subjects

evaluable for response at 6 months according to ITT principles. A total of 21 subjects were evaluable for response at the 6 month primary endpoint in the updated dataset.

Table 1 Haematologic Response in ELT112523 and ELT116826

Haematologic Response	ELT112523		ELT116826	
	Primary Response Assessment N=43	Best Response Observed N=43	3 Month Assessment N=24	6 Month Assessment N=21
Response, n (%)	17 (40)	17 (40)	11 (46)	11 (52)
Response Criteria; Response Due to, n (%)				
Uni-lineage	13 (76)	8 (47)	8 (73)	6 (55)
Multi-lineage	4 (24)	9 (53)	3 (27)	5 (45)
Bi-lineage	3 (18)	4 (24)	2 (18)	2 (18)
Tri-lineage	1 (6)	5 (29)	1 (9)	3 (27)

Detailed transfusion data are not available for the ongoing ELT116826 study.

In the supportive study (ELT116826), 4 subjects had a bleeding SAE reported (craniocerebral injury; epistaxis; haemorrhage intracranial; and gastrointestinal haemorrhage). None were considered related to eltrombopag. Three of the 4 subjects were non-responders to eltrombopag. The remaining subject fell and hit her head after 138 days on eltrombopag, prior to achieving a platelet response. Her platelet count was <20Gi/L and the fall resulted in a small intracranial haemorrhage. The subject was hospitalized overnight and received a platelet transfusion. The subject remained on the study, achieved a tri-lineage response to eltrombopag and as of the clinical cut-off, was continuing on study (Day 354). In summary, after achieving the platelet haematologic response criteria, no clinically relevant bleeding AEs have been reported across the 2 studies.

In the supportive study (ELT116826), a total of 6 subjects had at least 1 SAE of infection. Five of these subjects did not have an ANC response or had the infection prior to neutrophil response. One subject had a SAE of colitis reported during an ANC response (100% increase in ANC to 0.35Gi/L from a baseline of 0.14Gi/L).

Study ELT116643

Study Design

ELT116643 is an open-label, single-arm, Phase I/II single centre study to evaluate the safety and efficacy of eltrombopag in combination with hATG/CsA in treatment naïve subjects with SAA. Sixty-two subjects will be enrolled in this study; the first 31 subjects will be enrolled to Cohort 1 (eltrombopag treatment for 6 months) and the remaining 31 subjects will be enrolled to Cohort 2 (eltrombopag treatment for 3 months). This was an investigator-sponsored study conducted by the NIH.

The starting daily dose of eltrombopag was determined by subject age and ethnicity, 150 mg once daily in the >12 year old subjects (75 mg for East Asian subjects), in combination with a standard regimen of hATG/CsA. Eltrombopag was initiated on day 14 to avoid overlap with the known transient hepatotoxicities associated with hATG/CsA.

The dose of eltrombopag 150 mg dose was chosen for this trial based on the results seen in the pivotal study ELT112523, where nearly all subjects required escalation to 150 mg to achieve haematologic response. Dose delays or dosing interruptions of eltrombopag were permitted when clinically indicated at the discretion of the investigator. In both cohorts, the primary endpoint was complete haematologic

response at 6 months. Subject reported outcomes were collected at baseline, 3 months, 6 months, and annually for 5 years.

Eltrombopag was discontinued at 6 months along with the CsA regardless of response characteristics for Cohort 1 subjects. In Cohort 2 subjects, eltrombopag was discontinued at 3 months and CsA was continued until 6 months. This study is ongoing and data are included up to clinical cut-off 31 March 2014.

The primary endpoint was the rate of complete haematologic response at six months. A complete response (CR) was defined as meeting all 3 of the following values on 2 serial blood count measurements at least 1 week apart at landmark time points (3 and 6 months): ANC >1 Gi/L, Platelet count >100 Gi/L, Hgb >10 g/dL.

The key secondary efficacy endpoint was partial response (PR), defined as blood counts no longer meeting the standard ('Camitta') criteria for severe pancytopenia in SAA, equivalent to 2 of the following values obtained on 2 serial blood count measurements at least 1 week apart at landmark time points (3 and 6 months): ANC >0.5 Gi/L, platelet count >20 Gi/L and/or Absolute reticulocyte count (ARC) >60 Gi/L. The planned analyses include descriptive statistics on the proportions of responses (% subjects with partial or complete response).

Results

As of the clinical cut-off date of 31 March 2014, 31 of the planned 31 subjects have been enrolled in Cohort 1; 16 of the planned 31 subjects have been enrolled in cohort 2. A total of 44 patients have received treatment with eltrombopag: 13 are ongoing, 27 have completed the planned eltrombopag treatment period and 4 discontinued eltrombopag prior to completion of the planned treatment period.

Median age of subjects was 39 years (12, 72), with 7 subjects being less than 18 years of age (12-17).

At the 6 month assessment, the primary endpoint of CR was met by 10 (36%, [95% CI: 19%, 56%]) of 28 evaluable subjects and 22 subjects overall (79%) had a CR or PR. At the 3 month assessment, 6 (18%) of 33 subjects had a CR, and 26 subjects (79%) had an overall response.

As of the clinical cut-off date, 5 of the 6 subjects with a CR at 3 months were evaluable and maintained a CR at the 6 month assessment. The remaining subject had not had his or her 6 month assessment as of the clinical cut-off date. The remaining 5 subjects with a CR at 6 months had PR at the 3 month assessment. Five of the 10 subjects with CRs reported at 6 months met the SAA criteria in all 3 lineages at baseline. Of the subjects who responded, 5 subjects relapsed after per protocol discontinuation of eltrombopag at 6 months. No responding subjects relapsed while receiving eltrombopag treatment.

2.4.3. Discussion on clinical efficacy

The main evidence of the efficacy of eltrombopag in SAA is provided by study ELT112523, a non-randomized, single-arm, open-label, Phase II study of eltrombopag in subjects with SAA and insufficient response after treatment with ATG/CsA. Supportive efficacy is provided from an ongoing non-randomized, Phase II, single-arm, open-label dose modification study (ELT116826) in refractory SAA subjects, that intend to improve and replicate Study ELT112523 results. Additional data from an ongoing, non-randomized, Phase I/II, single-arm, open-label study (ELT116643) of eltrombopag in combination with horse anti-thymocyte globulin (hATG)/CsA in treatment naïve SAA subjects is provided, although this is less relevant for the claimed indication. These were investigator-sponsored

studies conducted by the Hematology Branch of the National Heart, Lung and Blood Institute/National Institutes of Health (NHLBI/NIH) and supported by GlaxoSmithKline (GSK).

Design and conduct of clinical studies

Considering the rarity of the disease in general, particularly the subset of patients with refractory SAA, and also bearing in mind that for these patients there are few treatment options available, mostly experimental, the challenges for conducting a randomized controlled trial are acknowledged, therefore the submitted evidence, mostly based on two single-arm, non-randomized and open label trials can be considered an acceptable approach.

Study ELT112523 was aimed to assess the safety and efficacy of eltrombopag in subjects with SAA and an insufficient response to IST. The primary endpoint was the response rate of investigator-assessed haematologic response measured by blood counts (at least improvement in one lineage: platelets, haemoglobin or neutrophils) or transfusion-independence at week 12. Changes in transfusion requirements might be a relevant palliative effect. Secondary endpoints were mainly aimed to assess the improvement or maintenance of the response with long-term treatment, HRQoL, changes in bone marrow cellularity/morphology. Patients who reached a response at the primary 12-week assessment entered the extension phase, where the dose of eltrombopag was at the lowest dosage that maintained a stable platelet count until subjects met off-study criteria. Eltrombopag was tapered and stopped in subjects who achieved tri-lineage haematopoiesis (defined as platelets >50 Gi/L, haemoglobin [Hgb] >10 g/dL in the absence of RBC transfusions, and ANC >1 Gi/L for more than 8 weeks).

The included patient population appears well defined and representative of the intended target population. Further, the criteria to define transfusion requirements have been clarified. Although no standardised criteria were applied in the study protocols, centre clinical practice criteria were to be followed and these appear rather conservative and in line with clinical practice in the EU. Durable of transfusion independence responses support that the risk of bias due to the open label design of the study and potential change in transfusion practice would be unlikely.

Efficacy data and additional analyses

A total of 44 patients age ≥12 years old with diagnosis of SAA with immunosuppressive therapy refractory thrombocytopenia were included. The starting dose of eltrombopag was 50 mg daily (25 mg for East Asian subjects), and the dose was increased to a maximum of 150 mg daily (75 mg for East Asian subjects).

