Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Eltrombopag

Proprietary Product Name: Revolade

Sponsor: Novartis Australia Pty Ltd

First round evaluation: 31 May 2015

Second round evaluation: 14 October 2015

TGA Health Safety Regulation

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
ABMTRR	Australian blood and marrow transplant recipient registry
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ATG	Anti-thymocyte globulin
BCRP	Breast cancer resistance protein
CBC	Complete blood count
CI	Confidence interval
CR	Complete haematologic response
CsA	Cyclosporine A
EPO	Erythropoietin
FDA	Food and Drug Administration
hATG	Horse anti-thymocyte globulin
Hb	Haemoglobin
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
HRQOL	Health related quality of life
HSP	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
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
PR	Partial (haematologic response)
PRA	Primary response assessment
rATG	Rabbit ATG
RBC	Red blood cell
SAA	Severe aplastic anemia
SAE	Serious adverse event
SD	standard deviation
TPO	Thrombopoietin
TPO-R	TPO receptor
ULN	Upper limit of normal

1. Introduction

This is a submission to extend the indications of Revolade (eltrombopag).

The current approved indications are

1. *Treatment of chronic idiopathic thrombocytopenic purpure (ITP)*
2. *Adult patients with chronic hepatitis C (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.*

The proposed additional indication is

> *Treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy (IST).*

The drug has Orphan Drug status in Australia.

2. Clinical rationale

SAA is a rare (1-2/million in Western countries) life threatening acquired bone marrow failure disorder with, prior to the introduction of current therapies, an almost uniformly fatal outcome. Current effective therapies, IST and allogeneic haematopoietic stem cell transplantation have however led to a substantial improvement in survival rates. However not all patients will respond to such therapy. For instance approximately 40% fail to respond to IST and not all patients are suitable for allogenic transplantation – either because of age limitations, medical co-morbidity or the lack of a suitable donor.

Thus the outcome of patients who have an insufficient response to 1-2 courses of IST and in whom an allogeneic transplant in not possible is poor.

Eltrombopag is agonist of the thrombopoietin receptor (TPO-R) which interacts with the membrane domain of the TPO-R present on megakaryocytes and human bone marrow progenitor cell. Efficacy in SAA may be via stimulation of multi-lineage haematopoiesis by the induction of proliferation and differentiation of early bone marrow progenitor cells

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Pivotal efficacy/safety study: ELT112523.
- Dosing evaluation as described in the above studies.
- Other relevant efficacy/safety studies: ELT116643 and ELT116826 (in combination with Cyclosporin A, CsA). Study PMA112509 provides additional safety data albeit in a different disease indication.

3.2. Paediatric data

The studies cited in the submission were primarily restricted to adult patients. The pivotal Study ELT112523 (efficacy and safety data) was restricted to patients 12 years or older but only

contained 2 patients <18 years of age (both age 17 at study entry). In supportive studies ELT116812 and ELT116643 7, 3 (20%) and 7 (15%) of participants respectively were in the 12-17 age group. Study PMA112509 (additional safety data) was conducted solely in adults.

3.3. Good clinical practice

ELT112523, ELT116826 and ELT116643 were undertaken in accordance with the standard operating procedures of the National Institutes of Health, USA, (NIH), which comply with the principles of Good Clinical Practice. According to the sponsor, PMA112509 was undertaken in accordance with standard operating procedures of the GSK Group of Companies, which comply with the principles of Good Clinical Practice. All studies were reported to have been conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authority.

4. Pharmacokinetics

No additional clinical biopharmaceutic studies were completed for this application.

Results from clinical biopharmaceutic studies have previously been submitted (the original Marketing Authorisation Application (MAA) to support eltrombopag use in adult patients with chronic idiopathic thrombocytopaenic purpura).

The following was however included by the sponsor for reference.

> *A preliminary pharmacokinetic (PK) result from Cohort 1 of Study ELT116643 has become available since the ISS and are presented here. In Cohort 1 of Study ELT116643, a PK sample was taken from 23 subjects at the 3 month visit. PK is not being performed in Cohort 2 of the study. In cohort 1 plasma concentrations of eltrombopag were sampled from 23 subjects at the 3-visit. 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* $AUC_{(0\ infinity)}$ *693.7 µg.h/mL (43%). The observed eltrombopag exposure in these 23 SAA subjects is 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 CyclosporineA (CsA). 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 [2006]. Eltrombopag is a substrate of BCRP'. GSK states that it is planning to conduct a drug interaction study in healthy volunteers to further evaluate the potential for a PK drug interaction between CsA and eltrombopag.

4.1. Evaluator's overall conclusions on pharmacokinetics

Note is made of the higher plasma levels seen in Study ELT116643 in which eltrombopag was given with CsA. No additional/new AEs appear to have been reported and the possible explanation, drug-drug interactions, seems reasonable.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

No additional data provided.

5.2. Evaluator's overall conclusions on pharmacodynamics

Not applicable.

6. Dosage selection for the pivotal studies

Eltrombopag 50 mg once daily was selected as the starting dose for the pivotal Study ELT112523 because this regimen has been demonstrated to be safe and effective in increasing platelet counts in patients with chronic ITP and HCV. A starting dose of 25 mg once daily was selected for East Asian patients due to ethno-pharmacologic differences in exposure. The dose of eltrombopag could be increased every 2 weeks in 25 mg increments up to a maximum dose of 150 mg once daily based on the following considerations:

1. The effective dose in SAA subjects was unknown.
2. 300 mg per day was the maximum dose previously studied in the eltrombopag programme.
3. In healthy subjects, a clear dose and exposure response was seen for eltrombopag doses of 10 mg to 200 mg once daily for 5 days, with geometric mean area under the curve ($AUC_{(0\ infinity)}$ values of 302 µg.h/mL for the 200 mg once daily regimen. Eltrombopag was well tolerated in healthy subjects at all dose levels.
4. There is evidence that higher doses of growth factors are required in bone marrow failure syndromes. For instance, the effective erythropoietin (EPO) dose in Myelodysplastic syndrome (MDS) is several times higher than the EPO dose used in anaemia of renal failure.
5. To ensure subject safety, a dose escalation scheme in which subjects were exposed to the lowest dose required to achieve desired platelet counts was used.
6. The dose of eltrombopag 150 mg/day in the two supportive studies (ELT116826 and ELT116643) was based upon the results of ELT112523. In ELT112523 nearly all subjects escalated to 150 mg once daily prior to observation of responses.

7. Clinical efficacy

7.1. Pivotal Study

Severe Aplastic Anaemia (SAA) with insufficient response to immunosuppressive therapy (IST) (Anti-thymocyte globulin, ATG and Cyclosporin A (CsA))

7.1.1. Pivotal efficacy study

7.1.1.1. Study ELT112523 (NIH 09-H-0154)

Phase II, open-label, non-randomised, single-arm, single centre (NIH Bethesda Maryland USA) investigator sponsored study to evaluate the efficacy to Eltrombopag in patients with SAA and an insufficient response to IST. Enrolment completed but some patients are still undergoing treatment. The cut-off date was 9/5/14 and results published in peer reviewed journals.

7.1.1.1.1. Study design, objectives, locations and dates

The study was designed as an open-label, single center, non-randomized, Phase II, dose modification study of eltrombopag in subjects with SAA and thrombocytopenia with a baseline platelet count ≤ 30 x 10^9/L, following insufficient response to immunosuppressive therapy (Figure 1).

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.

Secondary objectives included the analysis of the incidence and severity of bleeding episodes, and the impact on quality of life.

Study center(s): This study was conducted at 1 center (National Institute of Health [NIH]) in one country (US).

Study Period: 23 June 2009 - 09 May 2014 (Clinical Cut-Off Date)

7.1.1.1.2. Inclusion and withdrawal criteria

Inclusion criteria

1. Diagnosis of SAA, with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/cyclosporine.
2. Platelet count ≤ 30x 10^9/L
3. Age ≥ 12years old
4. A subject was *not eligible for inclusion* in this study if any of the following criteria applied:
    a. Diagnosis of Fanconi anemia
    b. Infection not adequately responding to appropriate therapy
    c. Patients with a PNH clone size in neutrophils of ≥ 50%
    d. HIV positivity
    e. Creatinine >2.5
    f. Bilirubin >2.0
    g. AST or ALT >5 times the upper limit of normal
    h. Hypersensitivity to eltrombopag or its components
    i. Female subjects who were nursing or pregnant or were unwilling to take oral contraceptives or refrained from pregnancy if of childbearing potential
    j. History of malignancy other than localized tumors 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)
    k. Unable to understand the investigational nature of the study or gave informed consent
    l. History of congestive heart failure, arrhythmia requiring chronic treatment, arterial or venous thrombosis (not excluding line thrombosis) within the last 1 year, or myocardial infarction within 3 months before enrollment
    m. Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or greater
    n. Treatment with horse or rabbit ATG or Campath within 6 months of study entry.
    o. Concurrent stable treatment with cyclosporine or G-CSF was permitted.

Withdrawal criteria

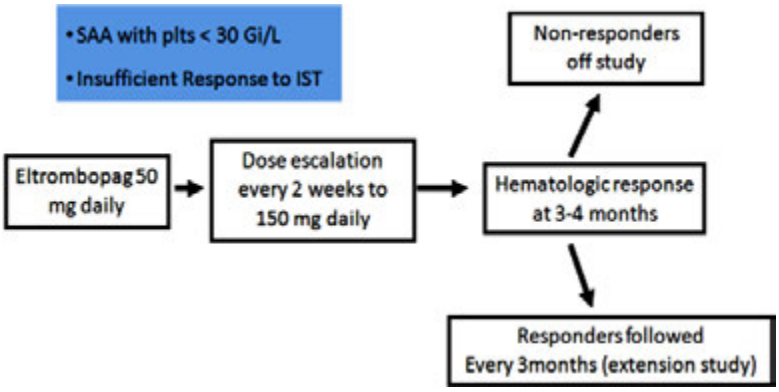
Eltrombopag was to be discontinued if any of the following occurred during treatment.

