Module 2.5

Clinical Overview

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ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
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 hematologic response
CsA	Cyclosporine A
CSR	Clinical study report
EPO	Erythropoietin
FDA	Food and Drug Administration
GSK	Glaxo Smith Kline
hATG	Horse anti-thymocyte globulin
HCV	Hepatitis C virus
HSPC	Hematopoietic stem and progenitor cells
HSCT	Hematopoietic stem cell transplant
IND	Investigational new drug
ISS	Integrated Summary of Safety
IST	Immunosuppressive therapy
ITP	Immune thrombocytopenic purpura
MDS	Myelodysplastic syndrome
NA	Not applicable
NHLBI	National Heart Lung Blood Institute
NIH	National Institutes of Health
PR	Partial hematologic response
rATG	Rabbit ATG
RBC	Red blood cell
SAA	Severe aplastic anemia
SAE	Serious adverse event
TPO	Thrombopoietin
TPO-R	TPO receptor
ULN	Upper limit or normal

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1. PRODUCT DEVELOPMENT RATIONALE

PROMACTA® (eltrombopag) tablets are approved by the U.S. Food and Drug Administration (FDA) for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy and for the treatment of thrombocytopenia in patients with chronic hepatitis C virus (HCV) to allow the initiation and maintenance of interferon-based therapy.

In addition to the studies leading to the approvals for chronic ITP and HCV, the clinical development program has investigated the use of eltrombopag in pediatric subjects with chronic ITP and in adult subjects with hematology/oncology-related thrombocytopenia.

1.1. Severe Aplastic Anemia

Severe aplastic anemia (SAA) is a rare, life-threatening, acquired bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack of hematopoietic stem and progenitor cells (HSPC) due to an immune-mediated attack on the bone marrow. SAA is a diagnosis of exclusion, with 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 [<60 GiL via automated counter]) [Camitta, 1975; Rosenfeld, 2003; Marsh, 2009]. Aplastic anemia affects approximately 2 out of every 1 million people in Western countries [Young, 2008].

Historically, SAA was nearly uniformly a fatal diagnosis due to infection or hemorrhage resulting from prolonged pancytopenia. Outcomes in patients with SAA have improved dramatically due to definitive treatment with either intensive immunosuppressive therapy (IST) with horse anti-thymocyte globulin and cyclosporine (hATG/CsA), or hematopoietic stem cell transplantation (HSCT). Due to the hematologic responses observed with these treatments, survival rates for patients with SAA have improved substantially [Rosenfeld, 2003].

Outcomes remain poor for patients who have an insufficient response to IST. Despite significant improvements in standard supportive care treatments (particularly antifungal antimicrobials and other antibiotics), approximately 40% of SAA patients unresponsive to initial IST die from the complications of pancytopenia (infection or bleeding) within 5 years of diagnosis [Valdez, 2011]. Such patients have a poor prognosis and a high unmet medical need; new treatment options are needed for patients with insufficient response to standard IST.

1.2. Current Therapies and Unmet Medical Need in SAA Unresponsive to IST

The standard treatment regimen for treatment-naïve SAA is hATG/CsA. Horse ATG (Atgam) is the only product FDA approved for treatment of aplastic anemia in the U.S. Since the establishment of hATG/CsA as a standard treatment for SAA, no subsequent improvements in treatment have been identified. Intensification of primary IST for

treatment-naïve patients with agents more immunosuppressive than hATG, including rabbit ATG (rATG), alemtuzumab, or high dose cyclophosphamide, have not been successful and the addition of sirolimus or mycophenolate to hATG/CsA have not improved response rates [Scheinberg, 2006; Scheinberg, 2009; Scheinberg, 2012a; Scheinberg, 2011].

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 [Marsh, 2013; Scheinberg, 2012b].

Alternative donor transplantation (matched unrelated donors) can be effective in select patients with SAA [Socie, 2013], but there are issues of donor availability, cost, and treatment-related morbidity and mortality. To date, outcomes following umbilical cord transplant have been extremely poor in patients with bone marrow failure syndromes. Cord and haploidentical transplants are not recommended outside of clinical trials [Marsh, 2013].

A second course of IST (ATG/CsA or alemtuzumab) salvages some SAA patients who were unresponsive to initial IST with hematologic responses observed in 21% to 37% of patients [Scheinberg, 2012a; Scheinberg, 2014]. A third course of IST has been shown to be ineffective in patients unresponsive to previous IST [Gupta, 2005; Scheinberg, 2012a].

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 [Scheinberg, 2012b].

There is a high unmet need for effective, well-tolerated therapies for SAA patients who have an insufficient response to IST.

1.3. Rationale for Treatment with Eltrombopag in SAA

Aplastic anemia is characterized by a very limited number of HSPC due to immune mediated attack on the bone marrow. Several preclinical experiments have demonstrated positive influence of thrombopoietin (TPO) and the TPO-receptor (TPO-R) on expansion of HSPC [Zeigler, 1994; Alexander, 1996; Kimura, 1998; Qian, 2007]. Multilineage bone marrow failure has been reported in patients with mutations of the mpl receptor in patients with congenital amegakaryocytic thrombocytopenia [Geddis, 2011].

Eltrombopag is an oral TPO-R agonist, which interacts with the transmembrane domain of the TPO-R on megakaryocytes and human bone marrow progenitor cells [Erickson-Miller, 2010; Sun, 2012]. Eltrombopag increases hematopoiesis by inducing proliferation and differentiation of early bone marrow progenitor cells. The multilineage effects of eltrombopag in patients with aplastic anemia may be through stimulation of bone marrow progenitor cells, as suggested by recent preclinical research [Sun, 2012]. In this research, eltrombopag treatment resulted in mulitlineage increases in human peripheral blood cells and bone marrow in mice transplanted with human cord blood CD34+ cells compared to placebo after 4 and 6 weeks of dosing. In addition, a 2-4 fold

increase in the number of CD34+ cells was observed after culture of cord blood CD34+ with eltrombopag for 7 days [Sun, 2012].