In contrast to the approved indications, responses to treatment in SAA took up to 16 weeks and nearly all subjects (40/43; 93%) escalated to the maximum dose of eltrombopag 150 mg daily. Subjects who achieved the 'trilineage haematopoiesis' criteria (defined as platelets >50 Gi/L, Hgb >10 g/dL in the absence of RBC transfusions, and ANC >1 Gi/□L for more than 8 weeks) were tapered off of eltrombopag in 75 mg increments every 8 weeks provided criteria continued to be met. Five subjects tapered off eltrombopag treatment after meeting these criteria in ELT112523; none of these subjects have subsequently relapsed, with median follow-up duration of 20.6 months. Although subject numbers are limited, these data support the proposal to reduce the dose by up to 50% once 'tri-lineage haematopoiesis' criteria have been sustained for 8 weeks. If counts stay stable after 8 weeks at the reduced dose, then discontinue eltrombopag and monitor blood counts. If platelet counts drop to < 30 Gi/L, Hgb to < 9 g/dL or ANC < 0.5 Gi/L, eltrombopag may be reinitiated at the previous effective dose (see SmPC section 4.2). It can be acknowledged that treatment effect may take some time in this refractory population where no optimal treatments are available and thus, following

recommendations of the pivotal study, the proposal to discontinue treatment if no response is reached at week 16 can be considered a reasonable approach (see SmPC section 4.2).

Overall, the main study included a heavily pre-treated SAA population. All subjects had an insufficient response to prior intensive immunosuppressive therapy (including hATG, rabbit ATG, alemtuzumab and cyclophosphamide), in fact 77% of patients were truly refractory patients while 33% were relapse-refractory (i.e. insufficient responses despite at least 2 prior IS treatment). Subjects were heavily pretreated with 84% of subjects having received at least 2 prior immunosuppressive regimens and more than 30% of subjects having received at least 3 prior immunosuppressive regimens. The median time since diagnosis of SAA until screening was 31 months (range: 10-190 months). All subjects met criteria for diagnosis of SAA and the baseline median values for ANC, platelets, haemoglobin and reticulocytes were indicative of the pancytopenic SAA patient population despite inclusion of laboratory values from patients recently transfused. At baseline, 91% of subjects were platelet transfusion-dependent and 86% were RBC transfusion-dependent. Subjects received a median of 4 platelet transfusions and 4 RBC transfusions in the 4 weeks prior to entry into the study.

Haematologic response was achieved in 17 out of 43 subjects (40%) in at least 1 lineage (95% CI: 25-56%). One subject had a tri-lineage response, 3 subjects had bi-lineage responses, and the remaining 13 had a uni-lineage response at week 12. The majority of responders (65%) met platelet response criteria, followed by ANC and haemoglobin response criteria (47% and 18%, respectively). Fourteen of the 17 responders entered into the extension phase. As of the clinical cut-off date, 10 responders (65%) were ongoing in the study and continued to maintain a response. Of the 14 subjects who entered the extension phase of the trial, 7 subjects had improvements in more than 1 lineage following continuation of treatment: 5 subjects with uni-lineage response improved to multi-lineage response (bi-lineage or tri-lineage), 2 subjects with bi-lineage response improved to tri-lineage response, the remaining 8 patients with a response at week 12 remained uni-lineage responders. For 14 of 17 subjects, including all 9 tri-lineage and bi-lineage responders, the last response assessed was the same as the best response. The remaining 3 subjects relapsed at the Month 3 Extension visit. Of the 17 subjects who responded, fifteen were evaluable for assessment of response duration and had a median duration of investigator-assessed response of 12.0 month. At the last response assessment of the 10 patients who were ongoing or completed the extension phase, the median duration of response was 32.9 months (range: 11.0 to 54.8 months). The remaining 5 subjects stopped treatment in the extension and are no longer being followed for efficacy (1 subject due to an AE, 1 subject due to a cytogenetic change and 3 subjects due to relapse).

The effect on transfusion dependence is considered another way to interpret the clinical relevance of the observed effect. In the absence of a control arm, the assessment of changes in transfusion requirements before treatment and after treatment is the most reasonable approach. According to the study protocol a patient was considered transfusion independent if remained free of transfusion during 28 days for platelet or 56 days for RBC at any time during the treatment period. A total of 59% and 27% of patients became platelet and RBC transfusion independent, respectively. The median of days free of platelet or RBC transfusions were 287 days and 266 days, respectively in the 17 responder patients, respectively. For non-responders, median days free of transfusions were 27 days for platelets and 28.5 days for RBC. So, responders to eltrombopag had a median duration of platelet and RBC transfusion independence of approximately 9 and 8 months, respectively, which is considered a relevant effect. As of the clinical cut off the maximum duration of platelet and RBC transfusion free days was over 3 years and was continuing. Another way of evaluating the transfusion requirements in this patient population is to compare the transfusion requirements of responders pre- and post-treatment with eltrombopag. Nearly half of the responders who were platelet transfusion dependent at baseline, had a 100% reduction in platelet transfusion requirements, and 60% had at least a 50%

reduction in platelet transfusion requirements. Nearly a quarter of the subjects who were RBC transfusion dependent at baseline, had a 100% reduction in RBC transfusion requirements, and 62% had at least a 50% reduction in RBC transfusion requirements. Based upon this analysis, eltrombopag treatment resulted in a > 80% reduction in transfusion requirement compared to baseline in 53% of platelet transfusion dependent subjects and 54% of RBC transfusion dependent subjects.

In addition, given the close relationship between transfusions and platelet/RBC counts,

Eleven (11) patients achieved a response by meeting the platelet response criteria, 8 of the 11 subjects met the criteria by having 'stable platelet counts with transfusion independence for a minimum of 8 weeks' at the Primary Response Assessment.

Bone marrow examinations in responders did not suggest any event of particular concern. By contrary, restoration of bone marrow cellularity and haematopoiesis was reported in some responder subjects. No changes in HRQOL were detected relative to baseline at the timepoint assessed (Week 12 or 16), which is not unexpected given the short period of time and considering that some patients continued improving during the long-term follow up. Despite that the MAH argues that there was a trend for improvements in responders as well as anecdotal reports of improvements in daily activities, actually HRQoL was not properly evaluated beyond week 12 and data available are of little value to make any conclusion.

Response of 40% (17/43 patients) in at least 1 lineage at week 12, with continuous improvements observed in 9 patients with continuous treatment, including 5 tri-lineage responses, are considered encouraging results for a difficult to treat SAA population. It is recognised that the proportion of patient with a relevant benefit maintained in the long term is limited to 9 out of the initially included 43 patients, which is a small subset of the included population, but might be of relevance in a truly refractory SAA population. In fact, it is highlighted that one quarter of responders had multi-lineage responses at the Primary Response assessment and that this improved to approximately half of responders over time. The median duration of response was 1 year and no subjects with multi-lineage responses have relapsed, indicating durability of response. Subjects meeting protocol-defined tri-lineage blood counts no longer required treatment with eltrombopag and all have maintained their responses off of eltrombopag, with a median time off-drug of >20 months.

The relevance of the effect is in fact further substantiated by the effect in transfusion requirements as well as some benefit in terms of bleeding and infections reduction following improvement in blood counts. A total of 17 subjects had at least one bleeding AE reported on-therapy; none were considered related to treatment and none were serious. The majority of these subjects (15) did not respond to eltrombopag or had the bleeding AE prior to platelet response. Following achieving the platelet haematologic response criteria, a total of 2 subjects had a single bleeding AE each (ecchymosis and contusion, respectively). Concerning the incidence of infectious, a total of 19 subjects in the study had at least 1 AE of infection. The majority (11) of the subjects with infections reported were non-responders. The proportion of non-responders with 3 or more AEs of infections was double (12%) that observed in responders (6%). No responders had more than one SAE of infection reported, compared to 15% of non-responders.

The effect on survival was not included as an endpoint and given that non-responders were not followed beyond week 16, no conclusions can be drawn. Kaplan-Meier curves have been generated for the overall population and for responders: the KM estimate of the 1- year survival rate is 79% for all 43 subjects and the Kaplan-Meier estimate of the 1-year survival rate for the 17 responders is 93%. In the context of the poor outcomes expected in patients who have an insufficient response to IST (40%

mortality from complications of pancytopenia within 5 years of diagnosis), these results should be interpreted with caution.

From an efficacy point of view, only Study ELT116826 provides relevant supportive information for the claimed indication. The MAH initially presented very preliminary results corresponding to March 2014 cut-off date, with only 5 out of 60 subjects reaching the 6 month time point for the primary assessment. Updated data with a cut-off date January 2015 (including data available for a total of 21 subjects with 6-month efficacy assessment) provided consistent results to the pivotal study in the refractory SAA population following treatment with eltrombopag. The primary endpoint of haematologic response, measured by blood counts (platelets, haemoglobin or neutrophils) or reduction in platelet or RBC transfusions was achieved by 46% of subjects at 3 months and by 52% of subjects at the 6 month primary endpoint. Consistent with the observations from the pivotal study, the improvements in response were observed over time, with a higher proportion of responders at 6 months than at 3 months, and with a higher proportion of multi-lineage responses at 6 months than at 3 months. Some support from bleeding events and infectious was observed.

Although there was no concurrent comparisons and these preliminary data should be interpreted with caution, the consistent results from the replicated ongoing phase II study is considered to add robustness to the observed effect. Further, in the context of available treatment options results are considered clinically relevant and a suitable option for patients otherwise not candidates to HSCT.