- Intolerance of eltrombopag not resolved by dose reduction
- Life threatening acute hypersensitivity reaction
- Thrombosis/embolism (deep vein thrombosis [DVT], pulmonary embolus [PE], stroke or transient ischemic attack [TIA], myocardial infarction) other than central line thrombosis
- Persistent hepatotoxicity (as defined in the Protocol)
- New or worsening morphological abnormalities or cytopenia(s) (as defined in the Protocol)
- No treatment at the Primary Response Assessment
- Any Grade IV toxicity considered related to study treatment excluding readily reversible metabolic or laboratory abnormalities or hematologic toxicities
- Significant progression of disease or a concomitant condition that would make the subject ineligible for further protocol participation
- Pregnancy or unwillingness to use acceptable forms of contraception
- Initiation of non-protocol therapy for aplastic anemia
- Development of study related cataracts

7.1.1.1.3. Study treatment.

Eltrombopag 50 mg once daily (25 mg in East Asian patients), increasing by 25 mg daily each 2 weeks based on platelet count response, to a maximum of 150 mg/day (75 mg in East Asians). 44 patients were entered and 43 treated. The primary response assessment (PRA) was after 12-16 weeks. Responders were enrolled in an extension study with 3 monthly assessments, to evaluate the lowest dose of study drug to maintain platelet counts until the subjects met off-study criteria or the study closed. Non-responders or those intolerant of study drug were taken off study (Figure 1).

Figure 1: Study Schema ELT112523



7.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Haematological improvements. Elevation in blood counts. Based on the following criteria
  - Platelet count increase to 20 x 10^9/L above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks.

- Haemoglobin (Hb) increase by >1.5 g/dL (15 g/L) for patients with pre-treatment Hb levels of <9 g/dL, or a reduction in the units of red blood cell (RBC) transfused by at least 4 for 8 consecutive weeks, compared with the 8 weeks pre-treatment.
- An Absolute neutrophil count (ANC) increase of 100% (for pre-treatment levels <0.5 x 10^9/L) or an ANC increase >0.5 x 10^9/L.

The primary efficacy outcome was- Investigator assessed haematological response at the Primary Response Assessment (PRA) 12-16 weeks after drug commencement.

Other efficacy outcomes included:

- Best lineage response: unilineage, bilineage or trilinage. To determine whether the response to Eltrombopag improved over time with continued treatment.
- Response at each subject's last assessment: to assess maintenance of effect over time during the extension
- Duration of response, maintenance of response after discontinuation of therapy: to evaluate durability of response
- Transfusion independence for platelets and RBC. Assessed by a shift from baseline transfusion dependence to independence and the maximum duration of transfusion independence.
- Bone marrow cellularity and haematopoiesis. To assess reconstitution of the marrow
- Health-related quality of life measures at base-line and at 12-16 weeks after baseline.

7.1.1.1.5. Randomisation and blinding methods

Not applicable

7.1.1.1.6. Analysis populations

The *All Enrolled Subjects* population comprises all subjects enrolled into the study. Any data in the database for subjects not treated with IP were included in listings but not in other displays, except for subject accounting summaries.

The *Safety population* comprises all subjects who received at least one dose of IP. This population was used in all displays of efficacy and safety data.

Table 1: Summary of Study Populations

	Total (N=44)
Enrolled	44
Safety population [a]	43

Data Source: Table 1.0010

a. Safety population is defined as subjects who received at least one dose of study treatment.

7.1.1.1.7. Sample size

A total of 44 subjects with SAA were enrolled in the study, 43 subjects received at least one dose of eltrombopag. The protocol was written originally to enrol and treat 25 subjects. Twenty-six subjects were enrolled under the original protocol; one enrolled subject was not treated. The protocol was amended 20-Apr-2012 to increase enrolment to a maximum of 45 subjects. Eighteen subjects were enrolled and treated under this amendment. The efficacy and safety populations study consisted of 43 treated subjects.

One subject was withdrawn prior to treatment. As this is a rare clinical scenario the number of enrolled and treated patients is appropriate.

7.1.1.1.8. Statistical methods

A 2 stage design: A maximum of 25 subjects were included in the first stage to test the null hypothesis that the response rate with this treatment was no greater than 10%. The trial was powered against an alternative hypothesis that the response rate was at least 30%. The null hypothesis of p ≤ 10% was to be rejected if the total number of responders out of 25 subjects was 6 or more. Eleven 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 trial.

Subsequently, to obtain more precision in the parameter estimates, a further 20 to 25 subjects were planned to have been added to the trial after completion of the original 25 subjects, bringing the total planned sample size to a maximum of 50 subjects. Eventually 44 were enrolled and 43 received study drug.

7.1.1.1.9. Participant flow

See Figure 1.

7.1.1.1.10. Major protocol violations/deviations

Forty-three of the 44 subjects enrolled in the study met all inclusion/exclusion criteria. One enrolled subject ([information redacted]) was not treated due to a change in diagnosis from aplastic anemia to hypocellular myelodysplastic syndrome prior to treatment with eltrombopag.

7.1.1.1.11. Baseline data

The following tables describe the baseline characteristics and disease at screening of the population.

Table 2: Summary of demographic characteristics (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: Table 1.0110

a. Categories NIH used to capture race/ethnicity

Table 3: Summary of disease characteristics at screening

	Eltrombopag: Total (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 (%)	
Normal	38 (88)
Abnormal	3 (7)
Insufficient metaphases	1 (2)
Baseline Labs, median (range)	
Platelet Count, Gi/L	20 (6-90)
Neutrophils, Gi/L	0.58 (0.07-2.81)
Hemoglobin, g/dL	8.4 (6.6-13.8)
Reticulocytes, Gi/L	24.3 (1.7-96.9)
Severe Cytopenias	
Neutropenia <0.5 G/iL	18 (42)
Thrombocytopenia <20 Gi/L	18 (42)
Anemia <10.0 g/dL	35 (81)

7.1.1.2. Results for the primary efficacy outcome

At the PRA a haematologic response was achieved in 17 (40%) in at least one lineage (95% CI: 25%, 56%) (Table 4). 65% met the platelet response criteria whilst 47% and 18% respectively met ANC and Hb criteria. 13 of the responses were unilineage and 4 patients had multilineage responses (3- bilineage, 1 trilineage) (Table 5).

82% of responders continue eltrombopag treatment in the extension phase of the study. At the clinical cut off 53% of responders had achieved multilineage responses with duration ranging from 3-54.8 months.

Table 4: Primary endpoint response

	Eltrombopag (N=43)
Response, n (%)	**17 (40)**
95% CI [a]	(25,56)

Data Source: Table 2.0010

a. Confidence Intervals for percentage using Klopper-Pearson method

Table 5: Responses to Eltrombopag. At PRA, Best Observed and at Last Assessment

	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 (%)			
Uni-lineage	13 (76)	8 (47)	5 (29)
Multi-lineage	4 (24)	9 (53)	9 (53)
Bi-lineage	3 (18)[a]	4 (24)	4 (24)
Tri-lineage	1 (6)	5 (29)	5 (29)
Relapsed by Last Assessment			3 (18)
Response By Lineages [b], n (%)			
Platelet	11 (65)	12 (71)	12 (71)
Hemoglobin	3 (18)	8 (47)	6 (35)
Neutrophils	8 (47)	11 (65)	10 (59)

Data Source: Table 2.0010, Table 2.0020 and Table 2.0030

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

7.1.1.3. Results for other efficacy outcomes

Best lineage response: Detailed in Table 5. Lineage response improved with ongoing therapy.

Response at each subjects last assessment: See Table 5. The majority of responders maintained responses at data cut-off. Three patients who relapsed were unilineage responders and relapses occurred early (<6 months of therapy).

Duration of response and maintenance of response after discontinuation of therapy: Of those who responded the response was maintained (at least 2 response assessments) for a median duration of 12 month's (3-54.8). 8 responders have been followed for at least one year without relapse; including 6 who have been followed for 2 years without relapse. No new therapy for SAA has been given.

Transfusion independence for platelets and RBC: See Table 6. Twenty-three of 39 subjects who were platelet transfusion dependent at baseline-line became platelet independent whilst 10 of 37 became RBS transfusion independent.

Table 6: Summary of transfusion free periods for responders compared to non-responders

Transfusion Free Duration (Days)	Responder (N=17)	Non-Responder (N=26)	Total (N=43)
Platelet Median (min-max)	287.0 (8-1190)	27 (7-84)	33 (7-1190)
RBC Median (min-max)	266.0 (15-1190)	28.5 (8-115)	32.0 (8-1190)

Bone marrow cellularity and haematopoiesis: 88% of responders had hypocellular bone marrows at baseline. Of these 6 became 'normocelluar' during the extension phase at ~2 tears of therapy. A further 6 were reported to have had improvements in cellularity. The remaining 5 had no change in cellularity. Upon tapering, 2 normocelluar patients became hypocellular although they maintained their trilineage haematologic response criteria. A total of 7 subjects had trilineage haematopoiesis documented in the bone marrow after a median of 635 days of therapy.

Health-related quality of life measures at base-line (HRQOL) and at 12-16 weeks after baseline: Slight to modest impairment of health outcome measures were seen in all patients at baseline. No change in was seen at the PRA time point. Some differences were reported for responders compared to non-responders and it is relevant to note that the ongoing improvements in haematologic response criteria in the responders. Note should also be made of the increases in days of independence of blood product transfusion.