1.4. Clinical Development Program in SAA

GlaxoSmithKline (GSK) has supported investigator sponsored studies of eltrombopag in patients with aplastic anemia (Table 1) conducted by the National Institutes of Health (NIH). The Hematology Branch of the National Heart Lung Blood Institute (NHLBI) has completed enrolment in NIH protocol 09-H-0154 (ELT112523) and is currently enrolling subjects into NIH protocol 12-H-0150 (ELT116643) (IND number: 104,877). Both studies are single-arm, open-label studies evaluating eltrombopag at doses of up to 150 mg/day.

The pivotal study (ELT112523) supporting use of eltrombopag in the treatment of patients with SAA was conducted in heavily pretreated SAA patients with insufficient response to immunosuppressive therapy. Study ELT116643 is an ongoing supportive study in patients with SAA who are receiving standard front-line treatment with hATG/CsA in combination with eltrombopag.

Additional supportive safety data is provided from a completed, placebo-controlled Phase I/II study, PMA112509, in subjects with advanced myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). To support the single-arm data from the SAA trials, PMA112509 provides comparative safety data of eltrombopag at doses up to 2-fold higher than the maximum dose in SAA, in another patient population with bone marrow failure with a similar risk for development of complications due to pancytopenia (e.g. infections and bleeding).

Table 1 Pivotal and Supportive Studies

Study	Patient Population Enrolled/Planned	Study Design	Primary Endpoint	Study Status Data Cut-off Date
NIH 09-H-0154 GSK ELT112523	Heavily pretreated SAA N=44	Open-label Eltrombopag 50-150 mg/day	Hematologic response at 3 months	Enrollment Complete Ongoing treatment 01 Jun 2013
NIH 12-H-0150 GSK ELT116643	1L SAA N=31/62	Open-label hATG/CsA + eltrombopag 150 mg/day	Complete hematologic response at 6 months	Ongoing enrollment 05 Nov 2013
GSK PMA112509	AML/MDS PBO n=34 Eltrombopag n=64	Randomized, placebo-controlled, double-blind Eltrombopag 50-300 mg/day	Safety and tolerability of eltrombopag treatment	Completed

1.5. Claimed Indication and Dosages

Based upon the results of the clinical studies reported in this submission, the proposed indication is:

PROMACTA is indicated for the treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

The recommended starting dose of eltrombopag is 50 mg once daily. After initiating eltrombopag, the daily dose should be adjusted in 50 mg increments every 2 weeks based upon platelet response up to a maximum dose of 150mg once daily.

1.6. Good Clinical Practice

ELT112523 and ELT116643 were undertaken in accordance with the standard operating procedures of the NIH, which comply with the principles of Good Clinical Practice. 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 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.

2. OVERVIEW OF BIOPHARMACEUTICS

Not applicable for this sNDA submission.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

Not applicable for this sNDA submission.

4. OVERVIEW OF EFFICACY

The primary evidence of the efficacy of eltrombopag in SAA subjects is provided by the pivotal study ELT112523, a non-randomized, single-arm, Phase II study of eltrombopag in subjects with SAA and insufficient response after treatment with ATG/CsA.

In addition to the pivotal study, efficacy data from an ongoing, non-randomized, single-arm study (ELT116643) of eltrombopag in combination with hATG/CsA in treatment naïve SAA subjects is summarized.

Efficacy data from these studies have not been pooled due to differences in efficacy endpoints, study designs and study populations across the clinical trials. In this section, a discussion of the dose selection, study designs, patient populations, efficacy endpoints

and an overview of the efficacy findings relevant to the overall benefit:risk conclusions are presented for the pivotal and supportive studies of eltrombopag in SAA.

4.1. Rationale for Dose Selection

Eltrombopag 50 mg once daily was selected as the starting dose for ELT112523 because this regimen has been demonstrated to be safe and effective in increasing platelet counts in patients with chronic ITP and HCV [Cheng, 2011; Afdhal, 2012]. A starting dose of 25 mg once daily was selected for East Asian patients due to ethnopharmacologic 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 (see m2.7.3 Summary of Clinical Efficacy, Section 4):

- The effective dose in SAA subjects was unknown.
- 300 mg per day was the maximum dose studied in the eltrombopag program.
- 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-τ) values of 302 µg.h/mL for the 200 mg once daily regimen. Eltrombopag was well tolerated in healthy subjects at all dose levels.
- There is evidence that higher doses of growth factors are required in bone marrow failure syndromes: the effective erythropoietin (EPO) dose in MDS is several times higher than the EPO dose used in anemia of renal failure.
- 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.

The dose of eltrombopag 150 mg/day in the treatment naïve study, ELT116643, was based upon the results of ELT112523. In ELT112523 nearly all subjects escalated to 150 mg once daily prior to observation of responses.

4.2. Pivotal Study ELT112523

4.2.1. Clinical Trial Design and Methodology

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 immunosuppression-refractory thrombocytopenia (m2.7.3 Summary of Clinical Efficacy, Section 1.3.1). This was an investigator-sponsored study conducted by the NIH (Figure 1).