In the SAA patient population eltrombopag is titrated to response based on platelet counts. The starting dose in ELT112523 was 50 mg once daily. Dose escalations in 25 mg increments every 2 weeks were performed based upon platelet response, up to a maximum dose of 150 mg daily. The starting dose in ELT116826 and ELT116643 was 150 mg.

The proposed dose escalating strategy (see SmPC section 4.2) has not been formally tested in any of the studies conducted; however, based on available data the proposed posology appears well justified and can be supported. The second phase II study which tests an starting dose of 150 mg is still ongoing it appears reasonable awaiting final study results before considering an alternative posology.

A priori no relevant factors could be identified to select patients likely to respond to eltrombopag. No apparent differences in response to eltrombopag based upon the following baseline demographics and disease characteristics: age, race, gender, prior treatments, transfusion requirements, number of cytopenias, abnormal karyotype, time since last IST and primary refractory or relapsed refractory to prior IST.

Given that hereditary AA were systematically excluded and considering that “insufficient response to prior IS therapy” appears too vague to properly define the target population, the CHMPconsiders that the indication should be revised to 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.

2.4.4. Conclusions on the clinical efficacy

Considering the rarity of the disease, the poor prognosis of subjects with refractory acquired SAA and the recognised unmet medical need, results from the two open label non comparative studies provide sufficient evidence of a clinically relevant effect in the treatment of adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior treatments or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation.

Additional efficacy data will be available from the supportive ongoing Study ELT116826 together with the requested safety data by Q4 2018 (see RMP)

2.5. Clinical safety

Introduction

The primary safety database comes from the pivotal Phase II Study ELT112523 (NIH); supportive safety data in SAA subjects are provided from the ongoing Phase II Study ELT116826 (NIH 13-H-0133) in subjects with an insufficient response to IST. An ongoing ELT116643 in subjects of 2 years of age or older with treatment-naïve SAA is also presented. Additional supportive safety data are provided from a completed, placebo-controlled Phase I/II Study PMA112509 in subjects with advanced MDS or acute myeloid leukaemia (AML)

Patient exposure

The Safety Population consists of all subjects who received at least 1 dose of eltrombopag in Studies ELT112523, ELT116826, and ELT116643, and all subjects who received at least 1 dose of eltrombopag or placebo in Study PMA112509. The safety data from the pivotal Study ELT112523 is not integrated with any other eltrombopag safety data.

Exposure in ELT112523:

Of the 43 subjects who received eltrombopag in Study ELT112523, 40 (93%) were escalated to the maximum dose of eltrombopag 150 mg. Three subjects received a maximum dose of eltrombopag 125 mg. Enrolment for Study ELT112523 was completed in February 2013. As of the data cut-off date, the majority of subjects (33) had completed treatment and follow-up in the study, the remaining 10 subjects were ongoing in the study (4 subjects continue to receive treatment with eltrombopag, 5 had tapered off eltrombopag due to trilineage haematopoiesis and 1 subject discontinued treatment due to a cytogenetic abnormality and continued in the study off-therapy for efficacy follow-up).

As of the safety update of 14.01.2015, 9 subjects were ongoing in the study and 1 was withdrawn from the study. Of the 9 subjects ongoing in the study, 3 subjects continue to receive eltrombopag (durations of ~2.5-4.5 years) and have maintained responses. Six subjects have tapered off eltrombopag due to tri-lineage haematopoiesis (1 additional subject since the Type II variation) and have maintained response without additional treatment for SAA as of the 14 January 2015 clinical cut-off. The subject withdrawn from the study as of this safety update had previously discontinued treatment due to a cytogenetic abnormality and continued in the study off-therapy for efficacy follow-up. After continuing follow-up for approximately 1 year after the last dose of eltrombopag, the subjects' counts began to decline and the subject was referred to another trial.

The majority of subjects (77%) have received eltrombopag for at least 3 months (Table x). A total of 12 subjects (28%) have received eltrombopag for over 6 months and 10 (23%) have been exposed to eltrombopag for at least 1 year.

Table 4 Summary of Eltrombopag Treatment Status in Study ELT112523

	Type II Variation Eltrombopag (N=43)	Safety Update Eltrombopag (N=43)
Treatment Status, n (%)		
Discontinued Treatment	39 (91)	40 (93)
Ongoing	4 (9)	3 (7)
Primary reason for eltrombopag treatment discontinuation[a], n (%)		
Completed scheduled treatment period	22 (51)	22 (51)
Adverse event	5 (12)	5 (12)
Responders tapered off due to continued efficacy	5 (12)	6 (14)
Lack of efficacy	2 (5)	2 (5)
Detection of cytogenetic abnormality	2 (5)	2 (5)
Lost to follow-up	1 (2)	1 (2)
Subject withdrew consent	1 (2)	1 (2)
Investigator discretion	1 (2)	1 (2)

a. Subjects may have only one primary reason for treatment discontinuation.

Exposure in ELT116826:

Of the 15 subjects who received eltrombopag up to 150 mg, 5 subjects completed 6 months of treatment with eltrombopag and 4 of the 5 subjects had entered the extension phase of the study. Enrolment is ongoing for Study ELT116826 in subjects with an insufficient response to prior immunosuppressive therapy. As of the clinical cut-off date (January 2015), 28 of the planned 60 subjects with previously treated SAA have been enrolled in Study ELT116826. Sixteen subjects have completed 6 months of treatment and are evaluable for the 6 month primary response assessment. Eleven of the 16 subjects are continuing treatment with eltrombopag in the extension. Seven ongoing subjects have received treatment for less than 6 months. The remaining 5 subjects discontinued treatment prior to completing 6 months of treatment.

ELT116643 Exposure:

Of the 44 subjects who received eltrombopag up to 150 mg, 19 subjects completed the planned 6-month eltrombopag treatment period in Cohort 1 and 8 subjects completed the planned 6-month period in Cohort 2. As of the clinical cut-off date of 14 January 2015, Cohorts 1 and 2 have been fully enrolled, and 1 of the planned 31 subjects have been enrolled in Cohort 3. A total of 62 subjects in Study ELT116643 have received treatment with eltrombopag compared with 47 subjects in the main study (Table 6). As previously reported, 1 subject received treatment with hATG/CsA but did not receive eltrombopag due to the detection of a cytogenetic abnormality on the baseline bone marrow aspirate. This subject is not included in the assessment of safety.

Adverse events

ELT112523

In Study ELT112523, on-therapy AEs were defined as those that occurred from the date of first dose of eltrombopag treatment to 30 days following the date of last dose of eltrombopag treatment. Nearly all subjects (93%) experienced at least 1 AE on-therapy and the majority of subjects had at least 1 AE considered by the investigator as possibly related to treatment. Five subjects had an AE that led to treatment discontinuation.

Nausea, fatigue, cough, diarrhoea, and headache were the most common AEs, reported by ≥20% of subjects. Thirty subjects (70%) in Study ELT112523 had at least 1 AE considered by the investigator

to be related to treatment, nausea, headache, and diarrhoea were the most common AEs (>20%) considered related to treatment. Abdominal pain was recorded 12%.

ELT116826

As of the clinical cut-off data (31 March 2014) in Study ELT116826, no AEs have led to discontinuation of eltrombopag treatment.

ELT116643

Serious adverse event / deaths / other significant events

Study ELT1125223

Thirty-three percent of subjects had an on-therapy SAE. Two deaths occurred during the on-therapy period of the study; a total of 6 deaths occurred during the entire study period.

As of the clinical cut-off data (31 March 2014) in Study ELT116643, there were 18 (41%) SAE, one of them was a SAE possibly related to eltrombopag. There was not AE leading to permanent discontinuation of study treatment.

Deaths

A total of 6 deaths (14%) were reported during this study. None of the 6 deaths were considered related to treatment by the investigator. No subjects died while receiving eltrombopag; 2 subjects died of sepsis/infection within 30 days of the last dose of eltrombopag and 4 subjects died more than 110 days after the last dose of eltrombopag.

The primary cause of death was disease under study, specifically sepsis/infection in 4 subjects; 3 of these subjects did not respond to treatment; 1 subject had a transient ANC response, which was not maintained at the Month 3 extension assessment.

One subject who had monosomy 7 detected in 4/20 metaphases at the Primary Response Assessment died from MDS/AML approximately 7 months after discontinuing treatment with eltrombopag. One subject died of an unknown cause approximately 4 months after the last dose of eltrombopag.

SAEs

The most common SAE reported on-therapy was febrile neutropenia, followed by sepsis and viral infection. The percent of responders with infectious SAEs (3/17; 18%) was less than that in non-responders (8/26; 30%) despite the shorter observation time for non-responders. Most subjects had recovered or were recovering from the SAE as of the data cut-off (09 May 2014), although 1 patient with aplasic anaemia and other with septic shock died. One subject had an SAE of abdominal discomfort that was considered related to treatment by the investigator.