7.1.2. Study ELT116826

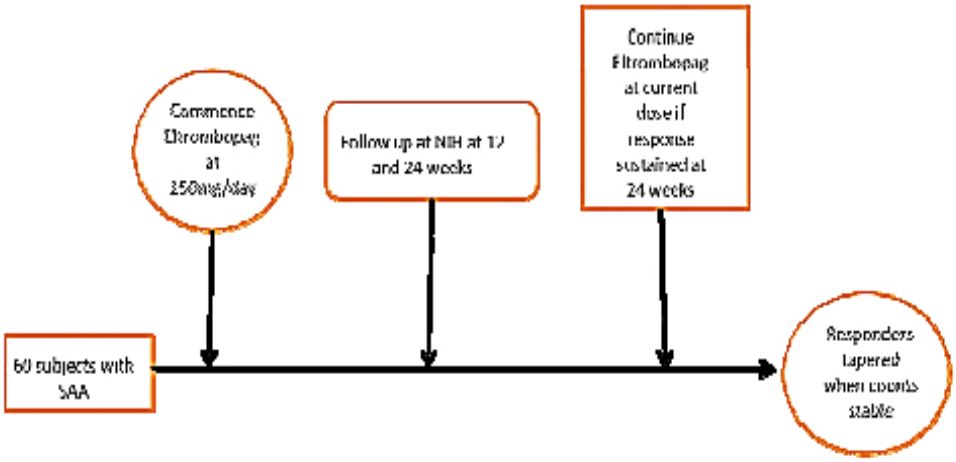
Extended dosing with Eltrombopag in Subjects with refractory severe aplastic anemia (SAA).

7.1.2.1. Study design, objectives, locations and dates

A follow-up and 'extension' of the pivotal study evaluating an alternative dosing schedule.

Study design (Figure 2): open-label, non-randomized, single-arm, Phase II, single centre study conducted by the NIH to evaluate the safety and efficacy of eltrombopag in subjects aged 12 and above with refractory SAA.

Figure 2: ELT116826 Study design



1. 60 subjects with SAA; 2. Commence Eltrombopag at 150 mg/day; 3. Follow-up at 12 and 24 weeks; 4. Continue eltrombopag at current dose if response sustained at 24 weeks; 5. Responders tapered when counts stable

Objective: To evaluate a starting daily dose of Eltrombopag of 150 mg, with dose adjustment for East Asians and children. The primary endpoint was haematological response (platelet count, erythroid or neutrophil) at 6 months. Subject-reported outcomes were collected at baseline, 3 months (12 weeks) and 6 months.

Location: This study was conducted at a single center in the United States.

Dates and enrolment: The planned enrolment is 60 subjects. 15 subjects have been enrolled as of the clinical cut-off date (31 Mar 2014). The starting daily dose of eltrombopag was 150 mg, with dose adjustment for East Asians (75 mg) and children. The primary endpoint was haematological response (platelet count, erythroid or neutrophil) at 6 months. Subject-reported outcomes were collected at baseline, 3 months (12 weeks) and 6 months.

7.1.2.1.1. Inclusion and exclusion criteria

Inclusion criteria:

1. Diagnosis of refractory SAA following at least one treatment course of antithymocyte globulin, or alemtuzumab or cyclophosphamide.
2. At least one of the following:
   a. platelet count ≤ 30 x 10^9/L or platelet-transfusion-dependence (requiring at least 4 platelet transfusions in the 8 weeks prior to study entry);
   b. neutrophil count less than 0.5 x 10^9/L;
   c. hemoglobin less than 9.0 g/dL or red cell transfusion dependence (requiring at least 4 units of RBCs in the eight weeks prior to study entry)

3. Age ≥ 2years old
4. Weight > 12 kg

Exclusion criteria:

1. Diagnosis of Fanconi anemia
2. Infection not adequately responding to appropriate therapy
3. Evidence of a clonal disorder on cytogenetics performed within 12 weeks of study entry.
4. Creatinine > 2.5 mg/dl
5. Direct Bilirubin > 2.0 mg/dl
6. Alanine aminotransferase or aspartate aminotransferase >5 times the upper limit of normal
7. Hypersensitivity to eltrombopag or its components
8. Female subjects who are nursing or pregnant or are unwilling to take oral contraceptives or refrain from pregnancy if of childbearing potential
9. Unable to understand the investigational nature of the study or give informed consent
10. Moribund status or concurrent hepatic, renal, cardiac, neurologic, pulmonary, infectious, or metabolic disease of such severity that it would preclude the patient's ability to tolerate protocol therapy, or that death within 7-10 days is likely
11. Treatment with ATG, cyclophosphamide or alemtuzamab within 6 months of study entry.

7.1.2.1.2. Study treatments

Starting daily dosage according to age and ethnicity are shown in (Table 7).

Table 7: Dose according to age and ethnicity

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

The daily dose of eltrombopag was adjusted according to the rules outlined in Table 8.

Table 8: Dose adjustment of eltrombopag

Platelet Count	Dose Adjustment or Response
>200 Gi/L (untransfused) at any time on study	Decrease dosage by 25mg every 2 weeks to lowest dosage that maintains platelet count ≥ 50 Gi/L. In children under 12, the dose will be decreased by 12.5 mg.
>400 Gi/L (untransfused) at any time on study	Discontinue eltrombopag for one week, if platelets fall to <200 Gi/L; restart at dosage decreased by 25 mg/day (or 12.5 mg in children under 12).

7.1.2.1.3. Efficacy variables and outcomes

The main efficacy variables were:

- Primary endpoint of the study was haematological response (platelet count, erythroid and neutrophil) at 6 months (24 weeks). Haematological response is defined as:
  - Platelet count increases to 20 x 10^9/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks; or
  - Haemoglobin increase by > 1.5 g/dL (for subjects with pre-treatment Hb < 9 g/dL), or a reduction in the units of red blood cell transfusion by at least 4 of 8 consecutive weeks pre-treatment; or
  - ANC increase of 100% (for pre-treatment levels <0.5 x 10^9/L), or an ANC increase >0.5 x 10^9/L.
- Other efficacy outcomes included:
  - 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 the 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).

7.1.2.1.4. Randomisation and blinding methods

None.

7.1.2.1.5. Analysis populations

Patients with SAA referred to the NIH.

Demographics of study population to date

1. Age range: 14 years to 69 years (median 46 years), with 12 of 15 subjects (80%) being greater than 18 years of age. Three subjects (20%) were in the 12-17 year range. The majority of subjects were female (10, 67%).
2. The majority of subjects were White (12, 80%) followed by Asian (2, 13%) and Black/African American (1, 7%).
3. Median baseline haematology parameters were consistent with that expected in the previously treated SAA population. Median baseline haematology parameters included ANC 0.53 x 10^9/L, platelets 11 x 10^9/L, absolute reticulocyte count (ARC) 34.7 x 10^9/L, and haemoglobin 8.6 g/dL.

7.1.2.1.6. Sample size

Planned number of subjects: 60

Number of subjects enrolled: 15/60

Study is Ongoing; data are included up to 31 March 2014

7.1.2.1.7. Statistical methods

Simple descriptive on the proportion of responders (% subjects with treatment response). Subjects were considered evaluable for response at 3 or 6 months if they completed 3 or 6 months of treatment, respectively, or were discontinued early for any reason.

7.1.2.1.8. Participant flow

See Figure 2.

7.1.2.1.9. Major protocol violations/deviations

None reported.

7.1.2.1.10. Baseline data

Baseline haematological data are described in Table 9 below.

Table 9: Baseline haematological parameters

	Median (range)
ANC (Gi/L)	0.53 (0.14, 1.4)
Platelets (Gi/L)	11 (4, 24)
ARC (Gi/L)	34.7 (9.5, 65)
Hemoglobin (g/dL)	8.6 (6.6, 12.4)

Median baseline lab values for neutrophils, platelets, reticulocytes, and hemoglobin are consistent with that expected in the previously treated SAA population.

7.1.2.2. Results for the primary efficacy outcome

The primary efficacy endpoint in Study ELT116826 was haematological response (platelet count, erythroid or neutrophil) at 6 months (24 weeks).

At clinical cut-off date, 11 and 6 subjects, respectively, were evaluable or had discontinued treatment at the 3 and 6 month response assessments (Table 10). At the 3 month assessment 4 of 11 (36%) evaluable subjects met the haematologic response criteria in at least one lineage. At the 6 month assessment (primary response assessment), 4 of 6 (67%) evaluable subjects met the haematologic response criteria in at least one 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.

Of the subjects who did not respond at 3 months and were evaluable at 6 months, 2 additional subjects responded at 6 months. The remaining 3 subjects had not had their 6 month assessment as of the clinical cut-off date.

Table 10: 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)
Multi-lineage	2 (50)	2 (50)
Bi-lineage	2	2
Tri-lineage	0	0

7.1.2.3. Results for other efficacy outcomes

No other results provided

7.2. Other relevant studies

7.2.1. ELT116643 study

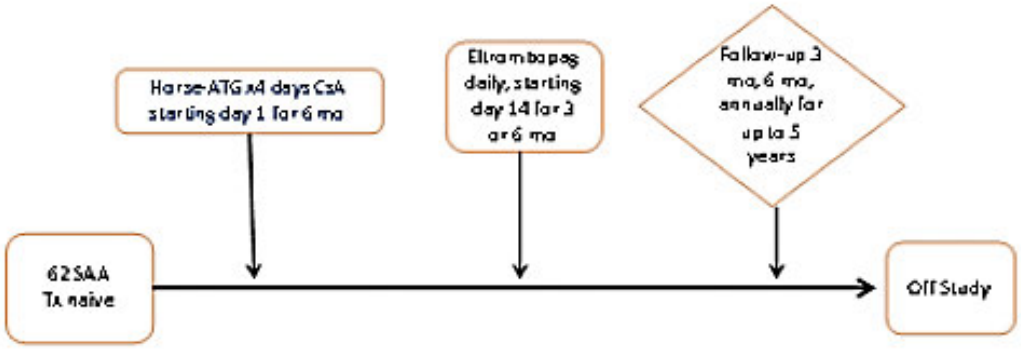
Eltrombopag added to standard immunosuppression in treatment naïve severe aplastic anemia.