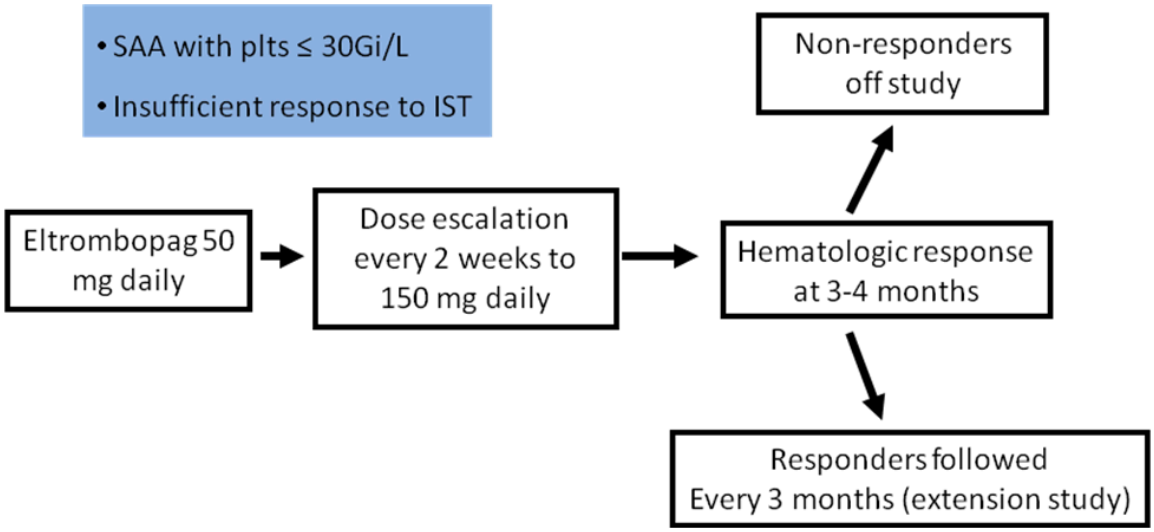
The starting dose of eltrombopag was 50 mg daily, and the dose was increased by 25 mg daily every 2 weeks based on platelet counts to a maximum of 150 mg daily.

The primary endpoint was Investigator-assessed hematologic response at the Week 12 or 16 visit (hereafter referred to as the Primary Response Assessment) defined by changes in the platelet count and/or platelet transfusion requirements, hemoglobin levels, and/or number of RBC transfusions, or ANC levels. Subjects with evidence of response at

12 weeks could continue study medication for an additional 4 weeks to ensure hematologic response prior to being consented for entry into the extended access part of the study.

Responding subjects were eligible to enter the extension portion of the trial. The dose of eltrombopag during the extension 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 treatment.

Figure 1 ELT112523 Study Schematic



4.2.2. Efficacy Endpoints and Statistical Analyses

Assessment of response in patients with SAA relies on hematologic improvements in blood counts. It is generally accepted that 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 [Marsh, 2009; Scheinberg, 2012b].

As such, the primary efficacy endpoint in ELT112523 was Investigator-assessed hematologic response at the Primary Response Assessment, defined as meeting 1 or more of the following criteria (m2.7.3 Summary of Clinical Efficacy, Section 1.3.1):

- Platelet count increases to 20 Gi/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks;
- Hemoglobin increase by ≥1.5 g/dL (for patients with pre-treatment hemoglobin <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.

The individual components of hematologic response were further evaluated to examine improvement in the number of cell lineages responding over time and maintenance of response over time, and duration of response.

Additional efficacy assessments included maintenance of response after eltrombopag discontinuation, platelet transfusion free days, RBC transfusion free days, and reconstitution of hematopoiesis.

Together with the primary endpoint, these efficacy assessments allow evaluation of clinical benefit of treatment with eltrombopag in patients with SAA.

4.2.3. Demography and Baseline Characteristics

The median (range) age of the 43 treated subjects was 45 years (range: 17-77) and the majority of subjects were between the ages of 18 and 64 years (63%) (m2.7.3 Summary of Clinical Efficacy, Section 3.1.1). Approximately half of subjects in the study were male (56%). The most common race/ethnicity in the study was White (47%), followed by Black (30%) and Hispanic (21%).

Baseline disease characteristics were consistent with that expected of a heavily pretreated SAA patient population, who have a poor prognosis. The median time since diagnosis of SAA until screening for the study was 31 months (range: 10-190 months). Cytogenetic abnormalities were present at baseline in 7% of subjects.

All subjects met criteria for diagnosis of SAA and the baseline median values for ANC, platelets, hemoglobin and reticulocytes were indicative of the pan-cytopenic SAA patient population (0.58 Gi/L, 20 Gi/L, 8.4 g/dL, and 24.3 Gi/L, respectively) despite inclusion of laboratory values from patients recently transfused. At baseline, 91% of subjects were platelet transfusion-dependent and 86% were RBC transfusion-dependent.

All subjects enrolled in the study received at least 1 prior intensive IST at least 6 months prior to entry into the trial. All subjects had received prior ATG-based IST, primarily horse (95%) or rabbit (58%) ATG-based regimens. Non-ATG based IST regimens previously received were alemtuzumab (35%) and cyclophosphamide (14%). Most subjects had received ≥2 prior immunosuppressive regimens (84%) and 33% of subjects had received ≥3 prior immunosuppressive regimens. In addition, 93% of subjects had received other medications for the treatment of their SAA, including androgens (37% of subjects).

4.2.4. Efficacy Results

4.2.4.1. Primary Efficacy Analysis: Hematologic Response

Hematologic response was achieved in 17 subjects (40%) in at least one lineage (95% confidence interval [CI]: 25%,56%) at the Primary Response Assessment (Table 2) (m2.7.3 Summary of Clinical Efficacy, Section 3.2.1.1).

Table 2 Primary Endpoint: Investigator-Assessed Response

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

m2.7.3 Summary of Clinical Efficacy, Section 3.2.1.1

At the Primary Response Assessment, the majority of responders (65%) met the platelet response criteria, with 47% and 18% of subjects meeting the ANC and hemoglobin response criteria, respectively (m2.7.3 Summary of Clinical Efficacy, Section 3.2.1.2). Multilineage responses were observed in 24% of responders (Table 3) and 82% of responders continued eltrombopag in the extension. In the extension, responders had improvements in additional lineages with continued eltrombopag treatment. As of the clinical cut-off, 47% of responders had multilineage responses. All multilineage responses were maintained at study withdrawal or the clinical cutoff, and ranged from 3 months to 42 months.

Table 3 Summary of Hematologic Response

	Primary Response Assessment	Response at Last Assessment
Response Criteria, n (%)	**Eltrombopag (N=17)**	**Eltrombopag (N=17)**
Unilineage	13 (76)	6 (35)
Multilineage	4 (24)	8 (47) [a]
Bi-lineage	3 (18)	4 (24)
Tri-lineage	1 (6)	4 (24)
Relapsed by Last Assessment	-	3 (18)

m2.7.3 Summary of Clinical Efficacy, Section 3.2.1.2

a. Two bilineage improved to trilineage; 1 unilineage improved to trilineage; 3 unilineage improved to bilineage.