Since the 9 May 2014 clinical cut-off date for ELT112523, no new SAEs or deaths have been reported up to the 14 January 2015 clinical cut-off date. Updated SAE narratives for the 16 subjects with SAEs (14 subjects with on-therapy SAEs) reported in the trial have been included. No new cytogenetic abnormalities, or cases of MDS or AML have been reported.

Adverse Events Leading to Permanent Discontinuation of Study Treatment At the time of the data cut-off for the Type II variation, 4 subjects (9%) in Study ELT112523 had discontinued treatment with eltrombopag due to AEs. As of the safety update clinical cut-off date, no additional subjects have discontinued treatment with eltrombopag due to AEs.

Study ELT116826

Deaths and SAEs

Six subjects out of 15 have had at least 1 SAE reported, none of which were considered related to treatment. No deaths have been reported. At the time of the data cut-off no deaths had been reported in Study ELT116826. As of the clinical cut-off date for this safety update, 2 subjects have died off therapy, one due to septic shock and diverticular perforation 146 days after the last dose of eltrombopag, and one due to sepsis 33 days after the last dose of eltrombopag. Both subjects and the events leading to death are presented below in the SAE section and narratives for the subjects are provided.

In Study ELT116826 at the time of the data cut-off for the Type II variation, 6 of the 15 subjects (40%) had 11 SAEs reported. As of the clinical cut-off date for this safety update, a total of 8 of 28 subjects (29%) have had a total of 25 SAEs reported. The most common SAEs reported in this study were infection and febrile neutropenia. None of the new SAEs for the safety update were considered related to eltrombopag treatment by the investigator.

Study ELT116643

Deaths and SAEs

As of the data cut-off date (31 March 2014), 1 subject died of encephalopathy and respiratory failure while on-therapy; neither event was considered related to study treatments. The 55-year-old male died of Grade 5 encephalopathy and respiratory failure 71 days after starting eltrombopag following ATG/CsA therapy. The subject was hospitalized approximately 1 month prior with recurrent Pseudomonas aeruginosa in the setting of severe neutropaenia. The events were complicated by cardiac tamponade and altered mental status requiring intubation and were considered unrelated to study treatment.

During the safety update period, 2 additional deaths have been reported, both occurred off therapy, ≥11 months after the last dose of eltrombopag.

-One subject died approximately 11 months after the last dose of eltrombopag. The subject died following transplant due to graft versus host disease (GVHD), Group B Strep bacteremia red cell and platelet destruction, and cerebral haemorrhage.

-One subject died approximately 2 years after the last dose of eltrombopag; the cause of death was reported as ‘post-BMT, relapsed AML’.

In Study ELT116643, 18 of the 44 subjects (41%) who received eltrombopag had 31 SAEs reported to the MAH. One event of squamous cell carcinoma was considered possibly related to treatment with hATG/CsA and eltrombopag. One subject had fatal events of encephalopathy and respiratory failure, which were not considered related to treatment. In Study ELT116643 at the time of the data cut-off for the Type II variation, 18 of the 44 subjects (41%) who received eltrombopag had 31 serious AEs reported. As of the clinical cut-off date for this safety update, a total of 26 of 62 subjects (42%) have had a total of 54 SAEs reported. The most common SAE reported in this study was febrile neutropenia in 8 subjects. One new event of rash was considered possibly related to eltrombopag.

Analysis of Adverse Events by Organ System or Syndrome

Several categories of AEs of special interest were analysed further: hepatobiliary events, treatment emergent events (TEEs), cytogenetic abnormalities, and haematologic malignancies.

Hepatobiliary

Two subjects in Study ELT112523 had ALT or AST >3x the upper limit of normal (ULN) concurrent with total bilirubin >1.5xULN. In both cases, bilirubin elevations were due to indirect bilirubin. Hepatobiliary AEs were reported for 16 subjects. Thirteen subjects had no changes to eltrombopag dosing; 2 subjects (Subjects 25 and 44) had treatment interrupted due to elevated LFTs and 1 subject (Subject 21) discontinued treatment due to acute hepatitis B.

Eleven of the 16 subjects had a maximum laboratory toxicity grade of Grade 1 (5 subjects) or Grade 2 (6 subjects). Seven of the 11 subjects with Grade 1 or Grade 2 elevations had a history of elevated LFTs or entered the study with elevated LFTs. Four subjects had a laboratory toxicity grade of Grade 3 ALT or AST reported during the study. One additional subject had CTCAE Grade 3 AEs of elevated ALT and AST reported. All 4 subjects with Grade 3 hepatobiliary laboratory values had prior history of transaminase elevations and/or elevations at baseline.

As of the clinical cut-off date of 31 March 2014, no hepatobiliary SAEs had been reported in either Study ELT116826 or Study ELT116643

Thromboembolic Events

No TEEs have been reported during treatment in Study ELT112523, Study ELT116826, or in Study ELT116643. One subject (Subject 12) in ELT112523 had an unrelated SAE of deep vein thrombosis which occurred 14 months after discontinuation of treatment with eltrombopag.

Cytogenetic Abnormalities

Consistent with the known occurrence of cytogenetic abnormalities in SAA, 7% of subjects in Study ELT112523 had a cytogenetic abnormality present at baseline. Eight subjects (19%) had a new cytogenetic abnormality detected after treatment in Study ELT112523. Of these, 5 subjects had cytogenetic abnormalities affecting the structure or number of chromosome 7; all 5 were non-responders to eltrombopag and the cytogenetic abnormality was detected at the Primary Response Assessment. One of these 5 subjects 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 1 subject, the monosomy 7 was transient and was not present on the repeat bone marrow 21 days later. The 3 remaining subjects had trisomy 8 and deletion of chromosome 13.

For the 8 subjects who had a cytogenetic abnormality detected during the study, the median time on study to a cytogenetic abnormality was 3.1 months. Three of the 8 subjects with a cytogenetic abnormality detected after treatment had evidence of dysplasia in their bone marrow examinations

A total of 3 subjects were considered to have MDS and are described. Of note, 1 subject with ‘mild dyserythropoiesis’ noted on the bone marrow report was not reported to have had MDS by the investigator.

For the 6 subjects who did not respond to eltrombopag, the cytogenetic abnormality was detected at the Primary Response visit. The two subjects who responded to treatment with eltrombopag had the cytogenetic abnormality detected 13.7 and 9.6 months after initiating treatment with eltrombopag. The median time from diagnosis of SAA to detection of cytogenetic abnormality was greater than 5 years. The time from last IST cytogenetic abnormality ranged from 1 to 4 years.

In Study ELT116826, cytogenetic abnormalities affecting chromosome 7 (one subject, non-responder) and 13 (one subject, non-responder), respectively, were detected post-baseline in 2 subjects (13%) at the 3 month response assessment

In Study ELT116643, cytogenetic abnormalities affecting chromosome 7 (one subject, non-responder) and chromosome 13 (one subject, complete response), respectively, were detected post-baseline in 2 subjects (4%) at the 3 month response assessment

Haematologic Malignancies

Three subjects in Study ELT112523 were diagnosed by the investigator with MDS following treatment with eltrombopag. As of the clinical data cut-off date (31 March 2014), the development of MDS or AML had not been reported in Study ELT116826. In Study ELT116643, 1 subject who did not respond after 3 months and developed monosomy 7-associated dysplasia consistent with MDS and discontinued treatment.

Updated safety report for the three ongoing studies

Study ELT112523: There were no new reports of thromboembolic, hepatobiliary SAEs or AEs leading to treatment discontinuation during the safety update period. There were no new reports of cytogenetic abnormalities or haematologic malignancies in the safety update period.

Study ELT116826: There were no reports of hepatobiliary, TEEs, SAEs or AEs leading to treatment discontinuation in Study ELT116826.

With this safety update, 2 (7%) of subjects enrolled in the study had cytogenetic abnormalities detected on their baseline bone marrow examination. Both subjects received treatment with eltrombopag through the 6 month primary endpoint assessment (1 non-responder and 1 tri-lineage responder). 2 additional subjects had new cytogenetic abnormalities detected at the 3 month assessment, for a total of 4 (14%). Both of these subjects were responders to treatment, 1 subject was discontinued from eltrombopag and 1 subjects is continuing to receive eltrombopag. No new cytogenetic abnormalities have been reported at the 6 month assessment or during the extension. A brief summary of each subject is provided below.

One subject had trisomy 6 detected in 7/20 metaphases at the 3 month assessment. The subject was a platelet responder at the 3 month assessment. Treatment with eltrombopag was discontinued due to the cytogenetic change. At the 6 month follow-up, trisomy 6 was present in 1/20 metaphases.

One subject had +Y detected in 2/20 metaphases at the 3 month assessment and in 1/20 metaphases at the 6 month assessment. The subject was an ANC responder at 3 months and an ANC and RBC responder at 6 months. The subject is continuing to receive treatment with eltrombopag in the extension portion of the study.

At the time of the data cut-off for the Type II variation, no subjects had haematologic malignancies reported in ELT116826. As of the clinical cut-off for this safety update, 1 subject had leukaemic progression reported following treatment in the study and is described below.