7.2.1.1. Study design, objectives, locations and dates

An ongoing study evaluating Eltrombopag in combination with standard, first line immunosuppressive therapy (hATG/CsA) for treatment-naïve patients with SAA (Figure 3).

Design: an open-label, Phase I/II single-centre study of eltrombopag in combination with standard regimen of hATG/CsA in 62 treatment-naive subjects ages 2 and above 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).

Figure 3: ELT116643 Study design



1. 62 SAA treatment naïve patients; 2. Horse-ATG x 4 days CsA starting Day 1 at 6 mg; 3. Eltrombopag daily, starting Day 14 at 3 or 6 mg; 4. Follow-up 3 months, 6 months, annually for up to 5 years; 5. Off study

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

- Platelet count increases to 20 x 10^9/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 x 10^9/L), or an ANC increase >0.5 x 10^9/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.

7.2.1.2. Inclusion and exclusion criteria

Inclusion criteria

1. SAA characterised by Bone marrow cellularity < 30% (excluding lymphocytes) AND

   at least two of the following: ANC < 0.5 x 10^9/L, Platelet count < 20 x 10^9/L, or ARC < 60 x 10^9/µL
2. Age > 2 years old
3. Weight > 12 kg

Exclusion criteria

1. Diagnosis of Fanconi anemia
2. Evidence of a clonal disorder on cytogenetics performed within 12 weeks of study entry

3. Prior immunosuppressive therapy with any ATG, alemtuzumab, or high dose cyclophosphamide
4. Alanine aminotransferase or aspartate aminotransferase > 3 times the upper limit of normal
5. Subjects with liver cirrhosis
6. Hypersensitivity to eltrombopag or its components
7. Infection not adequately responding to appropriate therapy
8. Moribund status or concurrent hepatic, renal, cardiac, neurologic, pulmonary, infectious, or metabolic disease of such severity that it would preclude the patient's ability to tolerate protocol therapy, or that death within 7-10 days is likely
9. Potential subjects with cancer who are on active chemotherapeutic treatment or who take drugs with hematological effects will not be eligible
10. Current pregnancy, or unwillingness to take oral contraceptives or use a barrier method of birth control or practice abstinence to refrain from pregnancy if of childbearing potential during the course of this study
11. Inability to understand the investigational nature of the study or to give informed consent

7.2.1.3. Study treatments

Dose: Eltrombopag, 150 mg is initiated on Day 14 to avoid overlap with the known transient hepatotoxicities associated with ATG/CsA. Eltrombopag, along with cyclosporine, is discontinued at 6 months regardless of response characteristics in this study.

Eltrombopag was initiated on Day 14 to avoid overlap with the known transient hepatotoxicities associated with ATG/CsA. Subjects initiate eltrombopag at a starting daily dose according to age and ethnicity (Table 11).

Table 11: Dose according to age and ethnicity

	Daily dose
Non-Asian	
12-85 years	150 mg
6-11 years	75 mg
2-5 years	2.5 mg/kg
East Asian, South East Asian	
12-85 years	75 mg
6-11 years	37.5 mg
2-5 years	1.25 mg/kg

The daily dose of eltrombopag was adjusted according to the rules outlined in Table 12.

Table 12: Dose adjustment of eltrombopag

Platelet Count	Dose Adjustment or Response
>200 Gi/L (untransfused) at any time on study	Decrease dosage by 25mg every 2 weeks to lowest dose that maintains platelets ≥ 50 Gi/L. In children under 12, the dose will be decreased by 12.5 mg.
>400 Gi/L (untransfused) at any time on study	Discontinue eltrombopag for one week, if platelets fall to <200 Gi/L; restart at dose decreased by 25 mg/day (or 12.5 mg in children under 12).

7.2.1.4. Efficacy variables and outcomes

The primary efficacy endpoint is the rate of complete hematologic response (CR) at six months and the key secondary efficacy endpoint was partial response (PR).

7.2.1.5. Randomisation and blinding methods

None.

7.2.1.6. Analysis populations

All subjects evaluated at the NIH who are age 2 and older with SAA who have not received prior ATG-based immunosuppressive therapy and lack a suitable matched sibling marrow donor (or are not allogeneic transplantation candidates due to patient choice, advanced age, or infeasibility of transplantation) will be considered for enrollment (Table 13).

7.2.1.7. Sample size

Planned number of subjects: Cohort 1: 31; Cohort 2: 31

Number of subjects enrolled: Cohort 1: 31; Cohort 2: 16

Study is Ongoing: data are included up to clinical cut-off 31 March 2014.

7.2.1.8. Statistical methods

Simple descriptive statistics on the proportions of responses (% subjects with partial or complete response).

Subjects were considered evaluable for response at 3 or 6 months if they completed 3 or 6 months of treatment, respectively, or were discontinued early for any reason.

7.2.1.9. Participant flow

See Figure 3.

7.2.1.10. Baseline data

Demographic and Baseline Characteristics: As of the clinical cut-off for this ongoing study, 47 of the planned 62 subjects (as of 31 March 2014) have been enrolled (Table 13). The first 31 subjects were enrolled to Cohort 1 and the remaining 16 subjects were enrolled to Cohort 2. The median (range) age of subjects was 39 years (12, 72), with 40 of 47 subjects (85%) being 18 years of age. Seven subjects (15%) were in the 12-17 year range. The majority of subjects were male (25, 53%). The majority of subjects were White (25, 53%) followed by Black/African American (15, 32%) and Asian (5, 11%). Baseline haematology values were consistent with the diagnosis of SAA (Table 14). The baseline median values for ANC, platelets and ARC were indicative of the pancytopaenic SAA patient population (0.33 x 10^9/L, 9 x 10^9/L and 12.8 x 10^9/L, respectively). The majority of subjects (61%) enrolled in the study met the criteria for SAA in all 3 lineages. All subjects were treatment naive at entry into the study and were scheduled to receive standard IST with hATG/CsA as part of the study.

Table 13: Subject disposition

	Eltrombopag N=47
Eltrombopag Treatment Status, n (%)	
Discontinued Treatment	31 (66)
Ongoing	13 (28)
Not Treated[a]	3 (6)
Primary reason for eltrombopag treatment discontinuation, n (%)	
Completed scheduled treatment period	27 (47)[b]
Detection of cytogenetic abnormality[c]	2 (4)
Allogenic bone marrow transplant[c]	1 (2)
Death[c]	1 (2)

a. Subject [redacted] received treatment with hATG/CsA but not eltrombopag due to cytogenetic abnormality detected on baseline bone marrow aspirate.
Subjects [redacted] and [redacted] had not reached Day 14 (start of eltrombopag) as of the clinical cut-off date.

b. Cohort 1: [redacted] subjects completed 6 months of eltrombopag treatment; 5 subjects tapered off eltrombopag due to increased platelet count (1 subject received 5 months of eltrombopag treatment, 1 subject 4 months, 1 subject 2 months and 2 subjects 1 month).
Cohort 2: 3 subjects completed 3 months of eltrombopag treatment.

c. Subject [redacted] went to allogeneic bone marrow transplant after ~2 months.
Subject [redacted] and [redacted] had a cytogenetic change at 3m (Subject [redacted] had a CR at 3m).
Subject [redacted] died before the 3 months assessment.

Table 14: Baseline haematology parameters

	Median (range) N=47
ANC Gi/L	0.33 (0.00, 1.38)
Platelets Gi/L	9 (1, 37)
ARC Gi/L	12.8 (1.6, 51.6)

7.2.1.11. Results for the primary efficacy outcome

Efficacy data reported: At the 6 month assessment, the primary endpoint of CR was met by 10/28 subjects (36%; 95% CI: 19%, 56%) and 22 subjects overall (79%) had a CR or PR (Table 15). At the 3 month assessment, 6/33 subjects (18%) had a CR and 26 subjects (79%) had an overall response. Five of the 6 subjects with a CR at 3 months were evaluable and maintained a CR at the 6 month assessment. The remaining subject has not had their 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.

Table 15: Three and Six Month Response Assessments. ELT116643

Haematologic Response, n (%)	3 Month N=33[a]	6 Month N=28[a]
Overall Response	26 (79)	22(79)
Complete Response	6 (18)	10 (36)
Partial Response	20 (61)	12 (43)
Non-responder	7 (23)[b]	6 (21)

a. Includes 5 non-responders (Subjects [redacted]), 1 subject (Subject [redacted] not evaluated for response due to discontinued treatment prior to 3 month assessment and 1 subject (Subject [redacted]) who died prior to the 3 month evaluation.

b. Includes 3 non-responders at 3 months (Subjects [redacted]) 2 subjects (Subject [redacted]) who discontinued or died prior to evaluation at 3 months and 1 subject (Subject [redacted]) with a PR at 3 months who discontinued treatment with eltrombopag at 3 months due to detection of a cytogenetic change.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

Not included.

7.4. Evaluator's conclusions on clinical efficacy

for patients with severe aplastic anaemia who had had an insufficient response to immunosuppressive therapy.

The pivotal Study EELT112523 and supporting Study ELT116826, whilst non-randomised, provide evidence for the efficacy of eltrombopag in a significant minority of patients who meet the study criteria.