The majority of responders (82%) maintained their response as of the data cut-off. The 3 subjects who relapsed (18%) were unilineage responders and relapses occurred within 6 months of initiating eltrombopag (ELT112523 CSR, Section 6.2).

Of the 17 subjects who responded, response was maintained in the 12 evaluable subjects (at least 2 response assessments) for a median duration of 14.8 months (range: 3 to 42 months) (m2.7.3 Summary of Clinical Efficacy, Section 3.2.1.3).

Of all 17 responders, 8 have been followed for at least 6 months without relapse; 6 have been followed for at least 1 year without relapse. No new therapy for SAA was administered.

4.2.4.2. Platelet and RBC Transfusion Free Duration

Ninety-one percent of subjects were platelet transfusion dependent at baseline (m2.7.3 Summary of Clinical Efficacy, Section 3.2.1.4). Of these subjects, 54% (21/39) became platelet transfusion independent (defined as at least one period of 28 days without platelet transfusions) during the study.

Eighty-six percent of subjects were RBC transfusion dependent at baseline. Of these 37 subjects, 24% (9/37) became independent (defined as at least one period of 56 days without RBC transfusions) during the study.

The maximum platelet (or RBC) transfusion free period for each subject was used to summarize the transfusion free period across the subjects in the trial (Table 4). The longest platelet transfusion free period in responders was 8-1096 days with a median of 200 days. Similarly, the longest RBC transfusion free period in responders was 15-1082 days with a median of 208 days.

Table 4 Summary of Maximum Transfusion Free Period (Study ELT112523; Safety Population)

Transfusion Free Duration (Days)	Responder (N=17)	Non-Responder (N=26)	Total (N=43)
Platelet Median (min-max)	200.0 (8-1096)	27.5 (7-84)	29.0 (7-1096)
RBC Median (min-max)	208.0 (15-1082)	29.0 (8-115)	34.0 (8-1082)

m2.7.3 Summary of Clinical Efficacy, Section 3.2.1.4

4.2.4.3. Maintenance of Response after Eltrombopag Discontinuation

As of the clinical cut-off date, 4 subjects met protocol specified 'tri-lineage hematopoiesis' criteria for at least 8 weeks and were tapered off eltrombopag treatment (m2.7.3 Summary of Clinical Efficacy, Section 3.2.1.5). All four subjects have maintained tri-lineage hematopoiesis after eltrombopag discontinuation (median follow-up: 8.1 months; range: 7.2-10.6 months) and remain in response as of the clinical cut-off date. The platelet/RBC transfusion-free periods for these 4 subjects were >30 months on treatment and >7 months following discontinuation of eltrombopag as of the clinical cut-off date.

Two additional subjects with multilineage response have discontinued or interrupted treatment with eltrombopag. In both cases, the responses were maintained after discontinuation of eltrombopag as of the clinical cut-off.

4.2.4.4. Reconstitution of Hematopoiesis

At baseline, the majority of responders (88%) had 'hypocellular' bone marrows which ranged from 'variably hypocellular' to 'severely hypocellular'. During treatment with eltrombopag, 5 subjects became 'normocellular' after approximately 2 years of treatment

with eltrombopag and 5 additional responders had an improvement in celluarity noted from baseline (m2.7.3 Summary of Clinical Efficacy, Section 3.2.1.6). Five subjects had no change in their bone marrow cellularity reported. None appeared to have worsened cellularity.

The majority of responders (10 subjects, 59%) had 'tri-lineage hypoplasia' or 'nearly absent hematopoiesis' noted in bone marrow reports at baseline. Two subjects had hypoplasia noted for 1 or 2 lineages at baseline and 4 subjects had no mention of hematopoiesis at baseline. A single subject had evidence of trilineage hematopoiesis noted at baseline. Six subjects with trilineage hypoplasia or no mention of hematopoiesis at baseline had 'tri-lineage hematopoiesis' documented after treatment with eltrombopag, indicating production of myeloid, erythroid and megakaryocytic blood cells.

4.3. Supportive Study ELT116643

Eltrombopag is being evaluated in an ongoing study in combination with standard, first-line immunosuppressive therapy (hATG/CsA) for treatment-naïve patients with SAA (NIH protocol 12-H-0150).

4.3.1. Clinical Trial Design and Methodology

This is an ongoing, open-label, phase I/II study of eltrombopag in combination with standard regimen of hATG/CsA in 62 treatment-naive subjects ages 2 and above with SAA (m2.7.3 Summary of Clinical Efficacy, Section 1.3.2). The primary endpoint of the study is complete hematologic response at 6 months. 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.

4.3.2. Efficacy Endpoints

The primary endpoint is the rate of complete hematologic response (CR) at six months. CR was defined as ANC >1 Gi/L, platelet count >100 Gi/L and hemoglobin >10 g/dL on 2 serial blood counts at least 1 week apart. Partial response (PR) is defined as 2 of the following: ANC >0.5 Gi/L, platelet count >20 Gi/L, absolute reticulocyte count >60 Gi/L on 2 serial blood counts at least 1 week apart. Secondary endpoints were relapse, robust hematologic blood count recovery at 3, 6, and 12 months, survival, clonal evolution to myelodysplasia and leukemia, and marrow stem cell content.

4.3.3. Demography and Baseline Characteristics

As of the clinical cut-off for this ongoing study, 31 of the planned 62 subjects have been enrolled (m2.7.3 Summary of Clinical Efficacy, Section 3.1.2). The median age of the 31 enrolled subjects was 39 years (range: 12-72 years); 84% were ≥18 years of age and 16% were between the ages of 12-17 years. Approximately half of the subjects were male (52%). The majority of subjects were white (55%) followed by Black/African American (32%) and Asian (10%).

The baseline median values for ANC, platelets and absolute reticulocyte count were indicative of the pan-cytopenic SAA patient population (0.22 Gi/L, 9 Gi/L and 20.3 Gi/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.