One subject, a 55 year old male, had no mitotic activity for karyotype analysis from the bone marrow aspirate at baseline. The subject received eltrombopag, 75 mg for approximately 3 months. The subject missed the 3 month assessment and had leukemic progression reported. The subject died from sepsis following treatment with induction chemotherapy 33 days after the last dose of eltrombopag.

Study ELT116643: There were no reports of hepatobiliary or thromboembolic SAEs or AEs leading to treatment discontinuation in Study ELT116643 during the safety update period. Updated cases of cytogenetic abnormalities and haematologic malignancies are presented below.

As of the clinical cut-off for this safety update, 2 additional subjects had new cytogenetic abnormalities detected off therapy, for a total of 4 subjects (6%) with new cytogenetic abnormalities detected. As

previously reported, 2 subjects had the cytogenetic abnormality detected on-therapy, at the 3 month response assessment. A brief summary of all 4 subjects is provided below.

- One subject (Cohort 1) had monosomy 7 detected at the 3 month response assessment, with no response to treatment with hATG/CsA and eltrombopag. Eltrombopag was discontinued.

- One subject (Cohort 1) had deletion in chromosome 13 detected at the 3 month response assessment; this cytogenetic change was not associated with dysplasia. This subject also had a CR following treatment with hATG/CsA and eltrombopag at the 3 month response assessment. Treatment with eltrombopag was discontinued due to both the CR and the cytogenetic change.

The 2 additional subjects had cytogenetic abnormalities detected off-therapy, 3 months and 2 years, respectively, after the last dose of eltrombopag.

- One subject (Cohort 2) had monosomy 7 detected in 3 of 22 metaphases at the 6 month primary endpoint assessment, 3 months after the last dose of eltrombopag. This subject had a CR at both the 3 and 6 month response assessments. Approximately 3 months after the detection of monosomy 7, the subject was transplanted.

- One subject (Cohort 1) had a PR at the 3 month response assessment and a CR at the 6 month primary endpoint. The CR was maintained at the 1 and 2 year time points. Approximately 2 years after the last dose of eltrombopag, a cytogenetic abnormality of +6, +15 was detected in 2 of 21 metaphases.

At the time of the data cut-off for the Type II variation, no subjects had haematologic malignancies reported in ELT116643. As of the clinical cut-off for this safety update, 1 subject had evidence of dysplasia and blasts; this subject subsequently died of relapsed AML post-transplant. No other cases of MDS or AML have been reported in the study.

- One subject (described above under Cytogenetic Abnormalities) had monosomy 7 detected at the 3 month response assessment, with no response to treatment with hATG/CsA and eltrombopag. Eltrombopag was discontinued. A repeat bone marrow examination 1 month later showed evidence of dysplasia and an increase in blasts consistent with development of myelodysplastic syndrome. The subject died approximately 2 years after the last dose of eltrombopag, cause of death was reported as ‘post-BMT, relapsed AML’.

Laboratory findings

The majority of Grade changes were to Grade 1-2. No chemistry lab parameters had a change to toxicity Grade 4.

Safety in special populations

Data from the pivotal ELT112523 Study per age range are presented in table:

MedDRA terms, n (%)	Age <65 N=29	Age 65-74 N=12	Age 75-84 N=2	Age 85+ N=0
Total AEs	27 (93)	11(92)	2 (100)	0
Serious AEs – total	7 (24)	5 (42)	2 (100)	0
Fatal	1 (3)	0	1 (50) 0	0
Hospitalization/prolong existing hospitalization	6 (21)	5 (42)	2 (100)	0
Life-threatening	1 (3)	2 (17)	0	0
Disability/incapacity	0	0	0	0
Other (medically significant)	1 (3)	0	0	0
AE leading to drop-out	2 (7)	1 (8)	2 (100)	0
Psychiatric disorders	9 (31)	2 (17)	1 (50)	0
Nervous system disorders	12 (41)	3 (25)	1 (50)	0
Accidents and injuries	4 (14)	4 (33)	0	0
Cardiac disorders	2 (7)	1 (8)	0	0
Vascular disorders	3 (10)	2 (17)	0	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	11 (38)	4 (33)	1 (50)	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	4 (14)	2 (17)	1 (50)	0
<other ae appearing more frequently in older patients>	0	0	0	0

Safety related to drug-drug interactions and other interactions

The observed eltrombopag exposure in 23 SAA subjects treated concomitantly with eltrombopag and ATG/CsA was 2 to 3 times higher than that observed in healthy subjects or patients with chronic ITP.

Discontinuation due to adverse events

Five subjects (12%) in Study ELT112523 discontinued treatment with eltrombopag due to AEs (see table 22)

Table 22 Summary of Adverse Events Leading to Discontinuation from Study Treatment in Study ELT112523 (Safety Population)

	Eltrombopag (N=43)
Any event, n(%)	**5 (12)**
Subject ID	**Preferred Term**
Subject 5	Cataract (unsubstantiated)
Subject 6	Abdominal discomfort
Subject 20	Viral infection
Subject 21	Acute hepatitis B
Subject 24	Sepsis

Data Source: m5.3.5.2 ELT112523 CSR Section 7.3.2

As of the clinical cut-off date of 31 March 2014, no subject had discontinued eltrombopag due to an AE in either Study ELT116826 or Study ELT116643.

Post marketing experience

Eltrombopag was first approved for marketing in the EU on 11 March 2010 for the treatment of thrombocytopaenia in patients with chronic immune ITP. Eltrombopag is now also approved in the EU for the treatment of patients with HCV.

Based on latest data available from Intercontinental Medical Statistics Health data, it is estimated that approximately 35,612 patient years of eltrombopag treatment have been prescribed worldwide as of June 2014. This calculation is based on available sales information volume and assumes a once-daily dose of 12.5 mg, 25 mg, 50 mg, or 75 mg tablets.

As of 31 March 2014, 10,020 spontaneous and post-marketing AEs (serious and non-serious) have been received from the marketed use of eltrombopag (4458 cases). The most frequently reported AEs from spontaneous and post-marketing cases are provided in Table 36 and represent AEs reported at a 1% or higher frequency. As of 31 March 2014, there were 769 cases with a fatal outcome out of the 4458 cases reported from marketed usage of eltrombopag.

Table 36 Most Frequently Reported Adverse Events from Spontaneous and Post-marketing Surveillance Cases (1% and higher)

MedDRA Preferred Term	AEs, n (%)
All Preferred Terms	**10,020 (100)**
Drug ineffective	1057 (10.5)
Death	288 (2.9)
Platelet count decreased	287 (2.9)
Off-label use	227 (2.3)
Fatigue[a]	154 (1.5)
Headache[a]	148 (1.5)
Platelet count increased	142 (1.4)
Nausea[a]	126 (1.3)
Anaemia[a]	110 (1.1)
DVT[a]	103 (1.0)
Thrombocytopaenia	98 (1.0)
Pulmonary embolism[a]	96 (1.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities
a. AEs included in the eltrombopag Core Safety Information.

2.5.1. Discussion on clinical safety

The safety database was limited to around 102 subjects with SAA studied in the clinical trials presented, with long term data limited to 36 patients followed for at least 6 months at submission. Only 12 (28%) patients from the pivotal study were enrolled for >6 months in the ELT112523 study, and only 9 (21%) >12 months. Given that the two main studies are ongoing and that a substantial proportion of patients will discontinue treatment before 6 months provided that no haematological response is achieved, safety data available are mostly short-term data. This is an important limitation of the current dossier. However, the rarity of the disease should be considered as well as the gained experience with eltrombopag in other indications which might provide some supportive safety information.

In general, the profile of adverse events reported seems in line with the well -known safety profile of eltrombopag in the already licensed therapeutic indications and no new safety finding have been identified. High incidence of SAEs was reported in all clinical trials presented. However, the majority were not considered related to the study drug but to the underlying condition. Similarly, the number of death cases appears related to the underlying disease and are within the expected rates.

The 4 SAE in the ELT 112523 (febrile neutropenia, sepsis, deep vein thrombosis and orthostatic hypotension) that occurred in the post therapy study were deemed not related to eltrombopag treatment.

Overall, 3 patients (7%) from Study ELT112523 were diagnosed of MSD following treatment with eltrombopag and 1 subject in Study ELT116643 also had MSD. This is a potential risk associated to eltrombopag use, which is still under evaluation in a number of studies (See RMP). In this particular case, it is difficult to judge if eltrombopag might have contributed given that this is an expected risk in SAA, and in particular in the refractory population. Similarly, the 8 subjects (19%) with cytogenetic abnormalities (5 affecting the chromosome 7) that occurred in Study ELT112523, the 2 patients in ELT116826 study and the 2 subjects of the ELT116643 study with cytogenetic abnormalities at the 3 month assessment time points might be of concern. The MAH argued that these data are in line with percentages published in the literature (15-20% according to Maciejewski 2002, Scheinberg 2011 and Scheinberg 2012) and that data from patients with insufficient response to ATG/CsA do not exist in the literature. The MAH has provided further evidence to substantiate that the percentage seen in these studies are truly within the expected in the general population with a refractory SAA disease. Given that >80% of subjects in the pivotal study had insufficient response to at least 2 ISTs, and the known increased risk of new cytogenetic abnormalities and the risk of development of MDS/AML in such heavily pre-treated patients, the 7% rate of MDS diagnosis and 19% rate of new cytogenetic abnormalities are consistent with the rates observed since the 1980's with the underlying disease and natural history of SAA. However, the uncertainties on the long-term risk remain and this will be further investigated in two controlled planned studies. (see RMP).