The evaluator does however have some comments that relate to inclusion criteria in these studies. The evaluator's impression is that already available, albeit not totally effective, alternative therapy options may have may have not been considered in some patients included in these studies. In particular;

1. Patients could be entered into these studies after having failed only one prior IST. It is well recognised from the literature, and it is accepted practice, that a proportion of patients who fail a first course of IST will respond to a second course.
2. It is also curious that little mention is made of the use of allogeneic haematopoietic stem cell transplantation in suitable patients with SAA. It is to be noted that not all patients with SAA are suitable recipients of such a transplant with availability of a suitable donor, patient age and co-morbidities being key inclusion/exclusion criteria. However, in the context of this rare condition this therapy is 'widely' practiced Australia (and the rest of the world). For instance, the Australian Bone Marrow Transplant Recipient Registry (ABMTRR, Annual Data Summary 3013) reports that in 2013, 4 children and 15 adults in Australia were the recipients of allogeneic stem cell transplants for the management of aplastic anaemia. The ABMTRR contains data on more than 160 recipients of such transplants with long term follow up >9 years. Survival in adult the adult cohorts (16+ years) was 72% (Human leukocyte antigen (HLA) matched sibling donor) and 56% (HLA-identical unrelated donor). In paediatric patients (n=43) survival for AA, SAA and very SAA was 95%. The evaluator's belief is that the majority of adult patients in this data base would have come to transplant after failure of at least 1 course of IST. In paediatric practice by contrast the evaluator believes that a transplant is therapy of choice provided that a suitable donor is available.

Given the caveats noted above the submitted data does support efficacy (with acceptable toxicity) in this group of patients. The efficacy endpoints reported (for instance reduction in red blood cell and platelet transfusion requirements) can be clinically meaningful to those patients who achieve them.

Particular note is made of the following that reflect on long-term efficacy and the ability for drug withdrawal. Note is also made of bi-lineage and tri-lineage responses, the ability to titrate down to the lowest effective dose and the ability for eventual drug withdrawal in a (limited) number of patients).

1. The gradual improvement of haematologic responses across multiple lineages over time and the maintenance of response for 1 year provide evidence of the long-term efficacy of eltrombopag in heavily pre-treated SAA patients.
2. Responses were maintained throughout the treatment period, with subjects receiving 150 mg eltrombopag for up to 39 months.
3. Relapses were few and occurred early in treatment course. No relapses occurred after 6months of treatment and no relapses occurred in subjects with multilineage responses.
4. Based upon these data, there is no evidence for development of tolerance to eltrombopag or loss of efficacy following continued treatment with eltrombopag.
5. In addition, all subjects meeting 'trilineage haematopoiesis' criteria who had eltrombopag tapered off, have maintained their response with a median follow-up of 20.6 months as of

data cut-off. This provides evidence supporting the persistence of efficacy following treatment with eltrombopag in patients with SAA

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

The primary safety data is from the pivotal Phase II Study ELT112523 (National Institute of Health [NIH] 09-H-0154); the safety and efficacy proposed for the labeling is based on this study. Available supportive safety data in SAA subjects is provided from the ongoing Phase II Study ELT116826 (NIH 13-H-0133) in subjects with an insufficient response to IST, as well as the ongoing Phase I/II Study ELT116643 (NIH 12-H-0150) in treatment naïve subjects.

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).

8.1.1. Efficacy data from ITP and Hepatitis C studies

Eltrombopag is an approved product with an established safety profile in chronic ITP and HCV indications based upon review of placebo-controlled databases:

1. Chronic ITP: randomized controlled safety database: n=427 (eltrombopag n=299, placebo n=128). Total eltrombopag chronic ITP safety database: n=446
2. HCV: randomized controlled safety database: n=1439 (eltrombopag n=955, placebo n=484). Total eltrombopag HCV safety database: n=1576

The sponsor reports that an estimated 3,900 subjects have been exposed to eltrombopag in sponsored ongoing and completed interventional studies; this includes subjects with ITP, liver diseases, haematology-oncology related thrombocytopaenia, as well as healthy volunteers. The eltrombopag SAA clinical development programme includes a safety database of 88 Eltrombopag-treated subjects with SAA from 3 open-label trials included in this submission. (Table 16)

Table 16: SAA and MDS/AML patients treated with Eltrombopag. Safety database

Study	Eltrombopag (SAA population)	Double-Blind Study Treatment (advanced MDS/AML patient population)	
		Placebo	Eltrombopag
ELT112523	43[a]	NA	NA
ELT116826	15	NA	NA
ELT116643	44[b]	NA	NA
PMA112509	NA	34	64

a. One additional subject was enrolled, but did not receive eltrombopag treatment.
b. Three additional subjects were enrolled, 1 did not receive eltrombopag treatment, 2 had not received eltrombopag treatment as of the clinical cut off date.

The sponsor also provided additional safety data from a placebo-controlled study in subjects with advanced MDS or AML receiving up to twice the maximum dose of eltrombopag in SAA. Both SAA and the MDS/AML population are characterised by sever pancytopenia and it complications.

Summary: The safety profiles observed in both SAA and MDS/AML populations (PMA112509) seem to be consistent with what has been reported for eltrombopag in chronic ITP and HCV. No new safety signals have been identified in the SAA population with doses up to eltrombopag 150 mg.

8.1.2. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) in SAA patients were assessed in the pivotal study (ELT112523) and the 2 supporting studies (ELT116826 and ELT116643)

  Of the 43 subjects who received eltrombopag in Study ELT112523, 93% were escalated to the maximum dose of eltrombopag 150 mg. Three subjects received a maximum dose of eltrombopag 125 mg. Given the design of the study, in which subjects who did not meet response criteria were discontinued from treatment after 3 months, the median (range) time on treatment was 3.6 months (2-39). Eltrombopag treatment was received for at least 3 months in 77% of subjects. As of the clinical cut-off date, 28% and 21% of subjects received eltrombopag for >6 and 12 months, respectively, with a maximum duration of 39 months

- AEs of particular interest in the SAA patient group including hepatobiliary, thromboembolic, haematological malignancies and clonal cytogenetic changes were monitored (relevant clinical and laboratory assessments) and are reported for all studies.

- Laboratory tests, including standard haematology, biochemistry were performed according to study protocol. Specialised investigations included bone marrow aspiration and biopsy and cytogenetic analysis.

8.1.3. Pivotal studies that assessed safety as a primary outcome

In addition to the pivotal Study ELT112523, studies ELT1116826, ELT116643 and **PMA112509** assessed safety as a primary outcome. The safety population consisted of all patients who had received at least one dose of eltrombopag. These studies are described in Section 8.2.

8.1.4. Dose-response and non-pivotal efficacy studies

Dose rationale and dosing strategy have been described above.

The ongoing non-randomised Phase II Study ELT1116826 dose-modification study evaluated patients who commenced treatment at the maximum dose used in ELT112523 (150 mg/day, with modifications for East Asians and children) and then evaluated, in responding patients, the lowest dose that maintained stable platelet counts.

Study ELT116643 provides data on dosing of Eltrombopag in combination with CsA/hATG.

8.2. Pivotal studies that assessed safety as a primary outcome

8.2.1. Study ELT112523

8.2.1.1. Study design, objectives, locations and dates/Inclusion and exclusion criteria/Study treatments

See section 7.1.1.1.3.1

8.2.1.2. Safety variables and outcomes

The main safety variables were:

- Tabulation of extent of exposure, AEs, serious adverse events (SAEs), deaths, clinical laboratory evaluations, and pregnancies are detailed in the RAP.

Other safety measures included:

- Complete blood count, differential, and reticulocytes
- Biochemistry parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], bilirubin, blood urea nitrogen [BUN], and creatinine)

- Cytogenetic testing.

8.2.1.3. Randomisation and blinding methods

N/A

8.2.1.4. Analysis populations/sample size/ statistical methods/major protocol violations/deviations/ baseline data

See section 7.1.1.1.6.

8.2.1.5. Participant flow

See Figure 1: Study Schema ELT112523.

8.2.1.6. Results for the primary safety outcome

Eltrombopag at doses up to 150 mg daily was generally well-tolerated in the SAA studies. Over 90% of subjects in Study ELT112523 escalated to the maximum dose, and 12% of subjects discontinued due to AEs.

In general, the safety profile of eltrombopag at doses up to 150 mg daily in Study ELT112523 is consistent with the expected safety profile for patients with SAA and the established safety profile of eltrombopag in the approved chronic ITP and HCV indications. No new safety signals have been detected. The most common AEs were nausea, fatigue, cough, diarrhoea, and headache. Serious AEs of febrile neutropaenia, sepsis, and viral infection were reported and were expected given the severe neutropaenia in this patient population. Of note, infectious SAEs were reported in a smaller proportion of responders (18%) than non-responders (30%) in ELT112523, despite the longer duration of follow-up in responders.

The incidence and cause (primarily sepsis/infection) of deaths reported in the pivotal Study ELT112523 were consistent with the disease under study.

8.3. Patient exposure

8.3.1. Study ELT112523 exposure

1. Forty-three subjects initiated treatment with eltrombopag 50 mg and were dose escalated in 25 mg increments every 2 weeks to a maximum of eltrombopag 150 mg.
2. Of the 43 subjects who received eltrombopag, 40 (93%) were escalated to the maximum dose of eltrombopag 150 mg Three subjects did not receive the maximum dose of 150 mg. The maximum dose received for these 3 subjects was 125 mg.
3. The median subject daily dose was calculated by dividing the cumulative dose received by the days of treatment. Due to the protocol-specified dose escalation, the average daily dose is < 150 mg for all subjects (Table 17).