4.3.4. Efficacy results

At the 6 month assessment, the primary endpoint of CR was met by 8/22 subjects (36%; 95% CI:17%,59%) and 17 subjects overall (77%) had a CR or PR (Table 5) (m2.7.3 Summary of Clinical Efficacy, Section 3.2.2.1). At the 3 month assessment, 4/23 subjects (17%) had a CR, and 18 subjects (78%) overall had a CR or PR. All 4 subjects with a CR at 3 months maintained a CR at the 6 month assessment. The additional 4 subjects with a CR at 6 months had a PR at the 3 month assessment. Five of the 8 subjects with CRs reported at 6 months met the SAA criteria in all 3 lineages at baseline.

Table 5 3 and 6 Month Response Assessments

Hematologic Response, n (%)	3 Month N=23[a]	6 Month N=22[a]
Overall Response	18 (78)	17(77)
Complete Response	4 (17)	8 (36)
Partial Response	14 (61)	9 (41)
Non-responder	5 (22)[b]	5 (23)[c]

m2.7.3 Summary of Clinical Efficacy, Section 3.2.2.1

a. Evaluable as of the 5Nov2013 clinical cut-off date.
b. Includes 3 non-responders, 2 subjects who discontinued or died prior to evaluation at 3 months.
c. Includes 2 non-responders, 2 subjects who discontinued or died prior to evaluation at 3 months and 1 subject with a PR at 3 months who discontinued eltrombopag at 3 months due to cytogenetic change.

No responding subjects relapsed while receiving eltrombopag treatment. Of the subjects who responded after 6 months of treatment, 12 subjects have maintained response after per protocol discontinuation of eltrombopag at 6 months as of the data cut-off.

4.4. Efficacy Summary/Conclusions

Results of eltrombopag in patients with SAA strongly support the clinical benefit of eltrombopag as a treatment option for patients with an insufficient response to immunosuppressive therapy.

- The median age and degree of baseline cytopenias were similar across both studies and highly representative of the poor prognosis in this SAA population.
- Treatment with eltrombopag produced a 40% hematologic response rate in the heavily pretreated patient population, where no established standard of care exists.

- Over time, responses continued to improve and included multi-lineage responses in 47% of responders. These responses were durable, with a median duration of response of >1 year, and were associated with platelet and RBC transfusion free intervals of over 6 months in a population that had been transfusion dependent.
- Multilineage responses were maintained over time, were associated with restoration of bone marrow cellularity and tri-lineage responses have been maintained after discontinuation of eltrombopag.
- Similar to the data in the heavily pretreated SAA population, the quality of responses improved over time in the ongoing study of eltrombopag in treatment naïve SAA patients, in combination with standard IST.
- The complete (36%) and overall response rates (77%) observed with eltrombopag in combination with standard IST are as expected, or higher than expected with standard IST alone (10-15% complete response and 50-60% overall response) based upon published literature in front line SAA [Scheinberg, 2006; Scheinberg, 2009; Scheinberg, 2011; Tichelli, 2011; Marsh, 2012].

The striking multi-lineage activity of eltrombopag is noteworthy in patients with SAA who have an insufficient response to immunosuppressive therapies, where responses are infrequently reported [Gupta, 2005; Scheinberg, 2012a; Scheinberg, 2014]. Results from both studies of eltrombopag in patients with SAA strongly support the use of eltrombopag as a treatment option for patients with an insufficient response to immunosuppressive therapy.

5. OVERVIEW OF SAFETY

5.1. Introduction

Eltrombopag is an approved product with a well-known safety profile established in randomized trials in chronic ITP up to 75 mg daily and HCV patient populations up to 100 mg daily. The eltrombopag SAA clinical development program includes a safety database of 73 eltrombopag-treated subjects with SAA from 2 open-label trials (Table 6). In addition, supportive safety data is provided from a completed, placebo-controlled study in subjects with advanced MDS or AML receiving up to twice the maximum dose of eltrombopag in SAA. Similar to the SAA patient population, patients with advanced MDS and AML face life-threatening complications due to pancytopenia. The safety profiles observed in both populations are 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.

Table 6 Safety Database

Study	Eltrombopag (SAA population)	Double-Blind Study Treatment (advanced MDS/AML patient population)	
		Placebo	Eltrombopag
ELT112523	43[a]	NA	NA
ELT116643	30[a]	NA	NA
PMA112509	NA	34	64

a. One subject in each study was enrolled, but did not receive eltrombopag treatment.

5.2. Exposure in the SAA Population

Of the 43 subjects who received eltrombopag in Study ELT112523, 93% were escalated to the maximum dose of eltrombopag 150 mg (m2.7.4 Summary of Clinical Safety, Section 1.3.1). Three subjects received a maximum 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 (2-37). Eltrombopag treatment was received for at least 3 months in 77% of subjects. As of the clinical cut-off date, 26% and 16% of subjects received eltrombopag for >6 and 12 months, respectively, with a maximum duration of 37 months.

Of the 30 subjects who received eltrombopag 150mg in ELT116643, 18 completed 6 months of treatment with eltrombopag. No further exposure data is available for this ongoing study.

5.3. Demography and Other Characteristics of the SAA Population

The demographics and baseline disease characteristics in the Safety Population for ELT112523 were presented in Section 4.2.3 (m2.7.4 Summary of Clinical Safety, Section 1.4.1.1).

In Study ELT116643, demographics and baseline characteristics of the Safety Population are as expected for patients with untreated SAA with respect to age and baseline cytopenias (m2.7.4 Summary of Clinical Safety, Section 1.4.1.1), and are similar to baseline characteristics of subjects in Study ELT112523.

5.4. Adverse Events in the SAA Population

In Study ELT112523, adverse events (AEs) on-therapy were defined as those that occurred from the date of first dose of eltrombopag treatment to the date 30 days 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 the investigator as possibly related to treatment (Table 7) (m2.7.4 Summary of Clinical Safety, Section 2.1). Two deaths occurred during the on-therapy period of the study; 6 deaths occurred during the entire study period.