An update of the safety database has been provided (cut-off date January 2015). Across the 3 SAA studies included in this submission, a total of 133 subjects have been enrolled, nearly all have received the maximum dose of eltrombopag 150 mg. A total of 71 subjects with an insufficient response to immunosuppressive therapy have been treated with eltrombopag. Of these 71 subjects, 80% received eltrombopag for at least 3 months, 39% received eltrombopag for at least 6 months and nearly a quarter of the subjects (23%) received eltrombopag for at least 1 year. Therefore updated results were consistent in terms of the incidence of SAEs, cytogenetic abnormalities, and haematological malignancies- with the initial data.

Examination of the safety data across the 2 studies conducted in subjects with an insufficient response to immunosuppressive therapy, showed similar rates of SAEs, detection of new cytogenetic abnormalities and diagnosis of MDS or AML. The proportion of subjects with SAEs in the ELT112523 and ELT116826 studies were similar, 33% and 29%, respectively. The most common SAEs reported in both studies were consistent with that expected for the previously treated SAA patient population, primarily infections and febrile neutropenia. At baseline in both studies, 7% of subjects had a cytogenetic abnormality detected prior to treatment with eltrombopag. New cytogenetic abnormalities were detected in similar proportions in both studies (ELT112523, 19%; ELT116826, 14%).

In summary, the safety profile across both studies in subjects with an insufficient response to immunosuppressive therapy was generally comparable in terms of overall exposure, SAEs and cytogenetic abnormalities.

In the treatment naïve study (ELT116643) 42% of subjects had SAEs based on the clinical cut-off for this safety update, the majority of SAEs observed were febrile neutropenia or infectious complications. New cytogenetic abnormalities were reported in 6% of subjects in this trial.

No new safety issues were identified for the administration of eltrombopag in subjects with SAA following review of safety data collected from ongoing clinical studies ELT112523, ELT116826, and ELT116643 through 14 January 2015.

In general, the assessment of safety of eltrombopag in the SAA population although hampered by the lack of a control arm and the overall limited database, is in line with the experience with eltrombopag in the currently approved indications. Final safety data from the supportive ongoing Study ELT116826 will be submitted by last quarter 2018; Final report from study ELT116643 in 1st line SAA treatment will be provided in May 2016 (See RMP).

2.5.2. Conclusions on clinical safety

Overall, the safety and tolerability of eltrombopag appears acceptable, in this refractory and heavily pretreated population. 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 are manageable in the clinical practice

The long-term risk of cytogenetic abnormalities remains as a matter of concern which requires additional follow up at post-approval. The MAH will submit final safety data from the supportive ongoing Study ELT116826 by Q4 2018.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

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 27 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 31 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	**ITP and HCV-Associated Thrombocytopenia <u>and Severe Aplastic Anaemia</u>** Hepatotoxicity Thromboembolic Events Post Therapy Reoccurrence of Thrombocytopenia

Summary of safety concerns	
	Cataract **HCV-associated Thrombocytopenia** Hepatic Decompensation Thromboembolic Events - Portal Vein Thrombosis Retinal Haemorrhage
Important potential risks	**ITP and HCV-Associated Thrombocytopenia and Severe Aplastic Anaemia** Potential for Increased Bone Marrow Reticulin Formation Haematological Malignancies Renal Tubular Toxicity Phototoxicity Potential for Haematological changes Potential for Endosteal Hyperostosis **HCV-Associated thrombocytopenia** QT/QTc interval prolongation **Severe Aplastic Anaemia** Cytogenetic abnormalities
Missing information	**ITP and HCV-Associated Thrombocytopenia and Severe Aplastic Anaemia** Paediatrics Pregnant or lactating females Asian population Black Race population Very elderly patients Patients with hepatic impairment Patients with renal impairment Off-label use **HCV-associated thrombocytopenia** Elderly patients HCV patients with FibroSURE score of F0, F1, F2 HCV patients infected with genotype other than 1, 2 or 3 HCV patients with Child Pugh score B (7-9) Safety and efficacy of eltrombopag in combination with new direct acting agents (telaprivir/boceprevir) **Severe Aplastic Anaemia** Cyclosporine

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns endorsed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
TRA105325/EXTEND Clinical Category 3	Extension study in adults with ITP long term safety including collection of bone marrow reticulin	Bone Marrow Reticulin Formation	Ongoing	Final Study Report September 2015
TRA112940/ Bone Marrow Study Clinical Category 3	Safety in adults with ITP long term safety including collection of bone marrow reticulin	Bone Marrow Reticulin Formation	Ongoing	Final Study Report September ~~April~~ 2015
US Pregnancy Registry Pharmacoepidemiology Category 3	Safety data on pregnant females	Pregnant and Lactating Females	Terminated ~~Ongoing~~	Released from FDA requirement ~~Final Study Report November 2019~~
TRA113101/Lactation Study Clinical Category 3	Safety data on lactating Females	Pregnant and Lactating Females	Terminated ~~Ongoing~~	Released from FDA requirement ~~Final Study Report April 2019~~
WW116951: Prospective observational study of ENABLE clinical trial patients to understand later outcome patterns among patients with and without a Thromboembolic event. Pharmacoepidemiology Category 3	TEE in patients with HCV associated thrombocytopenia	TEE	Ongoing	Final Study Report December 2017
Drug utilization study Pharmacoepidemiology Category 3	Collect data of “real-world” use of Eltrombopag post approval	Off label use	Ongoing ~~Planned~~	Final Study Report December 2016

Study / activity Type, title and category (1-3)	Objectives	Safety concerns endorsed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
GSK PASS Study: Proposed Post Authorisation Safety Study of HCV patients treated with Eltrombopag: Multicenter, Prospective Observational Cohort study of Thrombocytopenic HCV patients Receiving Eltrombopag Pharmacoepidemiology Category 3	Assess occurrence of safety events among HCV patients who receive Eltrombopag in the post approval, real world setting	TEE and Hepatic decompensation	Ongoing ~~Planned~~	6 months interim analysis, December 2016 12 months interim analysis, June 2017 18 months interim analysis, October 2018 ~~December 2017~~ Final report, November 2019
HCV-TARGET: Proposed Post Authorisation Safety Study of HCV patients treated with Eltrombopag: Hepatitis C Therapeutic Registry and Research Network Pharmacoepidemiology Category 3	Assess occurrence of safety events among HCV patients who receive Eltrombopag in the post approval, real world setting	TEE and Hepatic decompensation	Ongoing ~~Planned~~	First interim, October 2016 Final report, October 2019
HCV Research UK: Proposed Post Authorisation Safety Study of HCV patients treated with Eltrombopag Pharmacoepidemiology Category 3	Assess occurrence of safety events among HCV patients who receive Eltrombopag in the post approval, real world setting	TEE and Hepatic decompensation	Ongoing ~~Planned~~	First interim, October 2016 Final report, October 2019
Effectiveness of Eltrombopag Educational Materials for Hepatitis C associated thrombocytopenia	Measurement of the effectiveness of the Eltrombopag Risk Minimisation education	Key elements within the educational materials including hepatic decompensation,	Ongoing ~~Planned~~	Interim report, April 2015 Final report, September 2015

Study / activity Type, title and category (1-3)	Objectives	Safety concerns endorsed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Category 3	materials	TEEs and fatal adverse events		
ELT116826 Clinical Category 3	Safety of Eltrombopag in SAA patients unresponsive to IST	Safety in SAA patients unresponsive to IST and potential risk of cytogenetic abnormalities	Ongoing	April 2016
ELT116643 Clinical Category 3	Safety of Eltrombopag in SAA patients receiving front-line treatment	Safety in front-line SAA patients receiving treatment with IST and potential risk of cytogenetic abnormalities	Ongoing	May 2016
RAD201583 Clinical Category 3	Determine effect of cyclosporine on PK of eltrombopag	DDI – cyclosporine and eltrombopag	Planned	Sep 2015
RAD200936 Clinical Category 3	Safety of eltrombopag in paediatric SAA	Paediatrics	Planned	Dec 2020
Gem-Platinum/TRC112765 Category 3	Safety of Eltrombopag in subjects with solid tumors receiving gemcitabine plus cisplatin or carboplatin	May provide additional safety data regarding potential risk of Haematological changes	Ongoing	April 2016
ASPIRE/TRC114968 Category 3	Safety of Eltrombopag in subjects with advanced MDS or AML	May provide additional safety data regarding potential risk of Haematological changes	Ongoing	June 2015