Table 17: Summary of Exposure to Eltrombopag in pivotal Study ELT112523

	Eltrombopag (N=43)
Subject Daily Dose (mg)[a]	
Mean (SD)	113.2 (19.65)
Median (min-max)[b]	110.2 (47-147)
Time on Study Treatment (Months)[c]	
Mean (SD)	8.4 (10.44)
Median (min-max)	3.6 (2-39)
<3 months, n (%)	10 (23)
≥3 months, n (%)	33 (77)
>6 months, n (%)	12 (28)
>12 months, n (%)	9 (21)
Cumulative Actual Dose (mg)	
Mean (SD)	32508.1 (45466.65)
Median (min-max)	11300.0 (4025-175075)

Data Source: m5.3.5.2 ELT112523 CSR Section 7.1

Abbreviations: SD=standard deviation

a. The subject daily dose (the cumulative actual dose divided by the duration of exposure) is calculated for each subject first and the summary statistics are calculated based on the subject average daily dose.

b. Median subject daily dose was calculated by dividing the cumulative dose received by the days of treatment. Due to the protocol-specified dose escalation and the study design, the average daily dose is <150 mg for all subjects.

c. Time on study drug does not exclude dose interruptions.

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. The majority of subjects received treatment for at least 3 months. Nine subjects received eltrombopag for more than 12 months, with a maximum duration of 39 months.

8.3.2. Study ELT116826 exposure

Of the 15 subjects who received eltrombopag up to 150 mg in Study ELT116826, 5 subjects completed 6 months of treatment with eltrombopag and 4 of the 5 subjects had entered the extension phase of the study. As of the clinical cut-off date (31 March 2014), the 4 subjects received between 57 to 85 days of treatment in the extension phase. No further exposure data are available for this ongoing study.

8.3.3. Study ELT116643 exposure

Of the 44 subjects who received eltrombopag up to 150 mg in StudyELT116643, 19 subjects completed the planned 6 month eltrombopag treatment period in Cohort 1. Five Cohort 1 subjects tapered off eltrombopag due to increased platelet count: 1 subject received 5 months of eltrombopag treatment, 1 subject received 4 months, 1 subject received 2 months and 2 subjects received 1 month. Three subjects from Cohort 2 completed the planned 3-month eltrombopag treatment period. No further exposure data is provided.

8.3.4. Study PMA112509 exposure

Subjects received a starting daily dose of 50 mg eltrombopag or matching placebo. The dose could be increased, depending on platelet and bone marrow blast response, every 2 weeks up to a maximum dose of 300 mg/day (150 mg for East Asian subjects). The goal of this dosing schema was to maintain a stable platelet count in the safe range without exceeding platelet counts >400 x 10^9/L.

Most subjects in the eltrombopag group (56%) and in the placebo group (65%) received the maximum dose of IP (300 mg, or 150 mg for East Asian subjects) (Table 18). Nine subjects (14%) receiving eltrombopag and 1 subject (3%) receiving placebo continued treatment for >6 months in the extension treatment periods.

Table 18: Exposure to study drug

	Placebo (N=34)	Eltrombopag (N=64)
Total Days on Study Drug[a]		
Mean (sd)	76.6 (55.19)	111.1 (124.07)
Median (Min-Max)	69.5 (2-253)	71.5 (3-676)
Maximum Dose – East Asians, n (%)		
50 mg	0	1 (2)
100 mg	0	3 (5)
150 mg	7 (21)	14 (22)
Maximum Dose – Non-East Asians, n (%)		
50 mg	5 (15)	9 (14)
100 mg	4 (12)	7 (11)
150 mg	0	2 (3)
200 mg	3 (9)	6 (9)
300 mg	15 (44)	22 (34)

Data Source: Table 8.0000

a. Total days on study drug = total number of days on study drug, including interruptions; therefore, it was based on the first exposure date and the last exposure date.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal study - ELT112523

In Study ELT112523, on-therapy adverse events (AEs) were defined as those that occurred from the date of first dose of eltrombopag treatment to the date 30 day following the last dose of eltrombopag. Nearly all subjects (93%) experienced at least one AE on-therapy, and the majority of subjects had at least one AE considered by investigator as possibly related to treatment. Two deaths occurred during the on-therapy period of the study and 6 deaths occurred during the entire study period (see below). The most common AEs observed in Study ELT112523 largely reflect the well-known safety profile of eltrombopag treatment and events expected in the SAA population. Nausea, fatigue, cough, diarrhoea, and headache were the most common AEs, reported by at least 20% of subjects.

In this study, a total of 14 subjects had at least one serious AE (SAE) reported during treatment (Table 19).

Table 19: Adverse events reported in the pivotal Study ELT112523

n (%)	Eltrombopag (N=43)
Any AE	**40 (93)**
AEs related to study treatment	30 (70)
AEs leading to permanent discontinuation of study treatment	5 (12)
Any SAE	**14 (33)**
Deaths	**2 (5)**

The most common AEs observed in this study largely reflect the well-known safety profile of eltrombopag and events expected in this patient population.

Nausea, fatigue, cough, diarrhea, and headache were the most common AEs reported by at least 20% of subjects (Table 20).

Table 20: On therapy event occurring in >10% or more subjects in Pivotal Study ELT112523

Preferred Term	Eltrombopag (N=43)
Any event, n (%)	**40 (93)**
Nausea	14 (33)
Fatigue	13 (30)
Cough	10 (23)
Diarrhoea	9 (21)
Headache	9 (21)
Pain in extremity	8 (19)
Dyspnoea	6 (14)
Pyrexia	6 (14)
Dizziness	6 (14)
Oropharyngeal pain	6 (14)
Febrile neutropenia	6 (14)
Abdominal pain	5 (12)
Ecchymosis	5 (12)
Muscle spasms	5 (12)
Transaminases increased	5 (12)
Arthralgia	5 (12)
Rhinorrhoea	5 (12)
Chills	5 (12)
Insomnia	5 (12)

8.4.1.2. Other studies

8.4.1.2.1. ELT116826

As of the clinical cut-off data (31 March 2014) in Study ELT116826, no AEs have led to discontinuation of eltrombopag treatment (Table 21). Six subjects have had at least 1 SAE reported, none of which were considered related to treatment. No deaths have been reported

Table 21: Overview of Adverse Events in Study ELT116826 (Safety Population)

n (%)	Eltrombopag (N=15)
AEs leading to permanent discontinuation of study treatment	0
Any SAE	6 (40)
SAEs possibly related to eltrombopag	0
Deaths	**0**

8.4.1.2.2. ELT116643

As of the clinical cut-off data (31 March 2014, in Study ELT116643), the addition of eltrombopag to the standard immunosuppressive regimen of hATG/CsA has had acceptable tolerability to date with no discontinuations due to AEs (Table 22).

Table 22: Overview of Adverse Events in Study ELT116643 (Safety Population)

n (%)	Eltrombopag (N=44)
AEs leading to permanent discontinuation of study treatment	0
Any SAE	18 (41)
SAEs possibly related to eltrombopag	1 (2)
Deaths	**1 (2)**

8.4.1.2.3. PMA112509

Nearly all subjects (95 subjects [97%]) experienced 1 or more AEs that started on treatment (Table 23). A greater proportion of subjects in the eltrombopag group experienced SAEs (77%) and drug-related AEs (56%) compared with the placebo group (65% and 35%, respectively).

SAEs and AEs leading to withdrawal from study occurred less frequently in the eltrombopag group than in the placebo group.

Table 23: Overall summary of adverse events starting on-treatment

Subjects with Event	Placebo (N=34)		Eltrombopag (N=64)	
	n (%)	Events	n (%)	Events
Any AE	32 (94)	345	63 (98)	887
Any SAE	22 (65)	50	49 (77)	135
Drug-related AE	12 (35)	26	36 (56)	79
Drug-related SAE	3 (9)	4	1 (2)	2
AE leading to withdrawal from study	13 (38)	19	13 (20)	14
SAEs leading to withdrawal from study	11 (32)	15	12 (19)	13

The most commonly reported AEs were consistent with those expected for the disease under study and with those expected during treatment with eltrombopag. Pyrexia was the most common AE in both treatment groups. The most common AEs (that is, occurring in at least 10% of the subjects) reported on treatment in the eltrombopag group were pyrexia, nausea, diarrhea, fatigue, decreased appetite, and pneumonia. A greater incidence of nausea, vomiting, diarrhea, and pyrexia was reported in the eltrombopag group compared with placebo; the majority of these events were mild to moderate. The eltrombopag group, when compared with placebo, had lower incidences of infection-related AEs (sepsis [13% versus 18%] and febrile neutropenia [11% versus 21%]) and anaemia (17% versus 24%). Leukocytosis (including increased white blood cells) was more common in the eltrombopag (11%) group than in placebo (3%).

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

Thirty subjects (70%) had at least one AE considered by the investigator to be related to treatment (Table 24). Nausea, headache, and diarrhea were the most common AEs (≥ 20%) considered related to treatment

Table 24: On-Therapy Summary of Adverse Events Related to Study Treatment Occurring in ≥ 10% of Subjects (Safety Population)

Preferred Term	Eltrombopag (N=43)
Any event, n (%)	**30 (70)**
Nausea	12 (28)
Headache	9 (21)
Diarrhoea	9 (21)
Abdominal pain	5 (12)

8.4.2.2. Other studies

8.4.2.2.1. PMA112509

In the eltrombopag treatment group, 53% of the subjects experienced an adverse event related to study drug compared with 32% in the placebo group. The majority of AEs considered related to treatment with eltrombopag were gastrointestinal AEs (nausea, diarrhea, and vomiting).