Table 7 Overview of Adverse Events On-Therapy in Study ELT112523 (Safety Population)

n (%)	Eltrombopag (N=43)
Any AE	**40 (93)**
AEs related to study treatment	30 (70)
AEs leading to permanent discontinuation of study treatment	4 (9)
Any SAE	**14 (33)**
Deaths	**2 (5)**

m2.7.4 Summary of Clinical Safety, Section 2.1

5.4.1. Common AEs

The most common AEs observed in Study ELT112523 largely reflect the well-known safety profile of eltrombopag treatment and events expected in the SAA patient population (m2.7.4 Summary of Clinical Safety, Section 2.1.1 and Section 2.1.2). Nausea, fatigue, cough, diarrhea, and headache were the most common AEs, reported by at least 20% of subjects (Table 8).

Table 8 On-Therapy Adverse Events Occurring in 10% or More Subjects (ELT112523 Safety Population)

Preferred Term	Eltrombopag (N=43)
Any event, n (%)	**40 (93)**
Nausea	14 (33)
Fatigue	12 (28)
Cough	10 (23)
Diarrhea	9 (21)
Headache	9 (21)
Pain in extremity	8 (19)
Dizziness	6 (14)
Dyspnea	6 (14)
Febrile neutropenia	6 (14)
Oropharyngeal pain	6 (14)
Pyrexia	6 (14)
Abdominal pain	5 (12)
Arthralgia	5 (12)
Ecchymosis	5 (12)
Muscle spasms	5 (12)
Rhinorrhea	5 (12)
Transaminases increased	5 (12)

m2.7.4 Summary of Clinical Safety, Section 2.1.1

Thirty subjects (70%) in Study ELT112523 had at least one AE considered by the investigator to be related to treatment. Nausea, headache, and diarrhea were the most common AEs (≥20%) considered related to treatment.

5.4.2. Deaths

A total of 6 deaths (14%) were reported during Study ELT112523 (m2.7.4 Summary of Clinical Safety, Section 2.1.3). None of the 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. Four subjects died more than 110 days after the last dose of eltrombopag (sepsis/infection – 2 subjects; MDS/AML – 1 subject; unknown – 1 subject).

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 both studies.

5.4.3. SAEs

In Study ELT112523, a total of 14 subjects had at least one serious AE (SAE) reported during treatment (Table 9) (m2.7.4 Summary of Clinical Safety, Section 2.1.4). The most common SAE reported was febrile neutropenia.

Table 9 Serious Adverse Events On-Treatment (ELT112523 Safety Population)

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

m2.7.4 Summary of Clinical Safety, Section 2.1.4

In Study ELT116643, 14 of the 30 subjects (40%) who received eltrombopag have had 12 SAEs reported to GSK. As expected in this subject population, most of the SAEs

were infectious in nature. One event of squamous cell carcinoma was considered possibly related to treatment with hATG/CsA and eltrombopag.

5.4.4. AEs Leading to Discontinuation

Four subjects (9%) in Study ELT112523 discontinued treatment with eltrombopag due to AEs of suspected cataract, abdominal discomfort, acute hepatitis B, and sepsis (m2.7.4 Summary of Clinical Safety, Section 2.1.5.2). No event lead to discontinuation for more than 1 subject.

5.5. Safety Topics of Special Interest

Based on the known safety profile and mechanism of action of eltrombopag and the SAA patient population under study, several categories of AEs of special interest were analyzed further in ELT112523 and ELT116643: hepatobiliary events, thromboembolic events, cytogenetic abnormalities, and hematologic malignancies (Summary of Clinical Safety, Section 2.1.6).

5.5.1. Hepatobiliary Events

Transaminase elevations and elevations of indirect bilirubin have been observed in the eltrombopag clinical program and are described in the approved labeling 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.
- A total of 4 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.
- A total of 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%).

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

The hepatobiliary laboratory data from the SAA program is consistent with information described in the current approved labeling for eltrombopag.

5.5.2. Thromboembolic Events

No thromboembolic events have been reported during treatment in the ELT112523 study or in the ELT116643 study.

5.5.3. Cytogenetic Abnormalities

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, 2012a; Scheinberg, 2011]. 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 cytopenias. Consistent with the known occurrence of cytogenetic abnormalities in SAA, 7% of subjects in ELT112523 had a cytogenetic abnormality present at baseline.

Seven subjects (16%) had a new cytogenetic abnormality detected after treatment in ELT112523. In general, the incidence of cytogenetic abnormalities was lower in subjects with longer exposure to eltrombopag. These abnormalities were primarily detected in non-responders who discontinued treatment due to non-response at the Primary Response Assessment, 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 Primary Response Assessment. One additional non-responder had trisomy 8 detected at the Primary Response Assessment. One responder to eltrombopag had a deletion of chromosome 13 detected after >1 year of treatment.

Four of the subjects with cytogenetic abnormalities had no clinical sequelae of dysplasia or worsening cytopenias reported. Three subjects with cytogenetic abnormalities and considered to have MDS are described in the Hematologic Malignancies (Section 5.5.4).

In Study ELT116643, cytogenetic abnormalities affecting chromosome 7 and 13, respectively, were detected post-baseline in 2 subjects (7%) 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 pretreated patients with insufficient response to immunosuppressive therapies than in earlier lines of therapy. There is no literature on the incidence of cytogenetic abnormalities in the heavily pretreated population studied in the pivotal trial; however, the 7-16% incidence of cytogenetic abnormalities in the SAA studies of eltrombopag appear in line with published literature.

5.5.4. Hematologic Malignancies

Patients with aplastic anemia are known to be at risk for the development of MDS and AML [Maciejewski, 2004; Marsh, 2009]. Consistent with this, 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 was received a transplant.

In Study ELT116643, one subject with monosomy 7 (Section 5.5.3) had evidence of dysplasia and an increase in blasts on a subsequent bone marrow exam consistent with development of MDS.

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

5.6. Safety of Eltrombopag in Other Indications-MDS/AML

In PMA112509, a total of 44 subjects (69%) in the eltrombopag group received at least 150 mg daily, which was at or above the maximum dose studied in SAA (Summary of Clinical Safety, Section 1.3.2).