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatotoxicity	ITP - Current text in SmPC • Statement in Section 4.4. Warning and Precaution of the SmPC advising to monitor and manage patient with hepatotoxicity. Specify liver testing before initiation, every 2 weeks during the first 3 months, thereafter every 4-6 weeks • Liver stopping criteria: Specific instructions for discontinuation of eltrombopag to avoid further elevations of hepatobiliary laboratory values • Increased ALT, AST and indirect bilirubin have been added in Section 4.8 (Undesirable effects). HCV-Associated Thrombocytopenia - Current text in SmPC text • In the SmPC, a warning regarding the potential for Hepatobiliary laboratory abnormalities (ALT, AST, bilirubin, and alkaline phosphatase) in Section 4.4 (Special warnings and precautions for use). • Also, preferred terms related to hepatotoxicity in Section 4.8 (Undesirable effects).	Educational materials
Hepatic Decompensation	HCV-Associated Thrombocytopenia - Current text in SmPC • In the SmPC, a warning regarding the potential for hepatic decompensation will be proposed for addition to Section 4.4 (Special warnings and precautions for use). • Also, preferred terms related to hepatic decompensation in Section 4.8 (Undesirable effects). Also, preferred terms related to hepatic decompensation in Section 4.8 (Undesirable effects)	Educational materials
Thromboembolic Events - Portal Vein Thrombosis	ITP - Current text in SmPC • Section 4.2 (Posology and method of administration), section 4.4 (Special warnings and precautions for use), and section 5.2 (Pharmacokinetic properties) of the SmPC state that eltrombopag should not be used in patients with moderate to severe hepatic impairment unless the expected benefit outweighs the identified risk of portal venous thrombosis. • Section 4.2 of the SmPC further states that if the use of eltrombopag is deemed necessary [in patients with moderate to severe hepatic impairment] the starting dose must be 25mg once daily. • A statement in Section 4.4 (Special warnings and precautions) regarding the potential for thromboembolic events is included including caution for patient with known risk factors for TEE. The PIL also reflects this information • Thromboembolic events are included in Section	Educational materials

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.8 (Undesirable effects). • Information regarding patients with chronic liver disease and the risk of thromboembolic events is included in Sections 4.4 and 4.8 of the SmPC. Thromboembolic events HCV-Associated Thrombocytopenia -Current text in SmPC • In the SmPC, a warning regarding the potential for thromboembolic events including portal vein thrombosis in Section 4.4 (Special warnings and precautions for use). Also, thromboembolic events in Section 4.8 (Undesirable effects).	
Post therapy Reoccurrence of Thrombocytopenia	Current text in SmPC • A statement in Section 4.4 (Special Warnings and precautions) regarding the potential for decrease in platelet counts post discontinuation of therapy. The PIL also reflects this information. • A warning has been added to Section 4.4 (Special warnings and precautions) of the SmPC stating that in HCV clinical trials, gastrointestinal bleeding was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding. The PIL also reflects this information. • Thrombocytopenia following discontinuation of treatment is included in Section 4.8 (Undesirable effects).	Educational materials
Cataracts	Current text in SmPC • A statement in Section 4.4 (Special Warnings and precautions) regarding the routine monitoring for cataracts is included. The PIL also reflects this information.	None
Retinal haemorrhage	Current text in SmPC • A warning in Section 4.4. (Special warnings and precautions) is proposed that states retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2 % of the eltrombopag group and 2 % of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended. The PIL also reflects this information.	None
Cytogenetic Abnormalities	Proposed text in SmPC A statement in Section 4.8 (Undesirable effects) of the SmPC informing prescribers of the following: In the single-arm, open-label trial in SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported, including 5 patients who	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	had changes in chromosome 7. Additionally, Section 4.2 states: • Consider eltrombopag discontinuation if new cytogenetic abnormalities are observed	
Potential for increased bone marrow reticulin formation	Current text in SmPC • A statement in Section 4.4 (Special Warnings and precautions) of the SmPC informing prescribers to monitor for immature or dysplastic cells and the potential for increase in bone marrow reticulin fibres is included, the PIL also reflects this information.	Educational materials
Haematological malignancies	Current text in SmPC • Section 4.4 of the SmPC (Special Warnings and precautions) states that the diagnosis of ITP in adults and elderly patients should have been confirmed by the exclusion of other clinical entities with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs. • An update to Section 4.4 (Special warning and precautions) of the SmPC informing prescriber of a concern that thrombopoietin receptor (TPO-R) agonists may stimulate the progression of existing haematopoietic malignancies such as MDS	Educational materials
QT/QTc interval prolongation	Current text in SmPC • A statement in Section 4.4 (Special warning and precautions) of the SmPC stating a QTc study indicates that eltrombopag will not have a clinically significant effect on cardiac repolarisation at therapeutic or supra-therapeutic doses. QTc interval prolongation has been reported in clinical trials of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.	None
Renal tubular toxicity	Current text in SmPC • A statement in Section 5.3 (Pre-clinical safety data) that the clinical relevance of the renal tubular toxicity finding in rodents is unknown.	None
Phototoxicity	Current text in SmPC • A statement in Section 5.3 (Pre-clinical safety data) that there is a potential risk of photoallergy and that the clinical relevance of the in-vitro finding is unknown.	None
Potential for haematological changes	Current text in SmPC • A warning is in Section 4.4. (Special warnings and precautions) of the SmPC informing prescribers to monitor for immature or dysplastic cells. • A statement in Section 5.3 (Pre-clinical safety data) of the haematological changes findings in rats and dogs and that the clinical relevance of the finding is unknown.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Potential for Endosteal hyperstosis	Current text in SmPC • A statement in Section 5.3 (Pre-clinical safety data) of the endosteal hyperostosis findings in rodents and that the clinical relevance of the finding is unknown.	None
Paediatrics	Current text in SmPC • Section 4.2 (Posology and method of administration) of the SmPC, states that the safety and efficacy of eltrombopag in paediatric patients (< 18 years of age) has not been established.	None
Pregnant or lactating female	Current text in SmPC • The SmPC (Section 4.6) and package leaflet states that the risk to pregnant or lactating women is unknown.	None
Asian Populations	Current text in SmPC • A statement the SmPC (Section 4.2 Posology) states the following: *East Asian patients* Initiation of eltrombopag at a reduced dose of 25 mg once daily may be considered for ITP patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Thai or Korean) (see section 5.2). Initiate eltrombopag at a dose of 25 mg once daily in HCV patients of East Asian ancestry. Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed. For ITP or HCV patients of East Asian ancestry with hepatic impairment initiate eltrombopag at a dose of 25 mg once daily. **SAA** Proposed text in SmPC: A lower starting dose of 25 mg is recommended for patients of East Asian ancestry and patients with hepatic impairment.	None
Black race Populations	None	None
Elderly and very elderly	Current text in SmPC • The SmPC (Section 4.2 Posology) states that there are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. There are limited data on the use of eltrombopag	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	in HCV patients aged over 75 years. Caution should be exercised in these patients.	
Patients with hepatic impairment	The SmPC (Section 4.2 Posology) states the following: *Hepatic impairment* Eltrombopag should not be used in ITP patients with hepatic impairment (Child- Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment wait 3 weeks before increasing the dose. No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Thrombocytopenic patients with chronic HCV should initiate eltrombopag at a dose of 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment wait 2 weeks before increasing the dose. There is an increased risk for adverse events, including thromboembolic events, in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedures or in HCV patients undergoing antiviral therapy.	None
Patients with renal impairment	The SmPC (Section 4.2 Posology) states the following: *Renal impairment:* No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis.	None
HCV patients with a FibroSURE score of F0/F1/F2	The SmPC (Section 5.1 Pharmacodynamic properties) states the following: The majority of patients were HCV genotype 1 (64 %), had mild hepatic impairment (Child-Pugh Score 5-6), and had a FibroSURE score equivalent to Metavir F3 or F4, indicative of bridging fibrosis and cirrhosis.	None
HCV patients infected with genotype other than 1, 2 or 3	The SmPC (Section 5.1 Pharmacodynamic properties) states the following: The majority of patients were HCV genotype 1 (64 %), had mild hepatic impairment (Child-Pugh Score 5-6), and had a FibroSURE score equivalent to Metavir F3 or F4, indicative of bridging fibrosis and cirrhosis.	None
HCV patients with Child Pugh score B (7-	The SmPC (Section 4.4) states the following: Eltrombopag should not be used in patients with	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
9)	hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, exercise caution when administering eltrombopag to patients with hepatic impairment.	
Off label use	The SmPC (Section 4.1) states the following: Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated. Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia prevents the initiation or limits the ability to maintain optimal interferon-based therapy (see section 5.1). *Paediatric population* Revolade is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.	None
Safety and efficacy of eltrombopag in combination with new direct acting agents (telaprevir/boceprevir)	Current text in SmPC A statement in Section 4.4 that Safety and efficacy have not been established for eltrombopag in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection. The SmPC (Section 4.5) states that dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir	None
Cyclosporine	None	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2., 4.4, 4.8, 5.1 of the SmPC have been updated. Particularly, a new warning with regard to cytogenetic abnormalities and progression to MDS/AML has been added to the product information. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

N/A

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the non-randomized, single-arm, open-label, Phase II study of eltrombopag in subjects with SAA and insufficient response after treatment with ATG/CsA (study ELT112523) haematologic response was achieved in 17 out of 43 subjects (40%) in at least 1 lineage (95% CI: 25-56%). One subject had a tri-lineage response, 3 subjects had bi-lineage responses, and the remaining 13 had a uni-lineage response at week 12. The majority of responders (65%) met platelet response criteria, followed by ANC and haemoglobin response criteria (47% and 18%, respectively).