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

8.4.3.1.1. Deaths

A total of 6 deaths (14%) were reported during Study ELT112523. None of the deaths were considered related to treatment by the investigator.

No subject 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 (2 subjects sepsis/infection; 1 subject MDS/AML; 1 subject unknown).

All causes of death were consistent with the patient population under study.

Four subjects who died had an SAE reported with a fatal outcome:

- One subject [information redacted] whose primary cause of death was reported as unknown completed 12 weeks of study treatment and died due to an unknown cause 16 weeks post-therapy, one week after being referred to other therapies or supportive care.
- Three subjects [information redacted] whose primary cause of death was reported as disease under study (sepsis/infection) had fatal SAEs of aplastic anemia, sepsis, and septic shock respectively.

8.4.3.1.2. Serious adverse events

A total of 14 subjects had at least 1 SAE reported during treatment (Table 25). The most common SAE reported was febrile neutropaenia, 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. Infectious complications and cytopaenia are common in cytopenic SAA patients (Valdez, 2011). Most subjects had recovered or were recovering from the SAE as of the data cut-off (09 May 2014).

Table 25: SAEs in Pivotal Study ELT112523

Preferred Term	Eltrombopag (N=43)
Any event, n (%)	14 (33)
Febrile neutropaenia	6 (14)
Sepsis	2 (5)
Viral infection	2 (5)
Abdominal discomfort	1 (2)
Abdominal pain lower	1 (2)
Anaemia	1 (2)
Aplastic anaemia	1 (2)
Biliary colic	1 (2)
Clostridium difficile colitis	1 (2)
Pneumonia	1 (2)
Septic shock	1 (2)
Staphylococcal sepsis	1 (2)
Urinary tract infection	1 (2)

8.4.3.2. Other studies

8.4.3.2.1. Deaths

In Study ELT116826, no subject had died due to an AE as of the data cut-off date.

In Study ELT116643, 1 subject died of encephalopathy and respiratory failure in the setting of an infection while on-treatment as of the data cut-off date. Neither event was considered related to study treatments.

All causes of death were consistent with the patient population under study.

In Study PMA115209 a total of 61 deaths (62%) were reported during the study (including extension and follow-up periods): 40 deaths (63%) in the eltrombopag group and 21 deaths (62%) in the placebo group. The majority of deaths in both treatment groups (eltrombopag, 93%; placebo, 86%) were judged by the investigator to be due to the disease under study.

8.4.3.2.2. Serious adverse events

In Study ELT116826, 6 of the 15 subjects (40%) who received eltrombopag have had 11 SAEs. None of the events were considered related to eltrombopag treatment.

In Study ELT116643, 18 of the 44 subjects (41%) who received eltrombopag had 31 SAEs reported. Most of the SAEs were infectious in nature as expected in this patient population. 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 PMA115209, a greater proportion of subjects in the eltrombopag group than in the placebo group experienced SAEs (77% versus 65%). The most common SAE in both treatment groups was pneumonia. A smaller proportion of subjects treated with eltrombopag than with placebo reported SAEs of febrile neutropenia (6% versus 18%). A larger proportion of eltrombopag-treated subjects reported SAEs of pyrexia (9% versus 3%) and anaemia (6% versus 0%) compared with placebo.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

Five subjects (12%) in Study ELT112523 discontinued treatment with eltrombopag due to AEs; suspected cataract, abdominal discomfort, acute hepatitis B, viral infection and sepsis. No event lead to discontinuation for more than 1 subject.

8.4.4.2. Other studies

8.4.4.2.1. Studies ELT116826 or Study ELT116643.

No subjects discontinued eltrombopag due to an AE.

In Study *PMA112509* fewer subjects in the eltrombopag group (19%) discontinued treatment with IP due to AEs compared with the placebo group (38%) The most common AEs leading to discontinuation of IP in both groups were sepsis and pneumonia

8.4.5. Safety Topics of Special Interest

Safety issues that may potentially be of special interest in the SAA population treated with eltrombopag (ELT112523, ELT116826 and ELT116643) include hepatobiliary events, thromboembolic events, cytogenetic abnormalities, and haematologic malignancies. (Detailed below)

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

Transaminase elevations and elevations of indirect bilirubin have been observed in the eltrombopag clinical programme and are described in the approved labelling for eltrombopag. Transaminase elevations were observed primarily in subjects with either a medical history or baseline elevations of transaminases. No elevations of aminotransferases in conjunction with direct bilirubin elevations were noted. Two subjects had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x upper limit of normal (ULN) concurrent with total bilirubin >1.5xULN.

In both cases, bilirubin elevations were due to indirect bilirubin. Four subjects had transaminase elevations of >5xULN. All 4 subjects had elevations in ALT and/or AST at study entry and 1 was diagnosed with acute hepatitis B during the study. 9 subjects had an elevation

of either AST or ALT >3xULN All subjects with total bilirubin elevation >1.5xULN were due to indirect bilirubin (direct fractions ≤25%).

8.5.1.2. Other studies

In ELT116643, no SAEs related to liver function were reported as of the clinical cut-off date.

8.5.2. Kidney function

8.5.2.1. Pivotal studies

No unexpected adverse events reported.

8.5.2.2. Other studies

No unexpected adverse events reported.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

Nothing of apparent significance reported.

8.5.3.2. Other studies

Nothing of apparent significance reported

8.5.4. Haematology

8.5.4.1. Pivotal studies

No apparently new haematological toxicity reported. See relevant sections relating to haematological response and assessment criteria.

8.5.4.2. Other studies

No apparently new haematological toxicity reported. See relevant sections relating to haematological response and assessment criteria.

8.5.5. Thromboembolic events.

8.5.5.1. Pivotal studies

No thromboembolic events have been reported during treatment in Study ELT112523. One subject (Subject [information redacted]) developed a DVT 14 months after discontinuation of treatment with eltrombopag.

8.5.5.2. Other studies

No thromboembolic events have been reported during treatment in Study ELT116826, or in Study ELT116643

8.5.6. Cytogenetic events

8.5.6.1. Pivotal studies

A known complication of SAA is the appearance of cytogenetic abnormalities in bone marrow cells. Cytogenetic abnormalities have been reported in 15-20% of patients with SAA [Maciejewski, 2002; Scheinberg, 2011; Scheinberg, 2012a]. Consequently, testing for cytogenetic abnormalities is performed in all SAA studies conducted by the NIH. The clinical consequences are variable, depending upon the specific abnormality and the presence or absence of clinical sequelae such as dysplasia or worsening cytopaenias [Maciejewski, 2002]. 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. In general, the incidence of cytogenetic abnormalities was lower in subjects with

longer exposure to eltrombopag. The cytogenetic abnormalities were primarily detected in non-responders who discontinued treatment due to non-response at the PRA, after 3-4 months of treatment.

The most common cytogenetic abnormality (present in 5 subjects) affected the structure or number of chromosome 7; all 5 were non-responders to eltrombopag and the cytogenetic abnormalities were detected at the PRA. One additional non-responder had trisomy 8 detected at the PRA. Two responders to eltrombopag had a deletion of chromosome 13 detected after >9 months of treatment. Five of the subjects with cytogenetic abnormalities had no clinical sequelae of dysplasia or worsening cytopenias reported.

8.5.6.2. Other studies

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

In Study ELT116643, cytogenetic abnormalities affecting chromosome 7 and 13, respectively, were detected post-baseline in 2 subjects (5%) at the 3 month response assessment. This rate is consistent to rates in literature in treatment naïve patient population [Scheinberg, 2011].

The development of cytogenetic abnormalities is a known risk for patients with SAA, and this risk is thought to be higher in heavily pre-treated patients with insufficient response to IST compared to earlier lines of therapy and in responding patients. There is no literature on the incidence of cytogenetic abnormalities in the heavily pre-treated population studied in the pivotal trial; however, the 5-19% incidence of cytogenetic abnormalities in the SAA studies of eltrombopag appear in line with published literature.

8.5.7. Haematological malignancies

Patients with aplastic anaemia are known to be at risk for the development of MDS and AML [Maciejewski, 2004; Marsh, 2009].

8.5.7.1. Pivotal studies

Consistent with the above, 1 subject enrolled in Study ELT112523 had a change in diagnosis to hypocellular MDS prior to treatment with eltrombopag. This subject was not treated with eltrombopag and was not included in the Safety Population.

Three subjects in Study ELT112523 were diagnosed by the investigator with MDS following treatment with eltrombopag. One subject, with bone marrow dysplasia at baseline, developed monosomy 7 and subsequently died of MDS >6 months after the last dose of eltrombopag. One subject was diagnosed based solely on monosomy 7 without evidence of dysplasia on bone marrow or worsening peripheral blood counts. This subject was transplanted. One subject was a responder for 13 months, developed deletion of chromosome 13 with <5% ringed sideroblasts and received a transplant.

Based on available evidence, eltrombopag does not appear to increase the risk of progression to MDS or AML in the SAA patient population.

8.5.7.2. Other studies

As of the clinical data cut-off date, the development of MDS or AML had not been reported in Study ELT116826.

In Study ELT116643, one subject (Subject [information redacted]) with monosomy 7 had evidence of dysplasia and an increase in blasts on a subsequent bone marrow exam consistent with development of MDS.

8.6. Post-marketing experience

Noted above in relation to the use of eltrombopag in the currently approved indications ITP and Hepatitis C associated thrombocytopenia.

8.7. Safety issues with the potential for major regulatory impact

Note is made of the specific safety issues (thromboembolic events, development of new cytogenetic abnormalities and haematological malignancies) evaluated in the submitted studies and discussed in the supplied material. Within the limitations of available follow-up data there does not seem to be a new safety signal, and that the occurrence of these 'events', in particular cytogentic evolution and the development of a haematological malignancy, would seem to be consistent with the known clinical behaviour of patients with aplastic anaemia.