In this study, eltrombopag up to 300 mg was generally well tolerated with a similar overall pattern of AEs to that reported for the placebo group (Summary of Clinical Safety, Section 2.2). The most commonly reported AEs were consistent with those expected for the disease under study (AML or MDS) and with those expected during treatment with eltrombopag. The most common AEs (i.e., occurring in at least 10% of the subjects) reported on treatment in the eltrombopag group were pyrexia, nausea, diarrhea, fatigue, decreased appetite, and pneumonia. No imbalances in the number of subjects with hepatobiliary laboratory abnormalities were observed (AT>3xULN: 6% placebo, 8% eltrombopag; bilirubin>1.5xULN: 26% placebo, 23% eltrombopag). The incidence of thromboembolic events was equal between the treatment groups in the study (3% in both treatment groups) (PMA112509 CSR Section 6.5.1 and Section 6.5.3).

Similar proportions of subjects died in each group overall, with fewer eltrombopag subjects (33%) dying within 30 days of the last dose compared with placebo subjects (47%) (Summary of Clinical Safety, Section 2.2.4). Most deaths during the on-treatment period were considered by the investigator to be due to the disease under study; the most common sub-reason was sepsis. The median overall survival for subjects receiving eltrombopag was 27 weeks compared with 15.7 weeks in the placebo group.

5.7. Safety Summary/Conclusions

The safety profile of eltrombopag at doses up to 150 mg daily in Study ELT112523 is consistent with the established safety profile of eltrombopag in the approved chronic ITP

and HCV indications and with that expected in the SAA patient population. No new safety signals have been detected.

- Eltrombopag at doses up to 150 mg daily was generally well tolerated. Over 90% of subjects escalated to the maximum dose and <10% of subjects discontinued due to AEs. The randomized data from study PMA112509 further supports the tolerability of eltrombopag at doses of eltrombopag twice the dose proposed for the SAA population.
- The most common AEs reported were nausea, fatigue, cough, diarrhea, and headache. SAEs of febrile neutropenia, sepsis, and viral infection were reported and were expected given severe neutropenia in this patient population. Similarly, febrile neutropenia, sepsis and infection were the most common SAEs in PMA112509; of note, these events were numerically lower in the eltrombopag group compared to the placebo group.
- The incidence and cause (primarily sepsis/infection) of deaths reported in pivotal study ELT112523 were consistent with the disease under study.
- No thromboembolic events have been observed in the SAA studies and the incidences of thromboembolic events were balanced in the PMA112509 study (3% eltrombopag, 3% placebo).
- Transaminase elevations and elevations of indirect bilirubin were observed in the ELT112523 study and are consistent with information described in the approved labeling for eltrombopag. In the PMA112509 study at doses up to 300 mg daily, ALT or AST >3xULN were similar between treatment groups (8% eltrombopag, 6% placebo).
- The development of new cytogenetic abnormalities is a known risk in patients with SAA and has been reported to occur as frequently as 15-20%. This risk is thought to be higher in heavily pretreated patients with insufficient response to IST than in those receiving earlier lines of therapy. There is no literature on the incidence in the heavily pretreated population studied in the pivotal trial; however, the 7-16% incidence of cytogenetic abnormalities in the SAA studies of eltrombopag appear in line with published literature.
- Patients with aplastic anemia are known to be at risk for the development of MDS and AML. MDS was reported in 3 subjects in the pivotal study. One subject died and 2 subjects received transplants. The supportive randomized study PMA112509 was conducted in patients with advanced MDS/AML (baseline 10-50% bone marrow blasts) and provides some perspective on these observations in SAA subjects. With doses up to 300 mg daily, no evidence of worsening of leukemic progression was observed in the subjects with advanced MDS in PMA112509; in fact there was a trend for improved survival in the eltrombopag group. Based on the available evidence, eltrombopag does not appear to increase the risk of progression to MDS or AML in the SAA patient population.

In conclusion, eltrombopag 150mg daily is well tolerated with an acceptable safety profile in subjects with SAA with insufficient response to IST (m2.7.4 Summary of Clinical Safety, Section 7). The safety profile is consistent with the known safety profile

of eltrombopag in chronic ITP and HCV, and the population under study. Additional supportive safety data comes from the randomized study in MDS/AML subjects, which was up to twice the proposed dose for the SAA population. These MDS/AML subjects are at similar risk for infections and cytopenia due to bone marrow failure as the SAA population. Together, this safety profile supports a positive benefit:risk conclusion for eltrombopag 150mg daily in this population.

6. BENEFITS AND RISKS CONCLUSIONS

6.1. Benefit-Risk Discussion

Severe aplastic anemia (SAA) is a life-threatening, acquired bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack HSPC due to an immune-mediated attack on the bone marrow. Aplastic anemia is extremely rare disease which affects approximately 2 out of every 1 million people in Western countries [Young, 2008].

Historically, SAA was nearly uniformly a fatal diagnosis due to infection or hemorrhage resulting from prolonged pancytopenia. Outcomes in patients with SAA have improved dramatically due to definitive treatment with IST or HSCT. However, no established standard of care exists for patients with insufficient response to immunosuppressive therapy who lack a matched unrelated donor for HSCT, other than transfusion support and treatment of infections. Repeated immunosuppression, especially in patients who have not previously responded, is very unlikely to provide viable responses [Gupta, 2005; Scheinberg, 2012a; Scheinberg, 2014].

Furthermore, despite significant improvements in standard supportive care treatments (particularly antifungals, antimicrobials and other antibiotics), approximately 40% of IST-refractory SAA patients die of bleeding or infection within 5 years of diagnosis [Valdez, 2011]. Currently, these patients have a poor prognosis. Accordingly patients with insufficient response to immunosuppressive therapy have a high unmet medical need and new treatment options are needed for these patients [Metcalf, 2012].

All current treatment options for patients with SAA, with the exception of transplant or supportive care options are immunosuppressive. Eltrombopag, in contrast, stimulates hematopoiesis of early hematopoietic stem cells, thus offers a mechanistically new treatment option for patients with difficult to treat SAA.