Fourteen of the 17 responders entered into the extension phase and a total of 7 subjects had improvements in more than 1 lineage following continuation of treatment such that a total of 9 patients had tri-lineage or bi-lineage responses. Five out of 14 patients who entered the extension phase stopped treatment early due to AE, cytopenias or relapse (3 patients), while 9 were followed in the long term and maintained their best response; five of them despite tapering off and discontinuing eltrombopag according to the study protocol.

In terms of transfusion requirements a total of 59% and 27% of patients became platelet and RBC transfusion independent, respectively (meaning free of transfusion during 28 days for platelet or 56 days for RBC at any time during the treatment period). The median of days free of platelet or RBC transfusions were 287 days and 266 days, respectively in the 17 responder patients, respectively. Very preliminary results from the supportive Study ELT116826, an ongoing non-randomized, Phase II, single-arm, open-label study in refractory SAA subjects, show consistent results: hematologic response at 3-month was 46% (24 out of 60 patients) and at 6-month (PEP) was 52% (21 out of 60 patients).

Uncertainty in the knowledge about the beneficial effects

The main evidence is provided by one pivotal study which was open label, single arm and single centre. However, the difficulties in conducting randomised controlled studies are acknowledged considering the rarity of the disease. To minimise the uncertainties surrounding single arm trials, a second supportive study is being conducted; preliminary results show consistent results and add robustness to the pivotal study.

The effect on survival has not been determined and given the design of the study, where non-responders at week 16 were withdrawn, no reliable estimation can be provided. However, considering available treatment options, results are considered overall clinically relevant. The impact on HRQoL was not properly evaluated beyond week 12 and data available are of little value to make any conclusion. Additional post authorisation efficacy data form the ongoing supportive study are expected to clarify these points (see RMP).

No baseline predictors of response have been identified. However, appropriate stopping rules in order to avoid an unnecessary exposure in patients unlikely to respond despite continuing treatment have been included in the SmPC.

Concerning the elderly population, limited experience exists over the age of 75 in SAA. The overall incidence of SAEs was somewhat higher to that reported in the overall population, but data are too limited (17 over 65 yrs, 2 over 75 yrs) to draw firm conclusion. No dose adjustment is considered needed. However, caution is recommended in the SmPC (Section 4.2) when using eltrombopag in elderly patients.

Risks

Unfavourable effects

The safety of eltrombopag in severe aplastic anaemia was assessed in a single-arm, open-label trial (N=43) in which 12 patients (28 %) were treated for > 6 months and 9 patients (21 %) were treated for > 1 year.

Across the 3 SAA studies included in this submission, a total of 133 subjects have been enrolled, nearly all have received the maximum dose of eltrombopag 150 mg. A total of 71 subjects with an insufficient response to immunosuppressive therapy have been treated with eltrombopag. Of these 71 subjects, 80% received eltrombopag for at least 3 months, 39% received eltrombopag for at least 6 months and nearly a quarter of the subjects (23%) received eltrombopag for at least 1 year.

The most common AEs observed in Study ELT112523 largely reflect the well-known safety profile of eltrombopag and events expected in this patient population. Nausea, fatigue, cough, diarrhoea, and headache were the most common AEs, reported by ≥20% of subjects. Others like transaminases increases, pain in extremity, dyspnoea, pyrexia, febrile neutropenia, abdominal pain, ecchymosis, muscle spasms, abdominal pain, arthralgia and insomnia were also commonly reported.

The most common SAE reported on-therapy was febrile neutropenia, followed by sepsis and viral infection. The percent of responders with infectious SAEs (3/17; 18%) was less than that in non-responders (8/26; 30%) despite the shorter observation time for non-responders. Most subjects had recovered or were recovering from the SAE as of the data cut-off (09 May 2014), although 1 patient with aplasic anaemia and other with septic shock died. One subject had an SAE of abdominal discomfort that was considered related to treatment by the investigator.

Consistent with the known occurrence of cytogenetic abnormalities in SAA, particularly in heavily pre-treated patients, a 7% rate of MDS diagnosis and 19% rate of new cytogenetic abnormalities has been reported, which appears consistent with the rates observed since the 1980's with the underlying disease and natural history of SAA. However, the uncertainties on the long-term risk remain and this will be further investigated in two controlled planned studies (see RMP). A relevant warning has been added in the SmPC section 4.4.

In clinical trials with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment. Appropriate warnings and recommendations on cytogenetics testing of SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter are included in section 4.4 of the SmPC.

Uncertainty in the knowledge about the 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.

The safety risks and particularly cytogenetic abnormalities will be further investigate this risk at post-approval in two planned academic studies, within reasonable timelines (May 2019 and Dec 2020, see RMP).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

In the heavily pretreated patient population enrolled in ELT112523, where no established standard of care exists, a 40% response rate in at least 1 lineage was observed at week 12. Over time, responses

continued to improve and included multi-lineage responses in a total of 9 out of the 17 responders, which is around 20% of the overall treated population. In this small subset of patients responses were durable, with a median duration of response of 12 months among the evaluable subjects, and responses were associated with variable platelet and red blood cell transfusion free intervals, of over 8-9 months. Tri-lineage responses have been maintained after discontinuation of eltrombopag in 6 patients.

Available results are clinically relevant even considering that the benefit will be limited to a small subset of patients that reached a haematological response maintained in the long term (40% in the short term, around 20% in the long term). Clinical relevance was substantiated by a reduction in transfusion requirements, bleeding events and infections.

Preliminary results from the ongoing supportive study are consistent and add robustness to the results of the pivotal study.

From a safety point of view, the safety profile of eltrombopag is well known. The limited data provided suggest that treatment was in general well tolerated with no unexpected safety findings. The safety profile of eltrombopag is considered well characterised and overall it seems a well-tolerated drug in this patient population, although data in SAA are limited. Uncertainties remain on the potential risk of inducing cytogenetic abnormalities/MDS progression, given that these are expected findings in the studied population, hence, difficult to address in the current open label studies. However, the MAH commits to further address this risk at post-approval in two planned studies. Although not fully powered, these studies will consistently and prospectively assess the risk for developing cytogenetic abnormalities and for MDS/AML progression under eltrombopag treatment.

Benefit-risk balance

The benefit in terms of haematological response observed in this heavily pretreated population clearly outweighs the well-known risks of eltrombopag treatment. Therefore, the benefit/risk for the use of Revolade 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 – is positive.

Discussion on the Benefit-Risk Balance

Considering the rarity of the disease, the poor prognosis of subjects with refractory acquired SAA and the recognised unmet medical need, results from the two open label non comparative studies provide evidence of a clinically relevant effect in the treatment of adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior treatments or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation. The safety profile of eltrombopag in the treatment of SAA remains unchanged. However there remain some uncertainties on the potential risk of progression to MDS/cytogenetic abnormalities associated to eltrombopag treatment. Further investigations to address this concern will be conducted at post-approval. In the meantime, an appropriate warning will be included in the SmPC (Section 4.4).

4. Recommendations

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

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

Extension of Indication to include the treatment of 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; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated. The package leaflet is updated accordingly. In addition, the acronym used for full blood counts (FBC) in the SmPC, Annex II and PL is being corrected.

This variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include the treatment of 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; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated. The package leaflet is updated accordingly. In addition, the acronym used for full blood counts (FBC) in the SmPC, Annex II and PL is being corrected.

Summary

Please refer to the Scientific Discussion Revolade-H-C-1110-II-20.

6. Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 23 July 2015.
2. PRAC Rapporteur initial Assessment Report dated 3 February 2015
3. PRAC RMP Advice and assessment overview, adopted by PRAC on 12 February 2015
4. CHMP Rapporteur and Co-Rapporteur initial Assessment Report dated 16 February 2015
5. CHMP Request for supplementary information as agreed by the CHMP on 26 February 2015
6. Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 26 May 2015
7. PRAC RMP Advice and assessment overview, adopted by PRAC on 11 June 2015
8. CHMP 2nd Request for supplementary information as agreed by the CHMP on 25 June 2015

9. Joint Rapporteur/Co-Rapporteur updated Assessment Report on the responses provided by the applicant, dated 6 July 2015

10. Joint Rapporteur/Co-Rapporteur final Assessment Report dated 16 July 2015