However note should be made of the relatively short follow-up time and ongoing monitoring for these events would be appropriate and prudent.

In addition, safety data in the paediatric population is clearly limited.

8.8. Evaluator's overall conclusions on clinical safety

In the context of the particular patient group being evaluated it appears that the safety data reported are consistent with the known safety signals reported for eltrombopag in the currently approved indications (ITP and Hepatitis C associated thrombocytopenia).

Note is made of the three particular safety issues; thromboembolic events, the development of cytogenetic abnormalities and haematological malignancies.

1. No safety signal was detected for thromboembolic events
2. New cytogentic abnormalities and haematological malignancies were reported in a limited number of patients. It is well recognised that both occurrences are seen in long-term follow-up of patients with SAA treated along conventional lines. In addition such events do not seem to have been identified in the patients treated ITP and Hepatitis C associated thrombocytopenia.

Thus the evaluator agrees with the sponsor's assessment that there does not appear to be an unexpected increase in the incidence of these events. However this evaluator would strongly recommend that long-term follow-up for these complications is undertaken in the SAA patients treated with eltrombopag.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

SAA is a rare condition frequently treated with immunosuppressive therapy and or haematopoietic stem cell transplantation. Patients who fail 1-2 courses if IST and who are unsuitable for matched sibling transplantation, have very limited therapeutic options apart from supportive care (antimicrobials and transfusion support for platelets and red cells), an unrelated or mismatched allogeneic transplant or a novel clinical trial. Such patients have a very limited long-term survival and would be the potential beneficiaries.

The benefit of eltrombopag, reported in the pivotal clinical Study ELT112523 and supporting studies, is the availability of a new therapeutic option for patients who fail or are unsuitable for conventional therapies. The action of this agent (stimulation of haematopoietic stem cells) is

mechanistically distinct from conventional therapies (IST and transplantation) thus implying the potential for activity in patients resistant or relapsing from such therapy.

A significant minority of patient entered into the studies in reported for the target population achieved meaningful haematopoietic responses in at least one lineage. Bi- and tri-lineage responses and improvements in bone marrow cellularity are reported as is the ability for dose reduction and eventual cessation. Responses can be long-term. Limited quality of life data and improvements are also reported.

Eltrombopag is orally administered with a convenient dosing schedule. It is reported to be well tolerated with, in the context, an acceptable safety profile and no new safety signals have to date been identified in the SAA population. The safety profile in the SAA patient population is consistent with that observed in approved indications of eltrombopag. Transaminase and indirect bilirubin elevations observed were consistent with information described in the approved labelling for eltrombopag. Thromboembolic events were not observed in the SAA studies and no new identified safety risks were noted. The incidence of cytogenetic abnormalities in the SAA studies of eltrombopag observed were in line with the rates reported in the published literature in SAA patients.

In summary the benefits of eltrombopag in the proposed usage are:

- A novel therapeutic option, with a novel mode of action, for patients who have failed 'conventional therapy'
- Meaningful responses in a significant minority of patients
- Orally administered with the potential for drug cessation
  - in responders
  - in those who fail to respond to the initial trial of therapy.

9.2. First round assessment of risks

The risks of eltrombopag in the proposed usage are:

- Use in patients for whom a 'suitable/conventional' alternative therapeutic option is available.
  - This issue has been addressed above, but in brief, if the proposed indication included patients who had failed only one prior IST, then the use of this agent has the potential to replace current 'accepted' second line therapy.
  - It should be noted that the accepted second line therapies (a second IST or an allogeneic transplant) are far from ideal and are associated with significant costs and toxicities. There is however no available data comparing eltrombopag with these options to assess the relative efficacy and costs, and thus which would be the preferred second line option.
  - It could be well argued that the community would benefit from the availability of a range of options for these patients.
- Prolonged inappropriate use. Care should be taken to ensure that;
  - A defined trial period is identified and that ongoing use is restricted to appropriately defined 'responders'. The criteria used in the reported trials seem appropriate.
  - Appropriate dose tapering and cessation criteria are considered. The criteria used in the reported trials seem appropriate.
- Limited paediatric data.

- Possible safety signals, in particular new cytogenetic abnormalities or an increase incidence of haematological malignancies.
  - Note is made of the supplied safety data both in the accepted indications (ITP and hepatitis C) and in SAA population. However, given the action of eltrombopag in the haematopoietic stem cell and the well-recognised potential for patients with SAA to develop additional new cytogenetic abnormalities or progress to a haematological malignancy, ongoing monitoring of this issue would seem appropriate.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of eltrombopag, given the proposed usage, has the potential to be favourable. However the evaluator would recommend particular attention is paid to the exact wording of the indication.

The evaluator certainly thinks that the use of eltrombopag would be appropriate and the risks acceptable for SAA patients who;

1. Have failed 2 courses of conventional IST and for whom an allogenic stem cell transplant is not feasible or inappropriate due to lack of an available donor or patient co-morbidities.

   A significant issue in this context is to define 'acceptability of available donor'; fully matched sibling versus fully (molecularly)-matched unrelated donor versus mismatched related or unrelated donor. 'Acceptability' will clearly vary depending on the age comorbidities of the patient.

2. Have failed 1 course of conventional IST and for whom a second course of IST would be inappropriate and, in whom, an allogenic stem cell transplant is not feasible or inappropriate due to lack of an available donor (see above) or patient co-morbidities

10. First round recommendation regarding authorisation

The evaluator would not recommend a blanket approval for patients with SAA who have failed (one round) IST as proposed by the sponsors. Rather the evaluator would recommend initial approval a suggested in section 10 above. The sponsors could be asked to address the issues of the number of rounds of IST required and the place of allogeneic transplantation before in a subsequent submission.

11. Clinical questions

Refer to comments above.

12. Second round evaluation of clinical data submitted in response to questions

1. Question posed by RMP evaluator:

It is recommended the existing additional risk minimisation activities be updated to include the proposed indication and specific risks associated with that indication (e.g. cytogenetic abnormalities).

Sponsor's response:

This is covered on page 99 of European RMP v33.

No additional educational materials are proposed for the indication of SAA, but the existing educational materials will be updated to include an indication statement for SAA, following possible approval of the SAA application.

A known complication of SAA is the appearance of cytogenetic abnormalities in bone marrow cells. Cytogenetic abnormalities have been reported in 15 to 20 % of patients with SAA [Maciejewski, 2002; Scheinberg, 2011; Scheinberg, 2012]. The clinical consequences are variable, depending upon the specific abnormality and the presence or absence of clinical sequelae such as dysplasia or worsening cytopenias [Maciejewski, 2002]. Novartis does not propose to include any specific information about cytogenetic abnormalities in the educational materials. Information communicated to physicians through the Australian product information document is considered the primary tool to educate physicians about this risk.

No other regulatory body including the US Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) have requested the addition of such information in the currently implemented educational materials. [Information redacted].

Clinical evaluator comment:

Noted. From the reports available to date there does not seem to be an increase in haematopoietic cytogenetic abnormalities in SAA patients. However

- Experience with Eltrombopag in SAA is relatively short compared to the other indications
- It should be reinforced that SAA is (almost universally) accepted to be a disorder of the haematopoietic stem cell and is thus distinguished from the other indications. The TPO receptor (target of Eltrombopag) is present on haematopoietic stem can progenitor cells.

Thus the evaluator still has the opinion that this issue deserves further monitoring.

2. Question posed by clinical evaluator:

The sponsor is invited to comment at the s31 stage on any issues raised in this report, particularly those issues raised or summarised within Sections 9 and 10 of the report regarding benefit, risk, wording of indication and the sponsor's proposed approach to long-term monitoring of safety in SAA.

Clinical evaluator comment:

The evaluator has read the sponsors response to comments relating to the wording of the indication and note their interpretation and arguments. The evaluator certainly agrees that there is sufficient evidence to support activity in the particular patient groups evaluated, including patient who had failed only one round of IST.

The evaluator would like to make the following points;

a. The therapy for SAA patients who have failed initial therapy is suboptimal. There are however a number of well-established paradigms involving consideration of an allogeneic transplant for suitable patients or a second round of IST.

b. Australian and international registry data demonstrate significant use, in the context of a rare disease, of allogeneic transplantation in this area.

c. Given the small numbers of patients evaluated and the high likelihood for differences in patient selection criteria it is inappropriate to compare non-randomised studies. Whilst potential efficacy of all three approaches is demonstrated any attempt to imply that one therapy is better that any of the others is inappropriate.

Thus the recommendations can be considered in the context of a global paradigm for the management of SAA patients who have failed previous IST. The following is, the evaluator believes, appropriate;

1. Have failed 2 courses of conventional IST and for whom an allogeneic stem cell transplant is not feasible or inappropriate due to lack of an available donor or patient co-morbidities
2. Have failed 1 course of conventional IST and for whom a second course of IST would be inappropriate and , in whom, an allogeneic stem cell transplant is not feasible or inappropriate due to lack of an available donor (see above) or patient co-morbidities

12.1. Second round benefit-risk assessment

12.1.1. Second round assessment of benefits

Availability of a therapy for patients for whom no other appropriate therapy is possible or appropriate.

12.1.2. Second round assessment of risks

1. See comments under *1. Question by RMP evaluator*:
2. For patients who have failed only 1 course of IST and for whom neither a second course of IST nor an allogeneic transplant is contraindicated there is the potential for replacement, without proof of superiority, of currently accepted second line approaches. A cost benefit analysis should be considered.

12.1.3. Second round assessment of benefit-risk balance

The data clearly indicate a benefit for patients with no appropriate alternative (see previous comments).

13. References-supplied by sponsor

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