Results of eltrombopag in patients with SAA strongly support the use of eltrombopag as a treatment option for patients with previously treated SAA. The 40% response rate observed in ELT112523 is clinically meaningful, especially in the context of the heavily pretreated patient population studied, where no established standard of care exists and available treatment options are limited to lifelong intensive supportive care. The striking multi-lineage activity of eltrombopag is impressive in patients with SAA who have an insufficient response to immunosuppressive therapies, where responses are infrequently reported [Gupta, 2005; Scheinberg, 2012a; Scheinberg, 2014].

The observed safety profile of eltrombopag up to 150 mg was acceptable and as expected for this patient population and was consistent with the established safety profile of eltrombopag in the approved chronic ITP and HCV indications. Transaminase and indirect bilirubin elevations were observed in the SAA population, consistent with information described in the approved labeling for eltrombopag. Thromboembolic events were not observed in the SAA studies and no new safety signals were identified.

The development of cytogenetic abnormalities is a known risk for patients with SAA, and this risk is thought to be higher in heavily pretreated patients with insufficient response to immunosuppressive therapies than in earlier lines of therapy. In the pivotal trial, 6 of the 7 new cytogenetic abnormalities were detected at the Primary Response Assessment, primarily in subjects who discontinued treatment due to lack of hematologic response. There is no literature on the incidence of cytogenetic abnormalities in the heavily pretreated population studied in the pivotal trial, however, the 7-16% incidence of cytogenetic abnormalities in the SAA studies of eltrombopag appear in line with the 15-20% in published literature in the general SAA patient population.

Physicians who treat SAA are familiar with the management of cytogenetic abnormalities and current treatment guidelines recommend patients with SAA and cytogenetic abnormalities be treated and managed in the same fashion as SAA patients without cytogenetic abnormalities, with the exception of patients with monosomy 7. In patients with monosomy 7, the preferred treatment option is HSCT [Marsh, 2009, Scheinberg, 2012b].

It is unclear if the incidence of cytogenetic abnormalities observed in this study is different from the incidence reported in the literature. Although there is no evidence of an increased incidence of cytogenetic abnormalities with eltrombopag treatment, GSK proposes to include information on the occurrence of cytogenetic abnormalities within the label. Given the lack of experience with continued eltrombopag treatment in the presence of a new cytogenetic abnormality, GSK recommends that discontinuation of eltrombopag be considered if new cytogenetic abnormalities are observed.

In summary, eltrombopag offers a new treatment opportunity for patients with SAA and an insufficient response to immunosuppressive therapy.

6.2. Summary of Dosing Recommendations

Eltrombopag dosing recommendations are based on the results of the ELT112523. Since almost all subjects escalated to 150 mg once daily and responses were seen at the highest dose, the goal of therapy should be to reach the maximum dose of eltrombopag prior to determining if the treatment is effective.

- Initiate eltrombopag at a dose of 50 mg once daily for all patients.
- For East Asians or patients with mild, moderate, or severe hepatic impairment, consider initiating eltrombopag at a reduced dose of 25 mg once daily.
- After initiating eltrombopag, adjust the dose as necessary in 50 mg increments to achieve to achieve platelet count ≥50 Gi/L.

- Do not exceed a dose of 150 mg eltrombopag once daily.
- Dose adjustments are based on platelet count. Eltrombopag dose reductions and dose interruptions for elevated platelet counts will be consistent with the current recommendations for chronic ITP and HCV.
- During therapy with eltrombopag, assess complete blood counts (CBC) with differentials (including platelet counts) weekly until a stable platelet count has been achieved. Obtain CBCs with differentials (including platelet counts) monthly thereafter. After initiating eltrombopag, or after any subsequent dosing increase, wait 2 weeks before increasing the dose.
- Once platelet count is >50 Gi/L, hemoglobin >10 g/dL in the absence of RBC transfusions, and ANC >1 Gi/L for more than 8 weeks, the dose of eltrombopag should be reduced by up to 50%. If counts remain stable after 8 weeks at the reduced dose, then discontinue eltrombopag and monitor blood counts. If platelets drop to <30 Gi/L, hemoglobin to <9 g/dL, or ANC to <0.5 Gi/L, eltrombopag may be reinitiated back to the previous dose.
- Subjects should discontinue treatment with eltrombopag if no hematologic response has been observed after 16 weeks.
- If new cytogenetic abnormalities are observed, consider discontinuation of eltrombopag.

In summary, the dosing recommendations limit exposure by utilizing the lowest effective dose, discontinuing treatment for non-responding patients and tapering treatment in patients with trilineage response.

6.3. Benefit-Risk Conclusions

ELT112523 is the first clinical study to evaluate eltrombopag in subjects with SAA. All subjects had insufficient response to standard immunosuppressive therapies. Treatment options for this patient population are limited to life-long intensive supportive care (with antimicrobials and transfusion support for platelet and red cells), an unrelated/unmatched donor transplant or clinical trial. This patient population has a poor prognosis and a significant unmet medical need for new treatment options.

Eltrombopag stimulates hematopoiesis of early hematopoietic stem cells, and thus offers a mechanistically new treatment option for patients with difficult to treat SAA. In the context of this high unmet need, eltrombopag provides a well tolerated, oral treatment option with durable, multilineage hematologic responses, reductions in transfusion requirements and normalization of bone marrow cellularity in patients with insufficient response to immunosuppressive therapy. The safety profile is consistent with that observed in approved indications of eltrombopag and in the SAA patient population. As such, eltrombopag treatment represents a significant advance in the treatment paradigm for patients with SAA. Given the clear clinical benefit provided by eltrombopag, and the lack of effective treatment options, the results presented in this submission indicate a positive benefit:risk ratio that supports the approval of eltrombopag for the treatment of patients with previously treated SAA. GSK proposes that the final results of a single

arm, single center study conducted by the NIH supports the following indication statement:

"PROMACTA is indicated for the treatment of cytopenias in adult patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy".

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